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Single technology appraisal (STA)

Teriflunomide for the treatment of relapsing-remitting multiple sclerosis in adults

Specification for manufacturer/sponsor submission of evidence

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Glossary

Abbreviation	Definition
µg	Microgram
AAN	American Academy of Neurology
ABN	Association of British Neurologists
ABPI	Association of the British Pharmaceutical Industry
ACD	Appraisal Consultation Document
ACTH	Adrenocorticotrophic Hormone
ACTRIMS	Americas Committee for Treatment and Research in Multiple Sclerosis
ADL	Activities Of Daily Living
ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
AESI	Adverse Events of Special Interest(s)
AF	Atrial Fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
ANCOVA	Analysis of Covariance
ANS	American Neurological Society
APDDS	Adapted Patient Determined Disease Steps
ARR	Annualised Relapse Rate
AST	Aspartate Aminotransferase
BSC	Best Supported Care
BGR	Brooks-Gelman-Rubin
BNF	British National Formulary
BSC	Best Supportive Care
CE	Cost Effectiveness
CENTRAL	Cochrane Collaboration Central Register of Clinical Trials
CHMP	Committee for Medicinal Products for Human Use
CI(s)	Confidence Interval(s)
CIS	Clinically Isolated Syndrome
CPI	Consumer Price Indices
CONSORT	Consolidated Standards of Reporting Trials
CPMS	Chronic Progressive Multiple Sclerosis
CRD	Centre for Reviews and Dissemination

CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CU	Combined Unique
DAE(s)	Diagnostic Adverse Event(s)
DMT	Disease Modifying Treatment
DSA	Deterministic Sensitivity Analysis
ECG	Electrocardiography
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDSS	Expanded Disability Status Scale
EEACT	Economic Evaluation Alongside Clinical Trial
EED	Economic Evaluation Database
EFNS	European Federation of Neurological Societies
EMA	European Medicines Agency
ENS	European Neurological Society
EPAR	European Public Assessment Reports
EPTD	Early Permanent Treatment Discontinuation
EOT	End OF Treatment
ERG	Evidence Review Group
FAD	Final Appraisal Determination
FDA	US Food and Drug Administration
FIS	Fatigue Impact Scale
FS	Functional System
G/L	Gram per Litre
GA	Glatiramer Acetate
GdE	Gadolinium Enhancement
Giga/L	Gigagrams per litre
HA	Highly Active (disease)
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
HR	Hazard Ratio
HRG	Healthcare Resource Groups
HRQoL	Health-Related Quality of Life
HS	Health State

ICER	Incremental Cost-Effectiveness Ratio
IFN	Interferon
IFNβ-1a	Interferon Beta-1a
IFNβ-1b	Interferon Beta-1b
IFU	Intructions For Use
IM	Intramuscular
IP	Investigational Product
ITT	Intent-To-Treat
IV	Intravenous
IVRS	Interactive Voice Response Systems
KOL	Key Opinion Leader
LACTRIMS	Latin American Committee for Treatment and Research in Multiple Sclerosis
LLN	Lower Limit of the Normal range
LLOQ	Lower Limits Of Quantification
LOCF	Last Observation-Carried-Forward
LS mean	Least Squares mean
LY	Life Years
LYG	Life Years Gained
MedDRA	Medical Dictionary for Regulatory Activities
MESH	Medical Subject Heading
MG	Milligram
ML	Millilitre
mmol/L	Millimoles pre Litre
MMRM	Mixed-Model Repeated Measures
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS	Multiple Sclerosis Impact Scale
MSQoL-54	Multiple Sclerosis Quality of Life-54
MTC	Mixed Treatment Comparison
MUSIQoL	Multiple Sclerosis International Quality Of Life
NEC	Necrotizing Enterocolitis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	No Response
ONS	Office of National Statistics

OR	Odds Ratio
OTC	Over The Counter
PAS	Planning Advisory Service
PbR	Payment by Results
PCSA	Potentially Clinically Significant Abnormalities
PDDS	Patient Determined Disease Steps
PFT	Pulmonary Function Test
PICOS	Population Interventions Comparators Outcomes Studytype
PK	Pharmacokinetic
PMS	Premenstrual Multiple Sclerosis
PML	Progressive Multifocal Leukoencephalopathy
PP	Per Protocol
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive-Relapsing Multiple Sclerosis
PSA	Probabilistic Sensitivity Analysis
PASSRU	Personal Social Services Research Unit
PSS	Personal Social Services
PT	Preferred Term
QALY	Quality-Adjusted Life Year(s)
QoL	Quality of Life
QUOROM	Quality of Reporting of Meta-analyses
RCT	Randomised Controlled Trial
REM	Random-Effects Model
RES	Rapidly Evolving Severe (disease)
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
RSS	Risk Sharing Scheme
SAD	Sustained Accumulation of Disability
SAE	Serious Adverse Event
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form Health Survey
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase

SLR	Systematic Literature Review
SOC	System Organ Class
SPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
STA	Single Technology Appraisal
TEAE(s)	Treatment-Emergent Adverse Event(s)
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper Limit of Normal
USP	United States Pharmacopoeia
WBC	White Blood Cell

Executive summary

Overview of multiple sclerosis (MS)

MS is a chronic disease resulting in disability and premature death [Pugliatti et al. 2006]. MS is associated with axonal demyelination in the central nervous system (CNS) with considerable social impact and economic consequences.

In the UK, approximately 100,000 people have MS [MS Trust, 2012]. In England and Wales it is estimated that 88,766 people have MS (based on England and Wales having a population of 56.1 million out of a total UK population of 63.2 million) [ONS, 2012]. The mean age of onset of MS symptoms is between 20-50 years [NICE, 2003] with the highest prevalence in the age group 50-64 years [Pugliatti et al. 2006] and it predominantly affects women, with an approximate ratio of 3:1 [Ramagopalan et al. 2010].

In the UK, MS is classified into three key sub-types: relapsing-remitting (RRMS), primary-progressive (PPMS) and secondary-progressive (SPMS). The course of MS in an individual patient is largely unpredictable, but may lead ultimately to progressive disability and premature death.

Relapsing MS (RMS) and relapsing-remitting MS (RRMS)

RMS is a classification encompassing any MS patient who experiences periods of relapse during their disease course. A relapse is a clinically evident 'attack' of demyelination, characterised by gradual onset of symptoms over days, stabilising over days or weeks and then gradually resolving, completely or partially. For two relapses to be considered as such, a period of 30 days must have elapsed between the onset of new symptoms for each event [Coles, 2009].

The majority of RMS patients (approximately 85% of all MS patients at diagnosis) have RRMS [Murray, 2006]. Patients with RRMS experience recurring episodes of acute neurological dysfunction (relapses) followed by more or less complete recovery of function. In England and Wales it is estimated that 31,511 people will have RRMS (35.5%) [Kobelt et al. 2006] of which 9,769 (31%) will be treated [Zajicek et al. 2010].

Effect of MS on patients

There are some key elements of MS as a disease process that are of high importance to a patient in terms of symptoms. For a patient, relevant issues are: suffering relapses, becoming increasingly disabled with time and maintenance of an acceptable quality of life on both a daily and long-term basis.

The course of MS may be looked upon as the interaction between the two clinical phenomena of relapses and disability progression although the contribution of the former to the latter is not clear [Confavreux et al. 2006]. Relapses may require admission to hospital, and are associated with a level of disability and incapacity that

disrupts working, family and social life. Accumulation of disability clearly presents a challenge to patients and their carers, alongside the very real representation of worsening disease. Relapses can have a significant impact on quality of life [Orme et al. 2007].

Relapse rates in RRMS vary considerably over time for an individual and between individuals but there is a general pattern of exacerbations of more frequent relapses, followed by long periods of lower rates [Richards et al. 2002]. The initial relapse rate can be less than one per year and subsequently declines [Coles 2009]. This makes assessment of the effects of treatments in any individual extremely difficult.

Disability accumulation is a defining feature of RRMS and can be correlated with the extent of axonal injury and further associated with the degree of myelin inflammation [Leray et al. 2010]. It has been hypothesised that a close association between inflammation and neurodegeneration might exist in all disease stages of multiple sclerosis [Kutzelnigg et al. 2005; Frischer et al. 2009].

Patients with MS commonly experience fatigue, spasticity, bladder dysfunction, pain and cognitive dysfunction. Less common are depression, bowel dysfunction, and paroxysmal symptoms [Crayton et al. 2006]. Common symptoms in MS are interrelated: one symptom can exacerbate another or can be caused by the treatment of another symptom.

In the clinical trial programme for teriflunomide, the outcomes discussed above have been formally assessed by measuring annualised relapse rates, sustained accumulation of disability at 12-weeks/3-months (using changes in Expanded Disability Status Scale (EDSS) score), time to failure (i.e. relapse or permanent discontinuation of study drug) and quality of life measures.

Measuring disability

The most accepted tool to measure disability is the EDSS, which is a 10-point instrument that measures different areas of functional disability in the lower half of the scale and focuses on hard ambulatory disability in the latter half. A score of 6 on the EDSS is considered an important milestone as it represents the onset of walking disability and has implications for the suitability of treatment with DMTs [Kurtze, 1983]. The distribution of EDSS scores of patients being initiated on disease-modifying treatments (DMTs) through the UK Risk Sharing Scheme is bimodal with peaks around EDSS 2 and 6 (no patients start treatment at EDSS 7 or greater) [Pickin et al. 2009].

The impact of disability on patients and society is profound. Costs and utility are highly correlated with disease severity; in particular employment rates reduce substantially with increased EDSS while the costs of care and productivity losses increase more than tenfold between an EDSS score of 0-1 and a score ≥7. Utility decreases are aligned with increased EDSS scores, ultimately to a score worse than death at EDSS 9 [Kobelt et al. 2006].

The clinical trial programme for teriflunomide reports on sustained accumulation of disability for 3-months (12 weeks) as this acknowledges permanent deterioration in patient mobility.

Teriflunomide: product details and mechanism of action

Teriflunomide is a new immunomodulatory DMT with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH) required for de novo pyrimidine synthesis. As a consequence, teriflunomide blocks the proliferation of stimulated lymphocytes which need the de novo synthesis of pyrimidine to proliferate. Resting lymphocyte pyrimidine metabolism remains unaffected.

The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of lymphocytes. It is believed that these stimulated lymphocytes lead to inflammation and damage myelin in the CNS.

The benefit of teriflunomide is its ability to reduce the both the rate of sustained accumulation of disability (at 3-month) *and* relapse rate in patients with RRMS. The most common side effects are upper-respiratory-tract infections, urinary-tract infections, diarrhoea, nausea, paraesthesia (pins and needles), alopecia (loss of hair) and increase in the liver enzyme alanine aminotransferase.

Teriflunomide: indication

Teriflunomide (Aubagio®) 14mg film-coated tablet has a positive CHMP opinion for the treatment of adult patients with relapsing-remitting multiple sclerosis (MS) [EMA, 2013]. Teriflunomide 14mg is administered orally once daily.

Teriflunomide will be in tablet form with 28 tablets per pack. The anticipated list price will be £1037.84 per 28 tab pack equating £13,529 per year.

Genzyme have proposed a patient access sceme (PAS) to the Department of Health (DoH), which if accepted will reduce this to [redacted] per patient per year.

Comparators

Beta-interferons and glatiramer acetate are currently prescribed in line with ABN guidelines and the DoH Risk Sharing Scheme [ABN, 2009; DoH, 2002].

Interferon-beta and glatiramer acetate are the key comparators for teriflunomide in the treatment of RRMS. These are used when patients meet the requirement of two clinically significant relapses in the previous two years in line with both the ABN guidelines and DoH risk-sharing scheme (RSS) and we anticipate this is where teriflunomide will be used [ABN, 2009; Pickin et al. 2009].

Beta-interferons and glatiramer are both administered by injection (from once weekly to once daily dependent on the choice of treatment). For many patients this is a disadvantage and may influence their decision to start DMT therapy. The tolerability of both the treatments is also notable, especially with respect to flu-like symptoms, fatigue and depression [Costello et al. 2008]. Moreover, not all RRMS patients will respond to existing DMTs [Rio et al. 2011]; as a result of tolerability and/or efficacy issues, many patients disrupt or discontinue treatment. There is therefore an unmet need for further treatment options for patients with RRMS and teriflunomide offers the clear benefit of being both an oral therapy with once daily dosing coupled with a manageable side effect profile.

The scope for this submission also considers natalizumab and fingolimod as comparators.

Natalizumab is currently used for RRMS patients with rapidly evolving severe (RES) disease (i.e. two or more disabling relapses in one year with one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.).

Fingolimod is currently used for RRMS patients with high disease activity (HA) despite interferon-beta (i.e. patients who have failed to respond to a full and adequate course of interferon-beta; patients should have had at least one relapse in the previous year while on therapy and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion).

Genzyme do not believe that either fingolimod or natalizumab are relevant comparators for teriflunomide. This is because we anticipate that teriflunomide will be used in patients with RRMS who otherwise would receive beta-interferons or glatiramer acetate i.e. with a diagnosis of RRMS that is not RES/HA disease. However, a cost effectiveness sub group analysis of the use of teriflunomide in these two populations is presented in line with the NICE scope.

Summary of clinical evidence with relevance to the decision problem

Phase II: placebo-controlled

The first randomised, double-blind, placebo-controlled phase II “proof of concept” study was performed with teriflunomide as monotherapy in 179 patients with RMS which includes RRMS and SPMS with relapses. The primary efficacy variable was the number of combined unique (CU) active (new and persisting) lesions per MRI scan during the 36-week, double-blind treatment phase. Significant reduction in the number of lesions and the median number of new and enlarging lesions was observed and the results were published in a peer reviewed journal [O’Connor et al. 2006].

Following the positive phase II trial results, an extensive phase III clinical programme with teriflunomide as monotherapy was launched.

Phase III: placebo-controlled

TEMSO (ClinicalTrials.gov Identifier: NCT00134563) and TOWER (ClinicalTrials.gov Identifier: NCT0075188)

The first phase III trial to disclose data in October 2010 was TEMSO, a randomised, double-blind, placebo-controlled, parallel-group design study in 1086 patients, the majority of whom had RRMS (n=995). The remaining patients had SPMS (n=51) and progressive relapsing MS (n=42) [O'Connor et al. 2011]. The primary objective of the study was to determine the efficacy of teriflunomide in reducing the annualised relapse rate (defined as the number of confirmed relapses per patient-year). The key secondary objective was to determine the efficacy of teriflunomide in delaying the progression of disability over the study period, as assessed on the basis of changes in the EDSS score. In addition total lesion volume and patient-reported fatigue were assessed as additional secondary end-points. Full results of the study were peer reviewed prior to publication.

An additional phase III study is TOWER, which was designed to replicate TEMSO results (n=1,165) [Miller et al. 2013; Kappos et al. 2012]. The primary end point of this randomised, double-blind, placebo-controlled, parallel-group study was annualised relapse rate (ARR, number of relapses per patient-year) with the key secondary variable, time to disability progression (EDSS and FS). The study consists of 2 phases: a double-blind treatment phase where patients receive either teriflunomide 7 mg or teriflunomide 14 mg or placebo until a fixed common end date which is approximately 48 weeks after randomisation of the last patient and an open-label treatment phase where the patients who complete the double-blind treatment period have the opportunity to continue or switch to teriflunomide 14 mg for 48 weeks or until teriflunomide is commercially available in the country where the patient lives.

- Results for teriflunomide 14mg were consistent between the two Phase III trials (TEMSO and TOWER)
- Adjusted ARR results were: 0.370 and 0.319; teriflunomide significantly reduced the adjusted ARR with reported relative risk reductions compared to placebo of 0.685 (p<0.001) and 0.637 (p=0.0001) respectively
    - In addition to reducing the ARR, teriflunomide significantly reduced relapses leading to hospitalisation (59%; *P*<0.0001 versus placebo). Teriflunomide reduced relapses with investigator-assessed sequelae by 53% p<0.0001
- In TEMSO, sustained accumulation of disability for at least 12 weeks (SAD) was significantly reduced for teriflunomide vs. placebo, HR= 0.70 (95% CI 0.51-0.97) (n=358 and 363 respectively) but not in TOWER, HR vs. placebo = 0.685 ([redacted]), p=0.0442.
- With regards to the symptoms of MS, neither trial revealed major changes from baseline in fatigue impact scale (FIS) score, with no significant difference to placebo in TEMSO [redacted]

    - Similarly, health-related quality of life showed no significant differences in SF-36 or EQ-5D scores in TEMSO [redacted]

- 60.6% and [redacted] of patients remained relapse-free at study end (vs. 49.3% [redacted] for placebo)
    - MRI data within TEMSO revealed significantly fewer gadolinium –enhancing lesions per T_1-weighted scan (relative risk 0.20, p<0.001) and fewer unique active lesions per scan (relative risk 0.31, p<0.001) for teriflunomide vs. placebo
- The rate of discontinuation (all causes) was 26.5% and 33.9% respectively. 10.9% and 15.6% were due to adverse events.

Phase III: Head-to-head vs. interferon beta-1a (IFNβ-1a)

TENERE (ClinicalTrials.gov Identifier: NCT00883337)

The second phase III trial to disclose data was TENERE, an international, multicentre, randomised, parallel-group, rater-blinded study comparing the effectiveness and safety of teriflunomide versus sub-cutaneous IFNβ-1a (Rebif) in 324 patients with RMS [Vermersch et al. 2012]. The primary objective was to assess the effectiveness of two doses of teriflunomide in comparison to sc IFNβ-1a, evaluated by the time to failure, with failure being defined as either relapse or permanent study treatment discontinuation for any cause whichever comes first. Secondary end-points included annualised relapse rate, subject reported fatigue as assessed by the Fatigue Impact Scale (FIS) and subject satisfaction as assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM).

- A comparable efficacy of teriflunomide versus IFNβ-1a (Rebif) was observed with no significant differences between the groups in the time to treatment failure (HR vs. Rebif = 0.861), relapse rate (adjusted ARR 0.259 vs. 0.216, relative risk 1.197, p=0.5896) or disability progression (assessed by change in EDSS).
- The discontinuation rate was 19.8% for teriflunomide vs. 28.8% for Rebif.
    - 10.9% discontinued treatment with teriflunomide due to adverse events vs. 21.8% for Rebif.
- Patients expressed significantly greater treatment satisfaction (global score), with teriflunomide than with Rebif (p=0.0162); this was thought to be related to adverse events and convenience scores.

[redacted]

Long-term safety studies

Phase II extension and TEMSO extension studies

At the end of the 9-month treatment period in the Phase II trial, patients could enter a long-term extension study to assess the long-term safety of teriflunomide in patients with RMS. All patients originally on placebo were switched to either teriflunomide 7mg or 14mg. The results of 8.5-year follow-up data assessing the long-term efficacy and safety of teriflunomide in 147 patients were published following peer review in 2012 [Confavreux et al. 2012].

742 patients who completed the core TEMSO study entered a long-term, double-blind extension to assess the long-term safety and tolerability (ClinicalTrials.gov identifier: NCT00803049); patients originally allocated to placebo were re-randomised to teriflunomide, 7 mg or 14 mg, while actively treated patients continued on their original dose in a blinded fashion.

The long-term extension studies are ongoing until the first launch.

The Phase II results were reported at a median follow up of 7.1 years, patients in the TEMSO extension at interim cut-off had received up to 5 years of treatment. The primary outcome of these studies was safety and tolerability; however secondary efficacy endpoints demonstrate continued activity of teriflunomide**:**

- The ARR was reduced in comparison to the core studies: in the Phase II study ARR was 0.181 (vs. 0.55 in the core study – note this was not primary endpoint); in the TEMSO extension it was [redacted](adjusted) (vs. 0.37)
    - However patients had minimal disability accumulation during the periods; EDSS scores increased by a median of 0.5 in the Phase II extension study; there was no change during the core period. No obvious changes were observed in the TEMSO extension until week 144 (EDSS change was not reported in the core study)
    - SAD was collected in the TEMSO extension and showed [redacted] with SAD (3 months) with a risk of SAD at 5 years of [redacted] (vs. 20.2% at the end of the core study)

[redacted]

Meta analysis

Meta-analysis was performed on placebo-controlled studies of teriflunomide, i.e. Phase II “proof of concept” study, TEMSO and TOWER. Results from the meta-analysis indicate teriflunomide is better than placebo for all

measures of efficacy, using relative risks (95% CI). Versus placebo, patients on teriflunomide relapse less frequently, have an improved chance of remaining relapse-free and are less likely to achieve sustained accumulation of disability for 3 months:

- ARR = 0.664 (0.589, 0.749)
- Proportion relapse free = [redacted]
- SAD (3 months) = 0.694 (0.544, 0.886)

Statistical and clinical heterogeneity between studies appeared to be small.

Mixed Treatment Comparison (MTC)

A feasibility assessment was performed to determine which trials should be included in the MTC analyses and to account for the evidence of decreased relapse rates over time; KOLs recommended excluding studies with patient recruitment before 2000, taking into consideration:

- Reduction in the untreated ARR rate amongst MS patients at diagnosis in more recent years
- The introduction of new MS diagnostic criteria (McDonald)
- Earlier treatment following the publication of the CHAMPS study [Galetta, 2001]
- Timeframe for the development of the different DMTs
- For studies where the year(s) of recruitment were not reported, year of publication was used as a proxy.

Therefore, trials in the base-case network were restricted to studies with patient recruitment after 2000 and with ≥80% RRMS patients. Sensitivity analyses were run on datasets without the post 2000 restriction. Among the trials identified in the systematic literature review, 30 were deemed suitable for mixed MTC analyses. Among 21 of these trials, patient recruitment took place after 2000; for the remaining nine trials, recruitment was assumed to be after 2000 on the basis of publication year. Most (25) of the included trials utilised the McDonald diagnostic criteria.

All the relevant comparators were identified in the MTC in studies post 2000 with the exception of Rebif 22 µg, which is a dose used in UK practice. Studies were identified pre-2000 including Rebif 22 µg and are presented as part of a sensitivity analysis which considered all years from 1980 and ≥80% RRMS patient population.

Key results from the MTC are in relation to the interferons, glatiramer acetate and teriflunomide; the following are of note:

- ARR versus placebo: this is similar for all the relevant comparators (see below)

Annualised Relapse Rate Results from the MTC

	Teriflunomide 14mg	Placebo
	Rate ratio [95% CrI]	
Teriflunomide 14mg	N/A	0.67 [0.57, 0.77]
IFNβ-1b 250 µg	0.98 [0.73, 1.31]	0.68 [0.52, 0.88]
IM IFNβ-1a 30 µg	0.86 [0.69, 1.05]	0.78 [0.67, 0.91]
SC IFNβ-1a 44 µg	1.06 [0.84, 1.35]	0.62 [0.51, 0.76]
GA 20 mg	1.05 [0.83, 1.31]	0.64 [0.53, 0.76]

- Hazard Ratio (HR) versus placebo for SAD: with the exception of IFNβ-1b, all relevant therapies provide a signal that they are superior to placebo, but only teriflunomide is convincingly so.

Three Month Sustained Accumulation of Disability Results from the MTC

	Teriflunomide 14mg	Placebo
	Hazard ratio [95% CrI]	
Teriflunomide 14mg	N/A	0.71 [0.53, 0.92]
IFNβ-1b 250 µg	0.58 [0.30, 1.12]	1.21 [0.68, 2.16]
IM IFNβ-1a 30 µg	0.77 [0.50, 1.24]	0.91 [0.61, 1.33]
SC IFNβ-1a 44 µg	0.90 [0.54, 1.45]	0.79 [0.51, 1.24]
GA 20 mg	0.76 [0.45, 1.30]	0.93 [0.59, 1.45]

- Odds ratios (OR)for total discontinuation rate versus teriflunomide: [redacted]

Total Discontinuations Odds Ratios Results from the MTC

	Teriflunomide 14mg	Placebo
	Odds ratio [95% CrI]	
Teriflunomide 14mg	[redacted]	[redacted]
IFNβ-1b 250 µg	[redacted]	[redacted]
IM IFNβ-1a 30 µg	[redacted]	[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]

GA 20 mg	[redacted]	[redacted]

Safety and adverse events

The long-term extension studies for teriflunomide specifically investigated the safety and tolerability of the drug. We also report the results of a pooled analysis from the Phase II-III programme and the TOWER study, as these are placebo-controlled. In summary, almost all patients on teriflunomide report at least one treatment-emergent-adverse-event (TEAE), however for the majority of events, incidence is similar to placebo.

Adverse events of note are:

- Liver function analyses – elevations of liver enzymes have been observed in patients and occur mostly within 6-months of treatment initiation; it is for this reason that close monitoring of liver enzymes is recommended during the first 6-months of treatment [Teriflunomide SmPC]
- Diarrhoea, nausea and vomiting which are mild to moderate, transient and infrequently lead to discontinuation [Teriflunomide SmPC]
- Parasthesias and dysaethesias – both have been reported at a higher rate than with placebo and tend to improve with treatment cessation [Teriflunomide SmPC]
- Infections – teriflunomide is an immunomodulatory agent therefore an effect on immune function is expected. However, no increase in serious infection has been observed [Teriflunomide SmPC]
- Alopecia – most cases are diffuse or generalised over the scalp and largely resolve as treatment continues. In a pooled analysis of the core Phase II study with TEMSO, hair loss/thinning was shown to be more common with teriflunomide 14mg vs. placebo but in the majority was mild (73%) and recovered without sequelae (90.5%) whilst on therapy [Freedman et al. 2012]. Few patients discontinue treatment due to alopecia [Teriflunomide SmPC].

Before starting and during treatment with teriflunomide the following should be assessed: blood pressure and liver enzymes including alanine aminotransferase (ALT/SGPT Complete blood cell counts should be taken at initiation and subsequently performed based on signs and symptoms (e.g. infections) during treatment [Teriflunomide SmPC].

No additional type of monitoring is required for patients receiving teriflunomide over and above usual clinical practice, however there is an increased frequency of monitoring over the initial 6-month period.

Cost effectiveness

The patient population considered in the economic evaluation is adults with RRMS which is reflective of the licensed indication. The positioning of teriflunomide is as an alternative to beta-interferons or glatiramer acetate so these are the comparators used in the cost-effectiveness analysis. However, since there is not a typical treatment pathway defined in England and Wales, a blended comparator weighted by market share of beta-interferons and glatiramer acetate has been used in the base case analysis. Incremental results versus glatiramer acetate and each of the beta-interferons has also been presented for completeness.

A multi-state Markov model was developed which considered health states based on disease classification as RRMS or SPMS and severity, defined by the EDSS. The model was based on a structure developed by the School of Health and Health and Related Research in the evaluation of beta-interferons for the treatment of MS. Capturing disease classification and progression through EDSS health states within RRMS and SPMS meant that the costs and quality of life implications could be identified and captured for disability progression and relapses. Therefore, it was deemed that a Markov structure was the most appropriative structure to model the cost-effectiveness of teriflunomide. Costs and QALYs per patient were calculated over a lifetime horizon (50 years) and discounted at 3.5% per annum.

Clinical data used in the model are based on results from the teriflunomide trials and MTC. Patients transition through the model accounting for withdrawal, mortality, disease progression in terms of EDSS, conversion from RRMS to SPMS, and a DMT stopping rule as recommended by ABN guidelines [ABN, 2009]. Treatment effects are included in terms of 3-month SAD and ARR from the MTC. SAD hazard ratios are applied to natural history transition matrices derived from the London Ontario dataset and supplemented by the placebo arms of TOWER and TEMSO. Treatment transition matrices are used to estimate progression of patients through the disease scale (EDSS) as well as the disease classification in terms of RRMS and SPMS. Quality of life data used in the model accounted for EDSS level, whether a relapse had occurred, treatment related adverse events and carer disutility. Costs categories were based on the NHS & PSS perspective and included treatment acquisition costs, administration costs, monitoring costs, adverse event costs, disease costs (associated with EDSS level) and relapse costs split by severity.

Probabilistic results were considered as the base case analysis using the teriflunomide list price. The probability of teriflunomide being cost-effective at a willingness to pay of £20,000 is 38% in the base case.

Base-case probabilistic cost-effectiveness results

	Teriflunomide	Blended comparator
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)		[redacted]
QALYs	[redacted]	[redacted]
QALY difference		[redacted]
ICER (£)		[redacted]
QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio		

Incremental probabilistic cost-effectiveness results

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) vs. baseline (QALYs)	ICER (£) inc (QALYs)
Glatiramer acetate	[redacted]	[redacted]				
IFNβ-1a 22µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios, Inc, incremental						

Sensitivity analysis was conducted to explore parameter and structural uncertainty: one-way sensitivity analysis, parameter uncertainty analysis, structural scenario analysis, and treatment sequencing whereby patients may be treated with up to three lines of DMT during the model time horizon. In the one-way sensitivity analysis, results were most sensitive to the hazard ratio on disease progression and withdrawal rates, mildly sensitive to discount rate on outcomes, natural history disease costs and EQ-5D utility values. Results were also sensitive to treatment sequencing, with all sequences incurring greater costs and QALYs than seen in the base case. The model was structurally sensitive to the assumptions around waning of treatment effect. The parameter analysis indicated the model was sensitivie to the source of natural history costs and the choice of MTC used for clinical parameters.

Subgroup analyses compared teriflunomide with fingolimod for patients with HA RRMS and teriflunomide with natalizumab for patients with RES RRMS. For the purposes of assessing cost-effectiveness for these analyses, the ARR and SAD at 3-months were calculated for: teriflunomide compared to placebo in HA and RES; fingolimod compared to placebo in HA; and natalizumab compared to placebo in RES. The result from the model once updated with these values were that teriflunomide dominated fingolimod for the HA disease subgroup

analysis when the acquisition cost of fingolimod was £19,110 and also for scenarios exploring fingolimod PAS prices of as low as £11,000. A comparison of teriflunomide versus natalizumab resulted in an ICER of [redacted] where teriflunomide is cheaper but less effective.

Budget Impact

Uptake of teriflunomide is expected in two populations: patients currently treated with beta-interferons and glatiramer acetate; as well as patients who cannot tolerate the administration of beta-interferons or glatiramer acetate and are therefore not receiving a DMT. There is uncertainty in the uptake within the patient group that are currently receiving no DMT so a range of market uptake values have been explored: [redacted] uptake in year 2014 increasing to [redacted] uptake in 2018. The expected patient numbers with these anticipated market uptakes are [redacted] in 2014, increasing to [redacted] in 2018.

Cost savings occur in the displacement of beta-interferons or glatiramer acetate with teriflunomide in terms of administration costs and costs of treating adverse events. However, the monitoring costs and acquisition costs are greater for teriflunomide than beta-interferons or glatiramer acetate.

The estimated budget impact in England and Wales may range between [redacted] and [redacted] in 2014 (Year 1) and is anticipated to increase up to between [redacted] and [redacted] in 2018 (Year 5), depending on uptake in patients who in the absence of teriflunomide would not receive DMT.

Section A – Decision problem

1 Description of technology under assessment

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

Brand name: Aubagio®
Approved name: Teriflunomide
Therapeutic class: Selective immunosuppressants
ATC Code: L04AA31

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

Teriflunomide is a new immunomodulatory disease-modifying treatment (DMT) with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH) required for de novo pyrimidine synthesis. As a consequence, teriflunomide blocks the proliferation of stimulated lymphocytes which need the de novo synthesis of pyrimidine to proliferate. Resting lymphocyte pyrimidine metabolism remains unaffected.

The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this may be mediated by a reduced number of activated lymphocytes. It is believed that these activated lymphocytes may lead to inflammation and damage myelin in the CNS.

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).

Teriflunomide received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on March 21st 2013.

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 marketing authorisation).

On 21st March 2013, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product teriflunomide (Aubagio®) 14mg film-coated tablet intended for the treatment of multiple sclerosis [EMA, 2013]. The Committee also concluded that the active substance contained in Aubagio®, teriflunomide, could not be considered to be a new active substance.

The approved indication is: "treatment of adult patients with relapsing-remitting multiple sclerosis (MS)".

The benefit with teriflunomide is its ability to significantly reduce the relapse rate and delay the accumulation of disability in patients with RRMS compared to placebo. The most common side effects are upper-respiratory-tract infections, urinary-tract infections, diarrhoea, nausea, paraesthesia (pins and needles), alopecia (evidenced as reversible hair thinning; reversible in 90% of cases [Freedman et al. 2012]) and increase in the liver enzyme alanine aminotransferase.

A pharmacovigilance plan for teriflunomide will be implemented as part of the marketing authorisation.

Treatment with teriflunomide should be initiated and supervised by a physician experienced in the management of MS.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers there to be a favourable benefit-risk balance for teriflunomide and therefore recommends the granting of the MA.

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

Teriflunomide received a positive CHMP opinion for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS).

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.

The international programme of clinical development for teriflunomide presented in the MA submission to the European Medicines Agency (EMA) contained 5 controlled clinical studies pertinent to the indication. This submission will incorporate data from the phase II and phase III trials, including long-term extension studies, for the indication being appraised. A summary of the key controlled trials (RCTs) and extension studies investigating teriflunomide as monotherapy in relapsing MS are summarised in Table A1.1.

Phase II

The first randomised, double-blind, placebo-controlled phase II proof of concept (POC) study was performed with teriflunomide as monotherapy in patients 179 patients with relapsing multiple sclerosis (RMS) which includes RRMS and SPMS with relapses (ClinicalTrials.gov Identifier: NCT01487096). The primary efficacy variable was the number of combined unique (CU) active (new and persisting) lesions per MRI scan during the 36-week, double-blind treatment phase and the results were published in a peer reviewed journal [O'Connor et al. 2006].

At the end of the 9-month treatment period, patients could enter a long-term extension study to assess the long-term safety of teriflunomide in patients with RMS (ClinicalTrials.gov Identifier: NCT00228163). All patients originally on placebo were switched to either teriflunomide 7mg or 14mg. The results of 8.5-year follow-up data assessing the long-term efficacy and safety of teriflunomide were published following peer review in 2012 [Confavreux et al. 2012]. The long-term extension studies are ongoing until the first launch.

Phase III

Following the positive phase II trial results, an extensive phase III clinical programme with teriflunomide as monotherapy was launched.

TEMSO (ClinicalTrials.gov Identifier: NCT00134563)

The first phase III trial to disclose data in October 2010 was TEMSO, a randomised, double-blind, placebo-controlled, parallel-group design study in 1086 patients, the majority of whom had RRMS (n=995). The remaining patients had SPMS (n=51) and progressive relapsing MS (n=42) [O'Connor et al. 2011]. The primary objective of the study was to determine the efficacy of teriflunomide in reducing the annualised relapse rate (defined as the number of confirmed relapses per patient-year). The key secondary objective was to determine the efficacy of teriflunomide in delaying the progression of disability over the study period, as assessed on the basis of changes in the EDSS score. In addition total lesion volume and patient-reported fatigue were assessed as additional secondary end-points.

Patients who completed the core study could enter a long-term, double-blind extension to assess the long-term safety and tolerability (ClinicalTrials.gov identifier: NCT00803049); patients originally allocated to placebo were re-randomised to teriflunomide, 7 mg or 14 mg, while actively treated patients continued on their original dose in a blinded fashion. Full results of the core study and interim results of the long-term extension phase were peer reviewed prior to publication.

TENERE (ClinicalTrials.gov Identifier: NCT00883337)

The second phase III trial to disclose data is TENERE, an international, multicentre, randomised, parallel-group, rater-blinded study comparing the effectiveness and safety of teriflunomide versus sc interferon β-1a (IFNβ-1a) (Rebif) in 324 patients with RMS [Vermersch et al. 2012]. The primary objective was to assess the effectiveness of two doses of teriflunomide in comparison to IFNβ-1a, evaluated by the time to failure, with failure being defined as either relapse or permanent study treatment discontinuation for any cause whichever comes first.

Secondary end-points included annualised relapse rate, subject reported fatigue as assessed by the Fatigue Impact Scale (FIS) and subject satisfaction as assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM).

TOWER (ClinicalTrials.gov Identifier: NCT0075188)

An additional phase III study is TOWER, which was designed to replicate TEMSO results (n=1,165) [Miller et al. 2013; Kappos et al. 2012]. The primary end point of this randomised, double-blind, placebo-controlled, parallel-group study is annualised relapse rate (number of relapses per patient-year) with the key secondary variable, time to disability progression (EDSS and FS). The study consists of 2 phases:

- A double-blind treatment phase where patients receive either teriflunomide 7 mg or teriflunomide 14 mg or placebo until a fixed common end date which is approximately 48 weeks after randomization of the last patient.
- An open-label treatment phase where the patients who complete the double-blind treatment period have the opportunity to continue or switch to teriflunomide 14 mg for 48 weeks or until teriflunomide is commercially available in the country where the patient lives.

The clinical development programme also includes two additional phase III studies which enrolled patients with the first clinical symptoms of MS (TOPIC; ClinicalTrials.gov Identifier: NCT00622700) or in combination with interferon-beta in patients with relapsing MS (TERACLES; ClinicalTrials.gov Identifier: NCT01252355). The results of these studies have not been included in this submission as they are not relevant to the proposed indication.

Table A1.1 Clinical development programme for teriflunomide

Study No./ Acronym/ Author	Type of study	Treatment group	Primary endpoints
Phase III			
EFC6049/ TEMSO/ [O'Connor et al. 2011]	International, multi-centre, two-year, randomised, double-blind, placebo-controlled, parallel-group, designed to evaluate the efficacy and safety of teriflunomide in RMS	Monotherapy: • teriflunomide 7mg/day • teriflunomide 14mg/day • placebo	Annualised relapse rate, defined as number of relapses per patient-year

EFC10891/ TENERE/ Sanofi-Aventis [Vermersch et al. 2012]	International, multi-centre, two-year, randomised, rater-blinded comparator, parallel-group, in patients with RMS	Monotherapy: • teriflunomide 7mg/day • teriflunomide 14mg/day • high-dose IFNβ-1a (Rebif 44µg) given by sub-cutaneous injection three times a week.	Time to failure, defined as the first occurrence of confirmed relapse or permanent discontinuation for any reason, whichever came first
EFC10531/ TOWER/ Sanofi-Aventis [Genzyme, 2012]	International, multi-centre, randomised, double-blind, parallel-group, placebo-controlled study, designed to confirm TEMSO results	Monotherapy: • teriflunomide 7mg/day • teriflunomide 14mg/day • placebo	Annualised relapse rate
Phase II			
HMR1726D/2001 [O'Connor et al. 2006]	International, multi-centre, randomized, double-blind, parallel-group, placebo-controlled study	Monotherapy: • teriflunomide 7mg/day • teriflunomide 14mg/day • placebo	Safety and efficacy of teriflunomide in multiple sclerosis (MS) with relapses
Long-term extension studies			
Phase III ClinicalTrials.gov identifier: NCT00803049 Study number LTS6050 [O'Connor et al. 2011 supplementary appendix]	Extension EFC6049 (TEMSO)	Monotherapy: • teriflunomide 7mg/day • teriflunomide 14mg/day	Long-term safety and tolerability of teriflunomide in MS patients with relapse
Phase II ClinicalTrials.gov Identifier: NCT00228163 Study number LTS6048 (HMR1726D/2002) [Confavreux et al. 2012]	Extension of Protocol HMR1726D/2001	Monotherapy: • teriflunomide 7mg/day • teriflunomide 14mg/day	Long-term safety of teriflunomide in multiple sclerosis subjects
Excluded from the submission			
EFC6260/ TOPIC/ Sanofi-Aventis [Clinicaltrials.gov TOPIC, 2012]	International, multi-centre, randomised, double-blind, parallel-group, placebo-controlled study, designed to evaluate the efficacy and	Monotherapy: • teriflunomide 7mg/day • teriflunomide 14mg/day • placebo	Conversion to clinically definite MS

	safety of teriflunomide in CIS patients, ceased prematurely due to changes in diagnostic criteria rendering CIS as a historic phenomenon		
EFC6058/ TERACLES/ Sanofi-Aventis [Clinicaltrials.gov TERACLES, 2012]	International, multi-centre, randomised, double-blind, parallel-group, placebo-controlled study, ceased prematurely due to lack of evidence from the Phase II data of incremental benefit and lack of real world adherence to this strategy.	Adjunct therapy to IFNβ: • teriflunomide 7mg once a day concomitantly with Interferon beta (IFN- β) therapy • teriflunomide 14mg once a day concomitantly with IFN- β therapy • placebo once a day concomitantly with IFN- β therapy	Annualised relapse rate

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

Although teriflunomide has a positive CHMP, Sanofi-Aventis (Genzyme, a Sanofi company) are appealing the decision to not grant new active substance designation for the product. We anticipate that the process including the issuing of positive CHMP will be completed on 27th June 2013.

We anticipate that market authorisation of teriflunomide will be granted within 56 days of the CHMP opinion.

[redacted]

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

Teriflunomide has been approved by the U.S Food and Drug Administration (FDA) and is available for relapsing multiple sclerosis in the US (at both 7mg and 14mg doses), Argentina (14mg only) and Australia (14mg only).

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

Teriflunomide is expected to undergo assessment by the Scottish Medicines Consortium and the National Centre for Pharmacoeconomic Evaluation with subsequent advice posted in Q1 2014.

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 A1.2 Unit costs of technology being appraised

Pharmaceutical formulation	Film-coated tablet (tablet). Each tablet contains 14 mg of teriflunomide. Pale blue to pastel blue, pentagonal film-coated tablets with imprint on one side (dose strength given as number 14) and engraved with corporate logo on other side [Teriflunomide SmPC, 2013]
Acquisition cost (excluding VAT)	Provisionally £13,529 per year (NHS list price). Genzyme are submitting a PAS to support our submission to NICE.
Method of administration	Teriflunomide is administered orally, once daily and can be taken with or without food. The treatment should be initiated under the supervision of a physician experienced in multiple sclerosis [Teriflunomide SmPC, 2013].
Doses	The recommended dose of teriflunomide is 14 mg orally once daily [Teriflunomide SmPC, 2013]
Dosing frequency	Once daily [Teriflunomide SmPC, 2013]
Average length of a course of treatment	Teriflunomide may be taken indefinitely until discontinuation due to adverse events or treatment failure. The longest follow-up of patients has been during the extension to the Phase II study. Patients taking 14mg teriflunomide (licensed dose) throughout the study period have received a mean of 2068 days (295 weeks, 5.7 years) ; median 2884 days (412 weeks, 7.9 years) of treatment [Confavreux et al. 2012].
Average cost of a course of treatment	Teriflunomide is anticipated to be administered as a long-term treatment for a chronic condition and will be discontinued based on joint decision making between the patient and clinician. The average cost of treatment will be a function of the annual cost of treatment (estimated for those fully compliant with treatment to be provisionally £13,529 (NHS list price)) and the length of time on treatment. Follow up studies are of an insufficiently long period to provide a precise estimation of the average length of time in clinical practice however it is noted that in the longest follow-up of patients to date during the extension to the Phase II study patients taking 14mg teriflunomide throughout the study period (licensed dose) (n=147) have received a mean 5.7 years (median 7.9 years) of treatment and experienced a discontinuation rate of 42% [Confavreux et al. 2012].
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable

Dose adjustments	Older people Teriflunomide should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy [Teriflunomide SmPC, 2013]. Renal impairment No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment not undergoing dialysis. Patients with severe renal impairment undergoing dialysis were not evaluated and teriflunomide is contraindicated in this population [Teriflunomide SmPC, 2013] Hepatic impairment No dosage adjustment is necessary for patients with mild and moderate hepatic impairment. Teriflunomide is contraindicated in patients with severe hepatic impairment [Teriflunomide SmPC, 2013].

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.

N/A. Teriflunomide is not a device.

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

Before treatment

Before starting treatment with teriflunomide the following should be assessed:

- Blood pressure
- Alanine aminotransferase (ALT/SGPT)
- Complete blood cell count including differential white blood cell and platelet count.

During treatment

During treatment with teriflunomide the following should be monitored:

- Blood pressure
- Alanine aminotransferase (ALT/SGPT)
- Complete blood cell counts should be performed based on signs and symptoms (e.g. infections) during treatment.

Elevations of liver enzymes have been observed in patients receiving teriflunomide. These elevations occurred mostly within the first 6 months of treatment.

Liver enzymes should be assessed before initiation of teriflunomide therapy - every two weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. Teriflunomide therapy should be discontinued if liver injury is suspected or should be considered if elevated liver enzymes (greater than 3-fold ULN) are confirmed [Teriflunomide SmPC, 2013].

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

No additional type of monitoring is required for patients receiving teriflunomide over and above usual clinical practice, however there is an increased frequency of monitoring over the initial 6-month period.

Patients receiving beta-interferons require complete and differential white blood cell counts, platelet counts, and blood chemistry, including liver function tests. In some patients, thyroid function testing is also recommended [Avonex SmPC; Betaferon SmPC; Rebif SmPC; Extavia SmPC].

In patients receiving fingolimod, ECG and blood pressure monitoring is necessary around first dosing. Complete blood counts are recommended periodically throughout treatment, liver function tests should be performed three-monthly [Fingolimod SmPC].

Patients receiving natalizumab should have liver function monitoring and regular MRI scanning throughout treatment [Tysabri SmPC].

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?

Teriflunomide is licensed as a monotherapy for treatment of patients with RRMS, no other agents are expected to be administered concurrently.

2 Context

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

Overview of MS

MS is a chronic disease resulting in disability and premature death [Pugliatti et al. 2006]. MS is associated with axonal demyelination in the central nervous system (CNS) with considerable social impact and economic consequences. It is estimated that between 52,000 and 62,000 people have a diagnosis of MS in England and Wales [NICE, 2003] and is a major cause of non-traumatic disability in young adults [Trapp et al. 2008]. The mean age of onset of MS symptoms is between 20-50 years [NICE, 2003] with the highest prevalence in the age group 50-64 years [Pugliatti et al. 2006] and it predominantly affects women, with an approximate ratio of 3:1 [Ramagopalan et al. 2010].

Although considerable scientific progress has been made throughout a century of research, the underlying cause of MS is still unknown [Dutta et al. 2011]. It is thought that there is no single cause for MS but interplay between environmental triggers and genetic susceptibility is increasingly accepted as a valid aetiology of MS [Trapp et al. 2008].

In the UK, MS is classified into three key sub-types: relapsing-remitting (RRMS), primary-progressive (PPMS) and secondary-progressive (SPMS). The course of MS in an individual patient is largely unpredictable, but may lead ultimately to progressive disability and premature death.

Relapsing MS:

RMS is a classification encompassing any MS patient who experiences periods of relapse during their disease course. A relapse is a clinically evident 'attack' of demyelination, characterised by gradual onset of symptoms over days, stabilising over days or weeks and then gradually resolving, completely or partially. For two relapses to be considered as such, a period of 30 days must have elapsed between the onset of new symptoms for each event [Coles, 2009].

The majority of RMS patients (approximately 85% of all MS patients at diagnosis) have relapsing-*remitting* disease (RRMS) [Murray, 2006]. Patients with RRMS experience recurring episodes of acute neurological dysfunction (relapses) followed by more or less complete recovery of function.

There are some key elements of MS as a disease process that are of high importance to a patient versus clinical signs and symptoms. For a patient, relevant issues are: suffering relapses, becoming increasingly disabled with time and maintenance of an acceptable quality of life on both a daily and long-term basis.

The course of MS may be looked upon as the interaction between the two clinical phenomena of relapses and disability progression although the contribution of the former to the latter is not clear [Confavreux et al. 2006]. Relapses may require admission to hospital, and are associated with a level of disability and incapacity that disrupts working, family and social life. Accumulation of disability clearly presents a challenge to patients and their carers, alongside the very real representation of worsening disease. Relapses can have a significant impact on quality of life [Orme et al. 2007].

Relapse rates in RRMS vary considerably over time for an individual and between individuals but there is a general pattern of exacerbations of more frequent relapses, followed by long periods of lower rates [Richards et al. 2002]. The initial relapse rate can be less than one per year and subsequently declines [Coles, 2009]. This makes assessment of the effects of treatments in any individual extremely difficult.

Patients with MS commonly experience fatigue, spasticity, bladder dysfunction, pain and cognitive dysfunction. Less common are depression, bowel dysfunction, and paroxysmal symptoms [Crayton et al. 2006]. Common symptoms in MS are interrelated: one symptom can exacerbate another or can be caused by the treatment of another symptom.

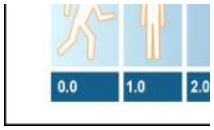
Epidemiology of MS

The National Institute for Health and Care Excellence (NICE) estimates that MS is diagnosed in 3.5 to 6.6 people per 100,000 of the population each year with a prevalence of 100 to120 per 100,000 (in comparison, the incidence of stroke is 240 per 100,000 each year) in England and Wales [NICE, 2003]. Other estimates have been higher including an estimation carried out by the London School of Hygiene and Tropical Medicine which suggested a prevalence of 100,000 patients for the UK [MS Trust, 2012].

Disease Progression

Whilst disability progression is a defining feature of primary and SPMS, disability accumulation is a defining feature of RRMS and can be correlated with the extent of axonal injury and further associated with the degree of myelin inflammation [Leray et al. 2010]. It has been hypothesised that a close association between inflammation and neurodegeneration might exist in all disease stages of multiple sclerosis [Kutzelnigg et al. 2005; Frischer et al. 2009]. The most accepted tool to measure disability is the Expanded Disability Status Scale (EDSS), which is a 10-point instrument that measures different areas of functional disability in the lower half of the scale and focuses on hard ambulatory disability in the latter half (Figure A2.1). A score of 6 on the EDSS is considered an important milestone as it represents the onset of walking disability and has implications for the suitability of treatment with disease-modifying treatments (DMTs) [Kurtze, 1983]. The distribution of EDSS scores of patients being initiated on DMTs through the UK Risk Sharing Scheme is bimodal with peaks around EDSS 2 and 6 (no patients start treatment at EDSS 7 or greater) [Pickin et al. 2009].

Figure A2.1 The Expanded Disability Status Scale adapted from Kurtze [Kurtze, 1983]



Whilst frequent and prolonged relapses with incomplete recovery at onset and a short interval between the initial episode and first relapse are adverse prognostic features; the onset of the progressive phase of the disease course is the main determinant of disability [Compston et al. 2002].

Current Treatment Options for patients with RMS

The treatment of RRMS is based on the use of DMTs and current opinion supports the use of early treatment with DMTs to reduce the accumulation of disability and neurodegeneration, in the hopes of delaying onset of progressive MS states.

In general, patients with RRMS (and an EDSS score <6.5) are likely to be started on interferon-beta or glatiramer acetate [Rio et al. 2011]. These may be prescribed provided patients meet the requirement of two clinically significant relapses in the previous two years in line with ABN guidelines and the Department of Health Risk Sharing Scheme [DoH, 2002; ABN, 2009]. The ABN Guidelines represent a consensus of British neurologists regarding the appropriate use of DMTs in patients with multiple sclerosis [ABN, 2009]. These were last updated in 2009 prior to licensing of fingolimod.

The interferon-betas and glatiramer acetate are self-injected therapies which are administered from once a day to once a week dependent on the treatment chosen. Some patients experience problems with these therapies due to the inconvenient mode of administration (injections) and poor tolerability, specifically injection-site reactions, flu-like symptoms, fatigue and depression [Costello et al. 2008]. Moreover, not all RRMS patients will respond to the existing DMTs and many will discontinue treatment [Rio et al. 2011]. There is no cure for MS. The available DMTs have demonstrated efficacy in reducing relapse rates and, in some cases, also delaying disability progression in patients with RRMS, however, the response in these patients is variable and many ultimately continue to experience relapses, progress and accumulate disability.

In addition, NICE and the SMC recommend:

- Fingolimod as an option for the treatment of highly active RRMS in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with IFN-β [NICE, 2012(a); SMC, 2012].
- Natalizumab as a treatment for rapidly evolving severe RRMS, defined by two or more disabling relapses in one year and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI [NICE 2007(a); SMC, 2007].

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

Teriflunomide is indicated for the treatment of adult patients with RRMS.

In the UK, approximately 100,000 people have MS [MS Trust, 2012].

- In England and Wales it is estimated that 88,766 people have MS (based on England and Wales having a population of 56.1 million out of a total UK population of 63.2 million) [ONS, 2012].
- Of this 31,511 will have RRMS (35.5%) [Kobelt et al. 2006] of which 9,769 (31%) will be treated [Zajicek et al. 2010].

Potentially therefore, 9,769 patients per annum in England and Wales could be treated with teriflunomide in the absence of any other DMTs.

- In addition to this group of patients currently receiving a DMT, it is estimated that there is a further 25% eligible to receive a DMT but are resistant to injectables [Genzyme KOL advisory board, 2011]. Therefore, the total eligible population for teriflunomide consists of 9,769 currently treated patients, plus 2442 patients (0.25 x 9,769) currently untreated patients.

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

MS has been associated with an almost threefold increase in the risk for death compared to the age matched general population, with excess mortality rates from other diseases such as cardiovascular disease and infectious and respiratory disease. The median time to death is around 30 years from disease onset, representing a reduction in life expectancy of approximately 10 years [Bronnham –Hansen et al. 2004].

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

NICE guidance

- **TA32 - Beta interferon and glatiramer acetate for the treatment of multiple sclerosis:** Although both glatiramer acetate and interferon-beta were found not to be cost-effective both are available as long as prescribing is in line with ABN guidelines and the Department of Health Risk Sharing Scheme

NICE guidance is also available for fingolimod and natalizumab in patients with highly active disease and rapidly evolving severe disease respectively. It is not anticipated that teriflunomide will be routinely used in these subgroups of MS:

- **TA254- Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis:** Fingolimod as an option for the treatment of highly active RRMS in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with IFN-β [NICE, 2012(a)].
- **TA127: Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis**: Natalizumab as a treatment for rapidly evolving severe RRMS, defined by two or more disabling relapses in one year and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI [NICE, 2007(a)].

NICE guidelines:

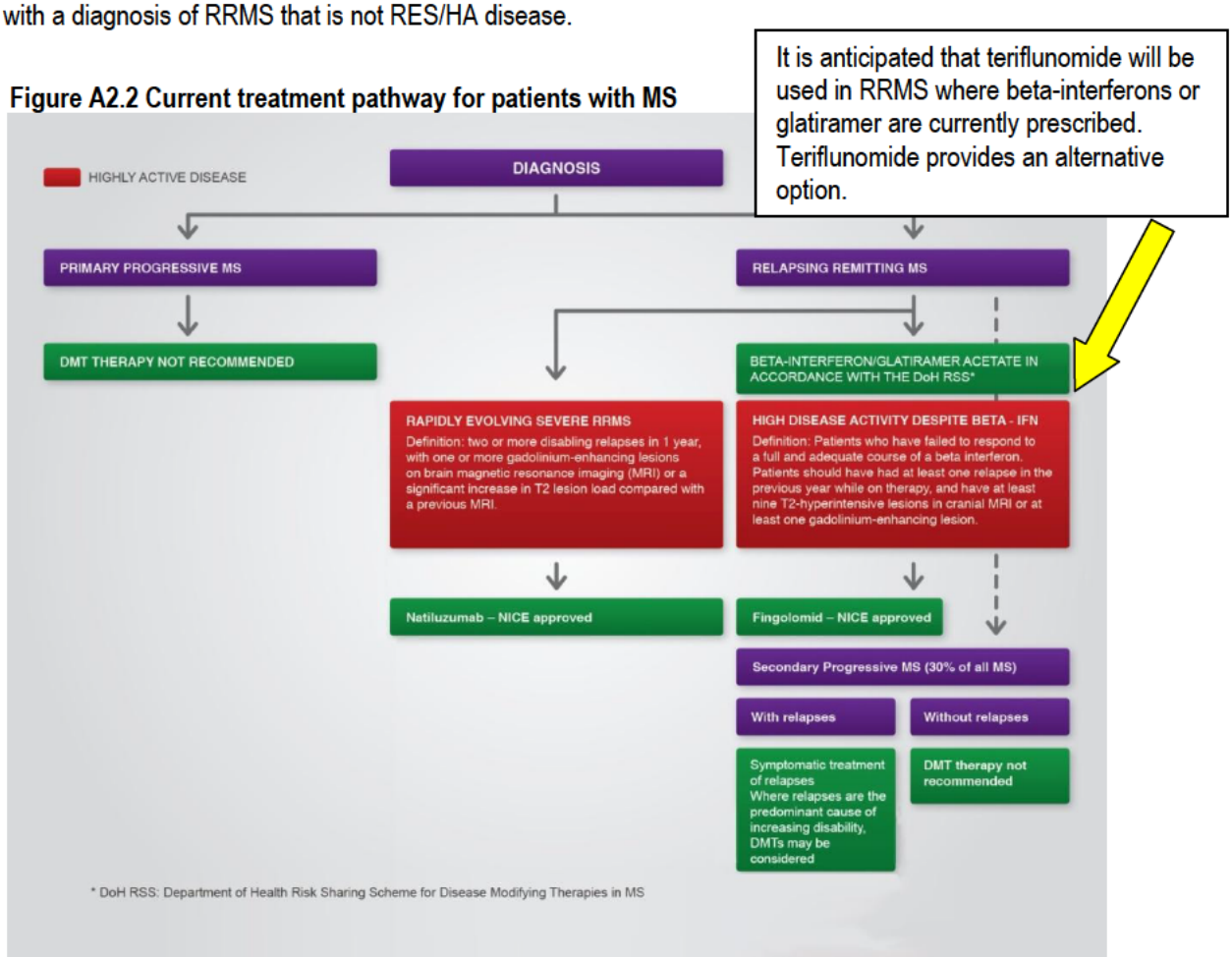
- **CG8: Multiple sclerosis: Management of multiple sclerosis in primary and secondary care :** Guidelines were published in 2003 and are currently under review for planned publication in 2014 [NICE, 2003].

There are ongoing NICE appraisals regarding RRMS for new therapies: alemtuzumab, laquinimod and dimethyl fumarate.

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

Guidelines previously published by NICE and the DH Risk Sharing Scheme clearly describe the approved pharmacological treatment pathway for RRMS, although in practice there may be local variation to this practice (see below). Despite the scope of the current submission, which considers teriflunomide for use in RRMS including those patients with rapidly-evolving severe RRMS and high disease activity (HA), it is expected that teriflunomide will largely be considered in practice as an alternative treatment to interferon-beta/glatiramer, i.e. with a diagnosis of RRMS that is not RES/HA disease.

Figure A2.2 Current treatment pathway for patients with MS



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

Pharmacological therapies for MS have been reviewed by influential bodies in England and Wales (i.e. NICE and the ABN); however these guidelines require updating to reflect newly available therapeutic entities. Whilst an element of clinical decision making will always be used to deviate from these guidelines, as befits individual situations, we are unaware that these best practice guidelines are being routinely breached.

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

Interferon-beta and glatiramer acetate are the key comparators for teriflunomide in the treatment of RRMS. These are used when patients meet the requirement of two clinically significant relapses in the previous two years in line with ABN guidelines, a consensus of British Neurologists regarding the appropriate use of DMTs, and the Department of Health Risk Sharing Scheme and we anticipate this is where teriflunomide will be used [DoH, 2002; ABN, 2009].

The scope for this submission also considers natalizumab and fingolimod as comparators.

Natalizumab is currently used for RRMS patients with rapidly evolving severe (RES) disease (i.e. two or more disabling relapses in one year with one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.) Patients with RES were included in clinical trials for teriflunomide and a sub-analysis of this group will be presented in the main submission, however, it is not anticipated that teriflunomide will be used routinely in this indication (as is the case for both interferon-beta and glatiramer).

Fingolimod is currently used for RRMS patients with high disease activity despite interferon-beta (i.e. patients who have failed to respond to a full and adequate course of interferon-beta. Patients should have had at least one relapse in the previous year while on therapy and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion.) Patients with high disease activity were included in clinical trials for teriflunomide and a sub-analysis of this group will be presented in the main submission, however, it is not anticipated that teriflunomide will be used routinely in this indication (as is the case for both interferon-beta and glatiramer).

Genzyme do not believe that either fingolimod or natalizumab are relevant comparators for teriflunomide. This is because we anticipate that teriflunomide will be used in patients with RRMS who otherwise would receive beta-interferons or glatiramer acetate. However, in line with the scope we are presently identifying whether robust, relevant data is available from our clinical trials to support comparison with natalizumab (in RES patients) and fingolimod (in patients with high disease activity despite interferon-beta).

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

Accelerated elimination procedure

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l, although due to individual variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of teriflunomide and could therefore be employed in managing adverse effects.

Elimination can be accelerated by either of the following procedures:

- Administration of cholestyramine 8 g every 8 hours for 11 days. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used.
- Alternatively, 50 g oral activated charcoal powder administered every 12 hours for 11 days.

If tolerability is an issue, days do not need to be consecutive.

At the end of 11 days, these regimens were effective in accelerating teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations [Teriflunomide SmPC, 2013].

Anti-infectives

During clinical trials serious opportunistic infections occurred in 0.2% of patients in both the teriflunomide and placebo groups. In the event of this occurring, cessation of treatment with teriflunomide should be considered [Teriflunomide SmPC 2013]. Anti-infective therapy would be prescribed according to site of infection and local microbiology protocols.

Very common adverse events with teriflunomide are nausea, diarrhoea and hair thinning [Teriflunomide SmPC 2013]. Nausea and diarrhoea may be managed if necessary with pharmacological therapies; none is specifically recommended and treatment choice would be at the treating physician's discretion. However, numerous anti-nausea and anti-diarrhoeal agents are available in generic form and are therefore inexpensive to prescribe. Hair thinning if distressing to the patient, is managed by withdrawing treatment with teriflunomide [Teriflunomide SmPC 2013].

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

Other than drug cost there is expected to be limited impact on resource use. Teriflunomide is an oral therapy and it is anticipated that this will be initiated and monitored by specialists in secondary care. Liver function monitoring is required at regular intervals and this may be carried out in the specialist centre or possibly under a shared care agreement with the GP.

Estimates of resource use in the submission will be based on drug acquisition costs, and NHS and Personal Social Services perspective.

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

Teriflunomide will not require additional infrastructure to be put in place.

3 Equality

3.1 Identification of equality issues

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

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

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

We have no concerns regarding equality issues at this time however it should be noted that teriflunomide is not recommended for use in patients below 18 years of age since the safety and efficacy of teriflunomide in children and adolescents aged 0 to 18 years has not yet been established; no data are available.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

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

We believe that teriflunomide is innovative as it is a new oral therapy. This accompanies a favourable benefit : risk profile and we perceive that teriflunomide could therefore provide clinical benefit to a broad spectrum of patients with RRMS. (The only other oral therapy for RRMS is fingolimod and this has been restricted for use based on NICE's recent Final Appraisal Determination).

Teriflunomide is a new oral once-daily disease modifier with a unique mode of action in RRMS which maintains generalised immune surveillance and which, unlike fingolimod, may be used in non-high- disease-activity RRMS patients.

The innovative nature of fingolimod as an oral therapy has been recognised in the associated final scope which states that "consideration should be given to the possible impact of fingolimod being an oral preparation" (ref http://www.nice.org.uk/nicemedia/live/12170/50871/50871.pdf) and was also highlighted in the Final Appraisal Determination where the committee accepted "its oral formulation represents innovation in the treatment of multiple sclerosis". (section 4.19, pg 36 at http://guidance.nice.org.uk/TA/Wave20/71/Scope/pdf/English)

We would thus argue that teriflunomide represents an innovative treatment for a broad spectrum of patients with RRMS.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

The benefits to both patients and carers of an oral therapy vs. a parenteral therapy cannot be fully captured within the QALY calculation. We would also comment that the societal impact of MS in terms of loss of productivity, patient and carer burden and ability to work etc. is much wider than accounted for in the analysis and not fully captured within the perspective adopted by NICE of the NHS and PSS.

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

The benefits achieved relating to oral versus parenteral administration have been assumed from commonly accepted beliefs.

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	• People with relapsing remitting multiple sclerosis • People with secondary progressive multiple sclerosis who experience relapses • People with progressive relapsing multiple sclerosis	• People with relapsing remitting multiple sclerosis	CHMP positive opinion for teriflunomide is for relapsing remitting multiple sclerosis only and therefore the other populations (ie. people with secondary progressive multiple sclerosis who experience relapses and people with progressive relapsing multiple sclerosis) will not be considered
Intervention	• Teriflunomide	• Teriflunomide	
Comparator(s)	• Beta-interferon • Glatiramer acetate • Natalizumab (for patients with rapidly evolving severe relapsing remitting MS) • Fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta-interferon	As identified by the final scope issued by NICE we will compare teriflunomide with: • Beta-interferon • Glatiramer acetate The following comparators will be presented if data are available from the phase III trials in these patient groups: • Natalizumab (for patients with rapidly evolving severe relapsing remitting MS) • Fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta-interferon	Beta-interferon and glatiramer are the key comparators for teriflunomide. Although natalizumab and fingolimod are not key comparators we are currently reviewing phase III trial data for teriflunomide to identify whether robust data are available for the specific subgroups in which natalizumab and fingolimod are used. If these data are available then the comparators, fingolimod and natalizumab will be included in the submission.
Outcomes	• Relapse rate • Severity of relapse • Disability (for example, expanded disability status scale) • Symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance)	• Relapse rate • Severity of relapse • Disability (for example, expanded disability status scale) • Symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance)	For teriflunomide, we will also include the following outcome which was prospectively evaluated in the Phase III programme in a post hoc analysis of the TEMSO and study • Resource utilisation: hospitalisation (for relapse or any causes)

	• Freedom of disease activity • Mortality • Adverse effects of treatment • Health related quality of life	• Freedom of disease activity • Mortality • Adverse effects of treatment • Health related quality of life • Resource utilisation: hospitalisation (for relapse or any causes) and emergency medical visits (any causes).	and emergency medical visits (any causes).
Economic analysis	• The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life. • The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs should be considered from an NHS and Personal Social Services Perspective. • The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. This includes the arrangements within the risk-sharing scheme, which was agreed for the supply of disease modifying treatments for Multiple Sclerosis	• Incremental cost per quality-adjusted life year. • The time horizon considered is lifetime (50 years). • Costs will be considered from an NHS and Personal Social Services perspective. • Costs of beta interferon and glatiramer acetate are obtained from the UK Risk Sharing Scheme. Beta-interferon and glatiramer are the key comparators for teriflunomide. • If data permits comparison with fingolimod or natilizumab, then where patient access schemes are in place and available to the manufacturer these will be taken into account.	

	in the NHS (See Health Service Circular 2002/2004)		
Subgroups to be considered	If the evidence allows, the following subgroups of patients will be considered: • Patients with relapsing-remitting multiple sclerosis whose disease has inadequately responded to treatment with disease modifying therapy • Patients with relapsing-remitting multiple sclerosis is intolerant to treatment with disease modifying therapy • Patients with highly active relapsing-remitting multiple sclerosis • Patients with rapidly evolving severe relapsing-remitting multiple sclerosis	• Patients with relapsing-remitting multiple sclerosis whose disease has inadequately responded to treatment with disease modifying therapy • Patients with relapsing-remitting multiple sclerosis that is intolerant to treatment with disease modifying therapy	We will address the additional sub groups of highly-active RRMS and rapidly-evolving severe RRMS if we are able to identify the necessary evidence to support the analyses.
Special considerations, including issues related to equity or equality			

Section B – Clinical and cost effectiveness

6 Clinical evidence

6.1 Identification of studies

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

A systematic review was conducted to identify published studies demonstrating the efficacy and safety of teriflunomide for the treatment of RRMS in relation to currently available therapies, including glatiramer, interferon-beta, natalizumab and fingolimod. The full search strategy can be found in Section 10.2 Appendix 2. Searches were conducted in MedLine, Embase, and the Cochrane Collaboration Central Register of Clinical Trials (CENTRAL) from 1st January 1980 to 30th June 2012.

Additional searches were conducted in FDA and EMA websites to search for unpublished clinical trial information and safety data.

Any high quality recently conducted systematic reviews, (i.e. new publications in higher tiered journals for example, Filippini et al., 2011; Smith et al., 2010) NICE guidelines and technology appraisals had their bibliographies reviewed. This was done by running supplemental, targeted, searches using words to describe the disease as well as the study type (systematic reviews and meta-analyses).

Proceedings from several key conferences in the past 2 years were reviewed for relevant abstracts:

- Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS)
- European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)
- Latin American Committee for Treatment and Research in Multiple Sclerosis (LACTRIMS)
- American Academy of Neurology (AAN)
- American Neurological Society (ANS)
- European Neurological Society (ENS)
- European Federation of Neurological Societies (EFNS)

Bibliographies of review articles were searched to obtain relevant references.

Two reviewers reviewed studies for inclusion according to pre-specified inclusion and exclusion criteria.

Data from relevant studies were extracted into a form in MS Excel for assessment of feasibility of a mixed treatment comparison.

6.2 Study selection

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

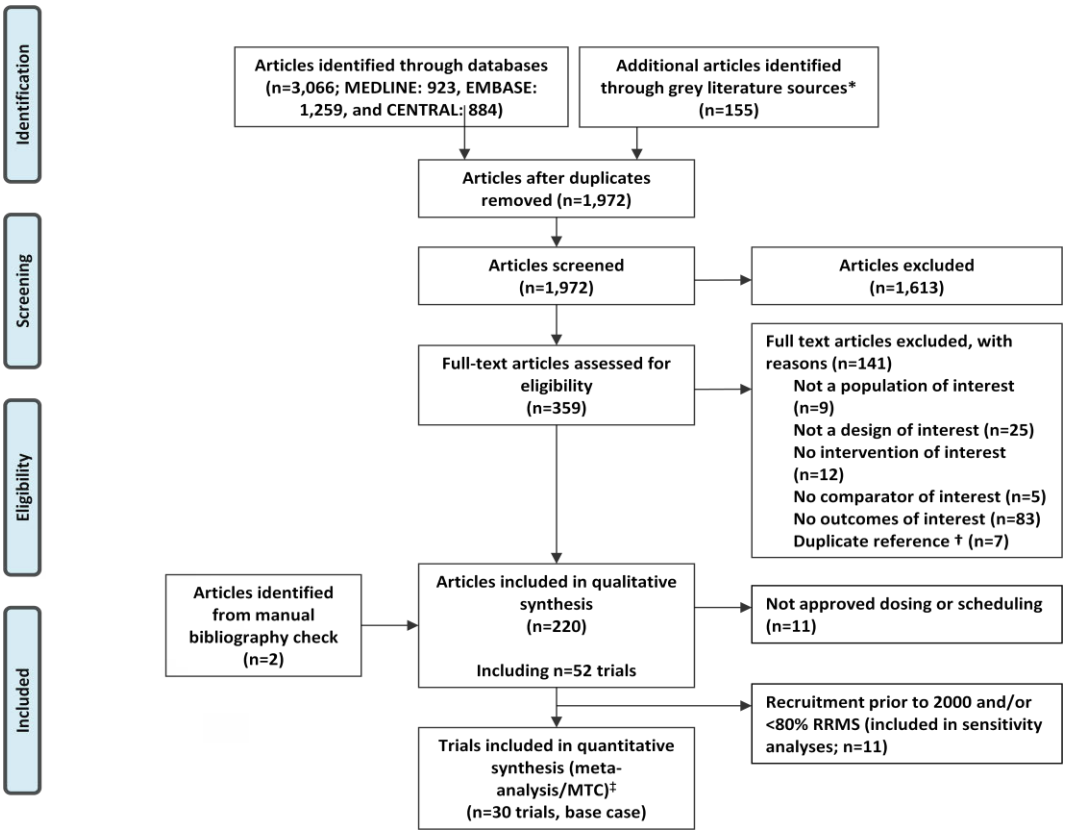
A full systematic literature review was performed to identify relevant RCTs involving *any* disease modifying treatment (DMT) used for treating RRMS/PMS in adults (see Section 10.2 Appendix 2). From these results, trials involving teriflunomide were extracted as a final step.

Table B6.2.1 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population Adult patients with the following classifications of MS: • RRMS • PMS (including SPMS and progressive relapsing) Interventions [beta-interferon, glatiramer acetate, natalizumab, fingolimod, teriflunomide] Outcomes (detailed information on outcomes extracted is provided in Section 10.2 Appendix 2) • Relapse • Disability Progression • MRI Outcomes • Discontinuation and Adverse Events Study design • Single- or double-blind randomised controlled trials (RCTs) and open-label extension phase of these trials Language restrictions • English
Exclusion criteria	Population • People who do not have MS Interventions • Not DMTs Outcomes • No relevant data on any of the outcomes of interest Study design • Studies that are not randomised, letters to the editor, citations with no abstract • Studies that are open label from the outset • Studies that were continuing to recruit • Studies where patient numbers treated with a specific intervention or disease status (RRMS, or PMS with relapse) could not be determined Language restrictions • Studies not written in English

6.2.2 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 6.2.4.

Figure B6.2.1 Systematic literature review



N.B. Of the 30 trials used for the quantitative synthesis, 17 references included teriflunomide (16 from the SLR then additional data for TOWER – a phase III placebo-controlled trial of teriflunomide that was provided by the sponsor in the form of a Clinical Study Report). Subsequent to the SLR being performed, data for the TOWER trial for teriflunomide was presented at ECTRIMS 2012.

*Includes the FDA and EMA websites, as well as proceedings from the following key conferences in the past two years: AAN, ACTRIMS, ANA, ECTRIMS, EFNS, ENS, and LACTRIMS.

† These seven citations were duplicates of abstracts from the grey literature that were also brought in through the MEDLINE, EMBASE, and CENTRAL searches.

‡Following the feasibility assessment and key opinion leader (KOL) recommendations, quantitative analyses were restricted to trials with recruitment from 2000 onward (16 trials were excluded) and with at least 80% RRMS patients (10 trials were excluded). These two restrictions combined (with some overlap) reduced the number of trials suitable for quantitative analyses from 52 to 30. See section 6.7.1 for full description of the feasibility assessment process.

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

There are four RCTs relevant to the decision problem:

Phase II "proof of concept" plus an open-label extension to this trial: two peer-reviewed published articles are the primary reference sources for this trial and its extension [O'Connor et al. 2006; Confavreux et al. 2012]. Other references identified are conference abstracts.

There are three phase III trials; TEMSO and TOWER are similar in design (vs. placebo), TENERE compares teriflunomide to interferon.

Phase III TEMSO trial: one peer-reviewed published article is the primary reference source for this trial [O'Connor et al. 2011]; other references identified are conference abstracts. This trial also has an open-label extension reported on in conference abstracts. Further data presented here is from the Clinical Study Report held at Genzyme.

Phase III TENERE trial: this trial has been reported on in conference abstracts. Further data presented here is from the Clinical Study Report held at Genzyme.

Phase III TOWER trial: this trial has been reported on in conference abstracts. Further data presented here is from the Clinical Study Report held at Genzyme.

Complete list of relevant RCTs

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

Table B6.2.2 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
STUDY 2001, HMR1726D/2001 **"Proof of Concept"** **(Phase 2)**	Teriflunomide 7mg o.d. or 14mg o.d.	Placebo o.d.	Patients with RMS, n=179: • RRMS (n =157) • SPMS with relapses (n =22) Age 18-65 years	O'Connor PW et al 2006. *Neurology*; 66:894-900.
LTS6048, HMR1726D/2002 **Phase 2 extension**	Teriflunomide 7mg o.d. or 14mg o.d.	None	Patients who completed the core study and entered the extension. n=147 (no breakdown recorded in main reference) Age 18-65 years	Confavreux et al. 2012. *Multiple Sclerosis Journal*; 18(9):1278-1289. Also: Li DK et al. 2010 *Multiple Sclerosis Journal*;16(10):S142. Confavreux et al. 2011. *Multiple Sclerosis Journal*;17(10):S409-S410. Li D et al. 2011. *Multiple Sclerosis Journal*;17(10):S183-S184.
EFC6049, HMR1726D/3001, 2004-000555-42 **TEMSO** **(Phase 3)**	Teriflunomide 7mg o.d. or 14mg o.d.	Placebo o.d.	Patient with relapsing MS, n=1,088 (1,086 received treatment) • RRMS (n =995) • SPMS with relapses (n =51) • Progressive relapsing (n=42) Age18-55 years	O'Connor et al. 2011. *N Engl J Med*; 365:1293-303. Also: Nelson et al. 2011. *J Neurol*;258. O'Connor et al. 2010. *Multiple Sclerosis Journal*; 16(10):S23. Wolinsky et al. 2010. *Multiple Sclerosis Journal*; 16(10):S347-S348. Wolinsky et al. 2013. *Multiple Sclerosis Journal;* ePub ahead of print. Miller A et al. 2011. Paper presented at: American Academy of Neurology Annual Meeting; Honolulu, Hawaii. Freedman MS et al. 2012.

				AAN; poster: PD5.007. Miller A et al. 2012. *Neurology*;78(1):P07.082
LTS6050, 2006-003361-14 **TEMSO extension**	Teriflunomide 7mg o.d. or 14mg o.d.	None	Patients who completed the TEMSO study and choose to continue to the extension n=742	O'Connor et al. 2011. *Multiple Sclerosis Journal*; 17(10):S414-S415. Also: Comi et al. 2011. *Multiple Sclerosis Journals*; 17(10):S182-S183.
EFC10891, 2008-006226-34, **TENERE (Phase 3)**	Teriflunomide 7mg o.d. or 14mg o.d.	High-dose IFNβ1-a (Rebif®44µg) given by sub-cutaneous injection three times a week	Patients with RMS, n=324 Age ≥18years	Vermersch et al. 2012. *ACTRIMS.* Also: Vermersch et al. 2012. *ENS*.
EFC10531, 2007-004452-36, **TOWER (Phase 3)**	Teriflunomide 7mg o.d. or 14mg o.d.	Placebo	Patient with MS, n=1,165 (treated): • relapsing MS Age 18-55 years	Kappos et al. 2012 *ECTRIMS* Sanofi. Clinical Study Report: Study Name: TOWER, Study Number: EFC10531, Date: 31-Jul-2012, Version Number:1, Compound: Teriflunomide (HMR1726). A multi-center double-blind parallel-group placebo-controlled study of the efficacy and safety of teriflunomide in patients with relapsing multiple sclerosis 2012.

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

The Phase III TENERE trial compares teriflunomide with high-dose beta-interferon.

All other trials of teriflunomide are vs. placebo (best supportive care) which is not a comparator in the decision problem.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale

for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

N/A all of the studies identified above are included within this submission.

List of relevant non-RCTs

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

There are no other non-RCTs considered relevant to the decision problem.

6.3 Summary of methodology of relevant RCTs

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

See Tables B6.3.1 and B6.3.2.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

See Tables B6.3.1 and B6.3.2.

Table B6.3.1 Comparative summary of methodology of the Phase II and Phase III RCTs

Trial no. (acronym)	**Phase II "Proof of Concept"** STUDY 2001 [O'Connor et al. 2006]	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TENERE** EFC10891 [clinicaltrials.gov; CSR]	**TOWER** EFC10531 [clinicaltrials.gov; CSR]
Location	France, Canada	127 centers in 21 countries. (United States, Austria, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Italy, Netherlands, Norway, Poland, Portugal, Russian Federation, Sweden, Switzerland, Turkey, Ukraine, United Kingdom)	53 centres in 13 countries. (Belgium, Canada, Czech Republic, France, Germany, Greece, Hungary, Italy, Poland, Spain, Switzerland, Tunisia, United Kingdom)	United States, Australia, Austria, Belarus, Belgium, Canada, Chile, China, Czech Republic, Estonia, France, Germany, Greece, Mexico, Netherlands, Philippines, Poland, Romania, Slovakia, Spain, Sweden, Thailand, Tunisia, Turkey, Ukraine, United Kingdom
Design	Randomized, double-blind, placebo controlled, parallel-group Phase 2	Randomized, double-blind, placebo-controlled, parallel-group Phase 3	Randomized, outcomes-assessor blinded, parallel group (active comparator) Phase 3	Randomized, double-blind, placebo-controlled, parallel-group Phase 3
Duration of study	Treatment period: 36 weeks	Treatment period: 108 weeks	Initial treatment period: between 48 and 118 weeks depending on when the participant was enrolled. Actual maximum was slightly under 115 weeks. Optional long-term extension treatment period until teriflunomide is commercially available locally.	Double-blind treatment period: between 48 and 154 weeks Safety extension open-label treatment period: 48 weeks or until teriflunomide is commercially available in the country where the patient lives.

Trial no. (acronym)	Phase II "Proof of Concept" STUDY 2001 [O'Connor et al. 2006]	TEMSO EFC6049 [O'Connor et al. 2011]	TENERE EFC10891 [clinicaltrials.gov; CSR]	TOWER EFC10531 [clinicaltrials.gov; CSR]
Method of randomisation	1:1:1 ratio Randomization was stratified by baseline EDSS score to give two patient groups: those with EDSS scores ≤3.5 and those with scores >3.5.	1:1:1 ratio Randomization was stratified according to the baseline EDSS score (≤3.5 or >3.5) and according to trial site, with a block size of 6.	1:1:1 ratio Randomisation was stratified by geographical region (or countries) and baseline disability (EDSS total score (≤3.5 or >3.5).	1:1:1 ratio Randomisation was stratified by study centre and baseline disability (EDSS total score (≤3.5 or >3.5). There was a slight imbalance possibly related to the stratification of the randomization scheme by site and baseline EDSS – with many of the sites enrolling less than 6 patients
Method of blinding (care provider, patient and outcome assessor)	Double-Blind (Subject, Investigator)	Double blind (Subject, Investigator)	Rater blind i.e. open label trial with blinded outcomes assessment. Two doses of oral teriflunomide administered in a double blind fashion; IFNβ -1a administered open-label	Double Blind (Subject, Caregiver, Investigator). All investigational product was identical in appearance.
Intervention(s) (n =) and comparator(s) (n =)	Teriflunomide: 7mg/day: n= 61 14mg/day: n= 57 Comparator: Placebo n= 61	Teriflunomide: 7mg/day: n= 365 14mg/day: n= 358 Comparator: Placebo n= 363	Teriflunomide: 7mg/day: n= 109 14mg/day: n= 111 Comparator: IFNβ-1a: n= 104 (3 were untreated)	Teriflunomide: 7mg/day: n = 408 14mg/day: n = 373 Comparator: Placebo: n = 389

Trial no. (acronym)	Phase II "Proof of Concept" STUDY 2001 [O'Connor et al. 2006]	TEMSO EFC6049 [O'Connor et al. 2011]	TENERE EFC10891 [CSR]	TOWER EFC10531 [clinicaltrials.gov; CSR]
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy variable was the number of combined unique (CU) active (new and persisting) lesions per MRI scan during the 36-week, double-blind treatment phase. MRI scans were performed at weeks -4 (visit 1) and 0 (baseline; visit 3), then every 6 weeks for 36 weeks (treatment phase; visits 4 to 10). Fifty contiguous, 3-mm-thick axial slices of the entire brain were acquired using unenhanced proton density/ T2-weighted (PD/T2) and pre- and post gadolinium enhanced (0.1 mmol/kg, 5-minute delay) T1-weighted sequences (Gd-T1). All scans were then sent to the University of British Columbia (UBC) MS/MRI Research Group for central	The primary objective of the study was to determine the efficacy of teriflunomide in reducing the annualised relapse rate (defined as the number of confirmed relapses per patient-year). A relapse was defined as the appearance of a new clinical sign or symptom, or clinical worsening of a previous sign or symptom that had been stable for at least 30 days and that persisted for a minimum of 24 hours in the absence of fever. Confirmed relapses required an increase of 1 point in each of two EDSS functional-system scores or of 2 points in one EDSS functional-system score (excluding bowel and bladder function and cerebral function) or an increase of 0.5 points in the EDSS score from the previous clinically stable assessment.	The primary objective was to assess the effectiveness of 2 doses of teriflunomide in comparison to IFNβ-1a, evaluated by the time to failure, with failure being defined as either relapse or permanent study treatment discontinuation for any cause whichever comes first. A relapse was defined as the appearance of a new clinical sign/symptom or clinical worsening of a previous sign/symptom (stable for at least 30 days) that persisted for a minimum of 24 hours in the absence of fever. Each episode of relapse was confirmed by the treating neurologist, based on the objective assessments by an independent evaluator (the examining neurologist) by documenting either of the following: A 1-point increase in at least 2 Functional System (FS) score, or a 2-point increase in at least 1 FS score (excluding bowel/bladder and cerebral) from the previous clinically stable assessment or; An increase of at least 0.5 points in the EDSS score (unless EDSS = 0, then an increase of at least 1.0 points is required) from the previous clinically stable assessment.	Annualized relapse rate (number of relapses per patient-year). A relapse was defined as the appearance of a new clinical sign/symptom or clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persisted for a minimum of 24 hours in the absence of fever. Each episode of relapse had to be confirmed by the treating neurologist, based on the objective assessments by an independent evaluator (the examining neurologist) by documenting either of the following: A 1-point increase in at least 2 Functional System (FS) functions, or a 2-point increase in at least 1 FS function (excluding bowel/bladder and cerebral) from the previous clinically stable assessment or; An increase of at least 0.5 points in the EDSS score (unless EDSS = 0, then an increase of at least 1.0 point was required) from the previous clinically stable assessment. Timing of EDSS and FS score by the examining neurologist at weeks 12, 24, 36 and every 12 weeks while on treatment

	review and analysis. The UBC MS/MRI Analysis Group had no clinical knowledge of the history or treatment of any of the patients analyzed. MRI lesion activity was determined from a sequential review of the patient's entire scan set by pairs of radiologists working together to reach consensus. When there was a disagreement, a third senior radiologist reviewed the films, and a final consensus was reached. Activity analysis was performed in three steps: 1) Gd-T1 scan analysis to identify newly enhancing and persistently enhancing T1 lesions; 2) PD/T2 scan analysis to identify new and enlarging T2 active lesions; 3) combined unique (CU) active lesion analysis (this final step was performed after the Gd-T1 and PD/T2 analyses to avoid double counting of simultaneous activity in single lesions).			

Trial no. (acronym)	Phase II "Proof of Concept" STUDY 2001 [O'Connor et al. 2006]	TEMSO EFC6049 [O'Connor et al. 2011]	TENERE EFC10891 [CSR]	TOWER EFC10531 [clinicaltrials.gov; CSR]
Secondary outcomes (including scoring methods and timings of assessments)	Other MRI outcome measures included the number of T1 enhancing lesions, number of T2 active lesions, number of patients with CU active, T1 enhancing, and T2 active lesions, and percentage change from baseline to endpoint in the burden of disease (T2 lesion volume). Clinical measures included the number of patients experiencing an MS relapse, annualised relapse rate, and number of relapsing patients requiring a course of steroids. A relapse was defined as the appearance of a new symptom or worsening of an old symptom due to MS lasting 48 hours in the absence of fever, preceded by period of stability of at	The key secondary objective was to determine the efficacy of teriflunomide in delaying the progression of disability over the study period, as assessed on the basis of changes in the EDSS score. Sustained disability progression was defined as an increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks. The key prespecified MRI end point was total lesion volume. Other MRI end points included the number of gadolinium-enhancing lesions on T1-weighted images, the volume of hypo intense lesion components on T1-weighted images, the number of unique active lesions (defined as the number of	• Annualized relapse rate (number of relapses per patient-year) • Subject reported fatigue as assessed by the Fatigue Impact Scale (FIS) (self-administered, interviewer-administered or telephone-administered). Total score and 3 sub-scales to assess the impact of fatigue on cognitive, physical and psychosocial function • Subject satisfaction as assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM); a self-administered instrument measuring the major dimensions of patients' satisfaction with medication. The TSQM is made of 13 questions on 3 common dimensions (effectiveness, side effects, convenience) and a global satisfaction question	• Key secondary variable: Time to disability progression (EDSS and FS) confirmed after at least 12 weeks Time Frame: Average of 2 years (between 1 and 3 years) Others: • Fatigue Impact Scale (FIS) total score and domain score (cognitive, physical and psychosocial function) Time Frame: at weeks 12, 24 and then every 24 weeks while on treatment • Time to first confirmed relapse • Proportion of patients without a relapse • Change from baseline in EDSS • Change from baseline in Short Form generic health survey [36 items] (SF-36) scale (2 summary scores (physical health component and mental health component) and 8 domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health). In addition, a single question assessed reported health transition

	least 30 days and accompanied by appropriate changes on neurologic examination. Disability was assessed over time by measuring between-visit changes in EDSS score at visit 1 (screening) and visit 3 (baseline) and then every 12 weeks thereafter. Additional assessments included the number of patients in whom disability increased (defined as an increase in EDSS score of ≥1.0 in patients with a baseline EDSS score of ≤5.5 or an increase in EDSS score of ≥0.5 in patients with a baseline EDSS score of ≤5.5). Treatment emergent events were reported in all patients. Both relapse and disability assessments were made by the treating (blinded) neurologist.	gadolinium-enhancing lesions on T1-weighted images or new or enlarged lesions on T2-weighted images, without double counting), and brain atrophy. Patient-reported fatigue, assessed with the use of the Fatigue Impact Scale (FIS, which ranges from 0 to 160, with higher scores indicating greater fatigue), was an additional secondary end point.		Time Frame: at weeks 12, 24 and then every 24 weeks while on treatment

Trial no. (acronym)	Phase II "Proof of Concept" STUDY 2001 [O'Connor et al. 2006]	TEMSO EFC6049 [O'Connor et al. 2011]	TENERE EFC10891 [CSR]	TOWER EFC10531 [clinicaltrials.gov; CSR]
Duration of follow-up	6-week post-treatment follow-up period. (Clinicaltrials.gov) Participants who successfully completed the double-blind treatment phase were offered the possibility to continue study treatment in the extension study LTS6048. (ClinicalTrials.gov)	Post-treatment wash-out follow-up period of 16 weeks (if not entering in the extension study LTS6050). The patients successfully completing the study treatment were offered the opportunity to enter an optional long-term extension study LTS6050.	Post-washout follow-up period: 4 weeks after last treatment intake.	Post-washout follow-up period: 4 weeks after last treatment intake.

Table B6.3.2 Comparative summary of methodology of the Phase II and Phase III extension arms

Extension Trial no. (acronym)	**LTS6048**, **HMR1726D/2002** Phase 2 extension to LTS6048 "Proof of concept" trial [Confavreux et al. 2012, *Multiple Sclerosis Journal*]	**LTS6050**, **2006-003361-14** Phase 3 extension to TEMSO [CSR]
Design	Randomized, open-label, parallel-group Phase 2	Randomized, double-blind, parallel-group Phase 3
Duration of study	Ongoing. At time of Confavreux et al 2012 reporting, mean and median duration of study treatment including both core and extension phase, from baseline to the interim cut-off, was 5.6 years (standard deviation:2.7 years) and 7.1 years (ranging from 0.05 to 8.5 years).	Ongoing. [redacted]
Method of randomisation	Following completion of the core study, patients who were originally randomised to teriflunomide continued their assigned treatment; those receiving placebo were re-allocated to teriflunomide 7mg or 14mg according to the predefined randomisation schedule.	Patients who completed the core study could enter the long-term, double-blind extension; patients originally allocated to placebo were re-randomised to teriflunomide, 7 mg or 14 mg, while actively treated patients continued on their original dose in a blinded fashion.
Method of blinding (care provider, patient and outcome assessor)	Open-label	Double blind
Intervention(s) (n =) and comparator(s) (n =)	Teriflunomide 7mg/day: n=81 Teriflunomide 14mg/day: n=66	Randomised and treated: [redacted]
Primary outcomes (including scoring methods and timings of assessments)	To assess the long-term safety of teriflunomide in patients with RMS The primary variable was the incidence of adverse effects. Blood tests were performed fortnightly for 24 weeks and 6-weekly thereafter. Other monitoring was performed according to a predetermined schedule of clinic and lab visits with routine patient contact every 6 weeks throughout.	To document the long-term safety and tolerability of teriflunomide in MS patients with relapses as assessed via incidence of adverse events. [redacted] Time Frame: Up to a maximum of 292 weeks (4 weeks after last treatment intake) or until teriflunomide is commercially available in the country where patient lives

Extension Trial no. (acronym)	**LTS6048**, **HMR1726D/2002** Phase 2 extension to LTS6048 "Proof of concept" trial [Confavreux et al. 2012, *Multiple Sclerosis Journal*]	**LTS6050**, **2006-003361-14** Phase 3 extension to TEMSO [CSR]
Secondary outcomes (including scoring methods and timings of assessments)	Secondary objectives were to assess the long-term efficacy of teriflunomide in terms of: • Annual relapse rate • Disability accumulation (EDSS scores, Multiple sclerosis functional composite (MSFC) score measured 3-monthly) • Magnetic resonance imaging (MRI) outcomes (burden of disease and brain atrophy as calculated from the MRI scans measured 6-monthly) • Quality of life (Using the following instruments: MSQOL-54 questionnaire and Fatigue impact scales (FIS) measured 3-monthly. Optional pharmacogenomic sub study aims at assessing the association between the main enzyme systems of teriflunomide metabolism and hepatic safety and other potential associations between gene variations and clinical outcomes. An optional investigation of the response to vaccine in patients treated with teriflunomide will be performed in a few voluntary sites under a separate protocol and reported separately)	• Time to disability progression as assessed by EDSS (every 3 months) • Proportion of patients free of disability progression at yearly time points • Annualised relapse rate (number of confirmed relapses per patient per year) • Burden of disease: Change from baseline in the volume of abnormal brain tissue as measured by brain MRI (every 6 months) [redacted] (Time frame; up to a maximum of 288 weeks)

Extension Trial no. (acronym)	**LTS6048**, **HMR1726D/2002** Phase 2 extension to LTS6048 "Proof of concept" trial [Confavreux et al. 2012, *Multiple Sclerosis Journal]*	**LTS6050**, **2006-003361-14** Phase 3 extension to TEMSO [CSR]
Duration of follow-up	Ongoing. At time of Confavreux et al 2012 reporting, mean and median duration of study treatment including both core and extension phase, from baseline to the interim cut-off, was 5.6 years (standard deviation:2.7 years) and 7.1 years (ranging from 0.05 to 8.5 years). The study plans to follow patients for approximately 8 years [CSR].	Double-blind treatment up to a maximum of 288 weeks or until teriflunomide is commercially available in the country where the patient lives. Post-washout follow-up: 4 weeks after last treatment intake.

Participants

6.3.3 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.

The teriflunomide trials have similar inclusion and/or exclusion criteria (see Table B6.3.3).

Minor exceptions are:

Age limit

Both TEMSO and TOWER studies (phase III, placebo controlled) recruited patients between the ages of 18-55. In the Phase II study, patients were 18-65 and in TENERE there was no upper age limit. This did not emerge as a significant issue on the baseline characteristics of the patients included in the trials (see Table B6.3.4).

EDSS score at entry

In all the Phase III trials EDSS score at entry could be between 0 and 5.5. In the phase II trial and both extension studies, EDSS score could be 0-6.0 at entry. Including an increase in EDSS score from the TEMSO core trial into the extension, from 5.5 to 6.0 is a reasonable way to ensure patients gaining a perceived benefit from teriflunomide could continue therapy. As 6.0 represent a significant change in walking ability, it is also reasonable to maintain this as the upper limit of inclusion.

There was a slight difference in EDSS scores at entry to the clinical trials (see section 6.3.4) – however this is not considered to be significant in terms of interpreting the trial results.

Table B6.3.3 Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Phase II "Proof of Concept" Study 2001 [O'Connor et al. 2006; CSR]	• 18-65 years (females to be of non-child-bearing potential or using adequate contraception) • Clinically definite multiple sclerosis (MS) with at least 2 documented relapses as defined by the Poser criteria • Clinical disease severity between 0 and 6 inclusively according to the expanded disability status scale (EDSS) • Screening magnetic resonance imaging (MRI) scan fulfilling the criteria for a diagnosis of MS • At least two clinical relapses in the 3 years prior to screening with at least 1 relapse in the last year • Willingness and ability to participate in a long-term, placebo-controlled trial • Willingness to undergo 9 MRI scans within 1 year and to provide consistent data as needed by the investigator to monitor progress	• Significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia • Congenital or acquired severe immunodeficiency, history of cancer (except for surgically excised basal or squamous cell skin lesions with no evidence of metastasis), lymphoproliferative disease, or treatment with lymphoid irradiation • Known HIV positive status • Persistent significant or severe infection in the 4 months before screening • Uncontrolled hypertension, uncontrolled diabetes, unstable ischemic heart disease, active inflammatory bowel disease, active peptic ulcer disease, terminal illness, or other medical condition which, in the opinion of the investigator, put the patient at risk in the study • Clinically relevant neurologic disease (including head trauma with residual deficit, stroke, or transient ischemic attack) • Clinically relevant cardiovascular, hepatic, endocrine, or other major systemic disease that made implementation of the protocol or interpretation of the study results difficult • Pregnancy and breastfeeding • Woman of childbearing potential except if she agreed to maintain adequate means of contraception throughout the study and for 24 months after the discontinuation of study treatment • Wish to parent children during the trial or following the trial (except if they agreed to comply with contraception requirements or rapid elimination procedure) • Treatment with disallowed medications (i.e. phenytoin, warfarin, tolbutamide, or cholestyramine) in the 4 weeks before screening • Treatment with systemic, inhaled, intra-articular, or widely applied topical corticosteroids or adrenocorticotrophic hormone (ACTH) in the 4 weeks before screening • Treatment with interferon, gamma-globulin, or other non-corticosteroid, immunomodulatory therapies in the 4 months before screening • Previous treatment with cladribine or mitoxantrone. Treatment with other chemotherapeutic agents such as azothioprine, cyclophosphamide, cyclosporine, or

		methotrexate in the 6 months before screening • Recent history of drug or alcohol abuse. • Hepatitis B or C • Hypoproteinemia • Moderate to severe renal impairment • Abnormal mental conditions • Previous treatment with lenalidomide or teriflunomide

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
LTS6048, HMR1726D/2002 Phase 2 Extension study [Confavreux et al. 2012; CSR]	• Satisfactory completion of HMR1726D/2001 study with respect to safety. • If female subject, non-childbearing potential or child bearing potential with adequate contraception. • Consent to practice/maintain adequate means of contraception throughout the study and for 24 months after the discontinuation of treatment. • Clinically definite Multiple Sclerosis (MS) as established on entry into HMR1726D/2001 study. • Extended Disability Status Score (EDSS) between 0 and 6 inclusively, when the subject entered HMR1726D/2001 study. • Magnetic Resonance Imaging (MRI) criteria must continue to support the diagnosis of clinically definite MS. • Willingness to participate in a long-term safety and efficacy trial.	• Subject who did not complete HMR 1726D/2001 study for safety reasons. • Subject who developed clinically relevant cardiovascular, hepatic, endocrine or other major disease. • Pregnancy and breast-feeding. • Wish to parent. • Likelihood of requiring treatment during the study period with drugs not permitted. • Disallowed therapies such as immunomodulators, immunosuppressants. • Recent history of drug or alcohol abuse. • Liver function impairment. • Abnormal mental conditions.

EFC6049/ TEMSO [O'Connor et al. 2011; CSR]	• 18-55 years • Multiple sclerosis (MS) subjects, who were ambulatory (EDSS of ≤ 5.5) • Exhibiting a relapsing clinical course, with or without progression (relapsing remitting, secondary progressive or progressive relapsing) • Meeting McDonald's criteria for MS diagnosis • Experienced at least 1 relapse over the 1 year preceding the trial or at least 2 relapses over the 2 years preceding the trial • No relapse onset in the preceding 60 days prior to randomization • During the 30 days prior to randomization, subjects should have been clinically stable, without adrenocorticotrophic hormone (ACTH) or systemic steroid treatment • Signed informed consent form	• Patients with clinically relevant cardiovascular, hepatic (including hepatitis), neurological, endocrine (including pancreatitis) or other major systemic disease (including severe renal impairment); • Patients with significantly impaired bone marrow function, significant anaemia, or severe immunodeficiency • Pregnant or nursing women or planning to conceive • Alcohol or drug abuse • Use of cladribine, mitoxantrone, or other immunosuppressant agents such as azathioprine, cyclophosphamide, cyclosporin, methotrexate or mycophenolate before enrollment • Prior use of interferons or cytokine therapy in the preceding 4 months • Prior use of glatiramer in the preceding 4 months or immunoglobulins in the preceding 6 months • Prior use of investigational drugs in the preceding 6 months • Prior use of natilizumab • Any known condition or circumstance that would have prevented in the investigator's opinion compliance or completion of the study • History of cancer (except for basal or squamous cell skin lesions which have been surgically excised, with no evidence of metastasis) • HIV positive subjects • Active tuberculosis not adequately treated • Persistent, significant or severe infection • Therapies that were disallowed: phenytoin, warfarin, tolbutamide, St.John's Wort, cholestyramine • Patients who used ACTH or systemic corticosteroids for 4-weeks prior to randomisation • Liver function impairment or persisting elevations of SGPT/ALT, SGOT/AST or direct bilirubin greater than 1.5-fold the upper limit of normal • Contraindication for MRI

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
LTS6050, 2006-003361-14 Phase 3 extension to TEMSO [CSR]	• Satisfactory completion of previous study (TEMSO) and not meeting criteria for withdrawal • If female subject, non-childbearing potential or child bearing potential with adequate contraception (and not pregnant). • Clinically definite MS on entry to TEMSO with EDSS between 0.0 and 6.0 • McDonald's criteria with MRI continue to support diagnosis of MS • Willingness and ability to participate • HIV testing consent	• Patients who did not complete TEMSO study • Patients who developed clinically relevant cardiovascular, hepatic, endocrine or other major systemic disease making implementation of the protocol or interpretation of the results difficult. • Any known condition or circumstance that would prevent in the investigator's opinion, compliance or completion of the study. • Pregnancy or breast feeding • Desire to conceive • Likelihood of requiring treatment during the study period with drugs not permitted by the protocol • Disallowed therapies: phenytoin, warfarin, tolbutamide, cholestyramine, hypericum containing treatments, e.g., St-John's Wort • Drug or alcohol abuse • Liver function impairment or persisting ALT or direct bilirubin elevations of >1.5x ULN • Mental conditions rendering the patient unable to understand the study

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
EFC10891/ TENERE [CSR Dec 2011]	• ≥18 years • Patients with relapsing forms of multiple sclerosis meeting McDonald's criteria for MS diagnosis at time of screening visit, and EDSS score ≤5.5 at screening visit • Provided informed consent with signature on informed consent form	• Did not consent top HIV testing • A relapse within 30 days prior to randomization • Mental condition rendering the patient unable to understand the study • Likelihood of non-compliance • Clinically relevant cardiovascular, neurological, endocrine or other major systemic disease making implementation of the protocol or interpretation of the study results difficult, or would put patient at risk • Patients with a congenital or acquired severe immunodeficiency, a history of cancer (except for basal or squamous cell skin lesions which have been surgically excised, with no evidence of metastasis), lymphoproliferative disease, or any patient who has received lymphoid irradiation • History of active tuberculosis not adequately treated • Hypoproteinemia (e.g., in case of severe liver disease or nephrotic syndrome) with serum albumin <3.0 g/dL • Moderate to severe impairment of renal function, as shown by serum creatinine >133µmol/L (or >1.5 mg/dL) • Patients with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia • Persistent significant or severe infection • Liver function impairment or persisting ALT or direct bilirubin elevations of >1.5x ULN • Hepatitis • Drug or alcohol abuse • Patient is the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol • Use of adrenocorticotrophic hormone (ACTH) or systemic corticosteroids for 2 weeks prior to randomization • Prior or concomitant use of cytokine therapy, glatiramer acetate or intravenous immunoglobulins in the 3 months prior to randomization • Prior or concomitant use of natalizumab (Tysabri®) • Prior or concomitant use of cladribine, mitoxantrone, or other immunosuppressant agents such as azathioprine, cyclophosphamide, cyclosporin, methotrexate or

		mycophenolate • Prior treatment with teriflunomide, and prior or concomitant use of leflunomide (ARAVA®) or hypersensitivity to any of the other ingredients or excipients of the investigational product. • Pregnant or breast-feeding women • Women of childbearing potential or men not utilizing effective contraceptive method and /or women of childbearing potential who are unwilling to or unable to be tested for pregnancy. • Patients wishing to parent children (be a partner in the conception of a child) during the course of the trial • Prior use of any investigational drug in the 6 months preceding randomisation **Exclusion criteria related to study treatments:** • Prior use of Rebif • Prior or concomitant use of other interferons in the 3 months prior to randomization, or any use of interferon beta in the past stopped due to AE, intolerability or lack of efficacy. • Known hypersensitivity to interferon beta-1a • History of severe depressive disorder and/or suicidality or seizure • Known hypersensitivity to human albumin, mannitol (United States Pharmacopoeia [USP]), or sodium acetate • Known history of hypersensitivity to teriflunomide or leflunomide • Persisting elevations (confirmed by re-test) of serum amylase or lipase greater than 2-fold the upper limit of normal • Known history of chronic pancreatic disease or pancreatitis • Prior use within 4 weeks before randomization or concomitant use of drugs metabolized by cytochrome P2C9 (CYP2C9) including phenytoin, warfarin, tolbutamide, cholestyramine; prior use of products containing St. John's Wort or hyperforin in an unknown percentage or>1% of the extract

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
EFC10531/ TOWER [CSR July 2012]	• Patients with relapsing forms of multiple sclerosis meeting McDonald's criteria for MS diagnosis at time of screening visit, and EDSS score ≤5.5 at the screening visit • The patient must have had at least 1 relapse in the 12 months preceding randomization, or at least 2 relapses in the 24 months preceding the randomization visit • Provided informed consent with signature on informed consent form: the informed consent process was to be completed with full discussion of approved therapies available for relapsing forms of MS. The patient was to be offered these therapies and was to choose to join the study instead of accepting therapy outside of the study	• <18 years of age or ≥56 years of age at randomization • Did not consent to HIV testing • A relapse within 30 days prior to randomization • Mental condition that rendered the patient unable to understand the nature, scope, and possible consequences of the study • Patient was unlikely to comply with protocol as determined by Investigator, e.g., uncooperative attitude, inability to return for follow-up visits, and known unlikelihood of completing the study • Clinically relevant cardiovascular, neurological, endocrine, or other major systemic disease that would make implementation of the protocol or interpretation of the study results difficult or that would put the patient at risk by participating in the study • Patients with a congenital or acquired severe immunodeficiency, a history of cancer (except for basal or squamous cell skin lesions which had been surgically excised, with no evidence of metastasis), lymphoproliferative disease, or any patient who had received lymphoid irradiation • HIV positive patients • Known history of active tuberculosis not adequately treated • Hypoproteinemia (e.g., in case of severe liver disease or nephrotic syndrome) with serum albumin <3.0 g/dL • Moderate to severe impairment of renal function, as shown by serum creatinine >133 µmol/L (or >1.5 mg/dL) • Patients with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia • Persistent significant or severe infection • Liver function impairment or persisting elevations (confirmed by retest) of ALT, aspartate aminotransferase (AST), or direct bilirubin greater than 1.5-fold the upper limit of normal • Known history of hepatitis • History of drug or alcohol abuse • Patient was the Investigator or any sub investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof, directly involved in the conduct of

		the protocol • Use of adrenocorticotrophic hormone (ACTH) or systemic corticosteroids for 2 weeks prior to randomization • Prior or concomitant use of cytokine therapy, glatiramer acetate, or intravenous immunoglobulins in the 3 months prior to randomization • Prior or concomitant use of natalizumab (Tysabri®) • Prior or concomitant use of cladribine, mitoxantrone, or other immunosuppressant agents such as azathioprine, cyclophosphamide, cyclosporin, methotrexate, or mycophenolate • Prior treatment with teriflunomide, and prior or concomitant use of leflunomide (ARAVA®) or hypersensitivity to any of the other ingredients or excipients of the investigational product • Pregnant or breast-feeding women • Women of childbearing potential or men not utilizing effective contraceptive method and /or women of childbearing potential who were unwilling to or unable to be tested for pregnancy • Patients who wished to parent children (be a partner in the conception of a child) during the course of the trial • Prior use of any investigational drug in the preceding 6 months
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

6.3.4 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.

Baseline characteristics for the Phase II and III trials of teriflunomide are generally well matched. There are two instances where some variation was observed:

Prior use of DMTs

In the Phase II study, a high proportion of patients had received prior DMTs (>70% in all three groups); in contrast, prior use of DMTs was substantially lower in the Phase III trials (approx 11-35%).

[redacted]

EDSS scores at entry

In the Phase II trial, mean EDSS scores at entry ranged between 2.0-2.5; similarly, [redacted]

Table B6.3.4 Characteristics of participants in the RCTs across randomised groups (Phase II, TEMSO and TENERE)

Trial	**Phase II** [O'Connor et al. 2006; CSR] NB. slightly lower values were noted for most MRI variables reported in the low-dose teriflunomide group, although these differences were not considered to be clinically important			**TEMSO*** [O'Connor et al. 2011]			**EFC10891/ TENERE** [CSR Dec 2011]			
Baseline characteristics	Placebo	Teriflunomide 7mg/day	Teriflunomide 14mg/day	Placebo	Teriflunomide 7mg/day	Teriflunomide 14mg/day	High-dose beta-interferon (Rebif® 44µg) injection three times a week	Teriflunomide 7mg/day	Teriflunomide 14mg/day	All
Number	61	61	57	363	366	359	104	109	111	324
Mean Age (years)	39.2 (8.7)	40.1 (9.3)	40.1 (9.1)	38.4±9.0	37.4±9.0	37.8±8.2	37.0 (10.6)	35.2 (9.2)	36.8 (10.3)	36.3 (10.0)
Male	20 (32.8)	15 (24.6)	12 (21.1)	88 (24.2)	111 (30.3)	104 (29)	33 (31.7)	39 (35.8)	33 (29.7)	105 (32.4)
Females (%)	41 (67.2)	46 (75.4)	45 (78.9)	275 (75.8)	255 (69.7)	255 (71.0)	71 (68.3%)	70 (64.2%)	78 (70.3%)	219 (67.6%)
White (%) †	-	-	-	356 (98.3)	355 (97.3)	347 (96.9)	[redacted]	[redacted]	[redacted]	[redacted]
Region (%)										
Western Europe and Africa ¦	-	-	-	167 (46.0)	167 (45.6)	170 (47.4)	[redacted]	[redacted]	[redacted]	[redacted]
Eastern Europe	-	-	-	114 (31.4)	116 (31.7)	108 (30.1)	[redacted]	[redacted]	[redacted]	[redacted]
Americas	-	-	-	82 (22.6)	83 (22.7)	81 (22.6)	[redacted]	[redacted]	[redacted]	[redacted]
Time from first symptom of MS — yr mean (SD)	-	-	-	8.6±7.1	8.8±6.8	8.7±6.7	7.71 (7.60)	7.02 (6.91)	6.64 (7.63)	7.11 (7.38)
Time Since diagnosis	4.4 (5.7)	6.0 (5.6)	5.4 (6.2)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]
Disease duration, yr Mean (SD)	8.6 (7.9)	10.3 (8.1)	8.5 (7.1)	-	-	-	-	-	-	-

Trial	**Phase II** [O'Connor et al. 2006; CSR] NB. slightly lower values were noted for most MRI variables reported in the low-dose teriflunomide group, although these differences were not considered to be clinically important			**TEMSO*** [O'Connor et al. 2011]			**EFC10891/ TENERE** [CSR Dec 2011]			
Relapses — no.										
In previous year	1 (Range : 0–3)	1 (Range: 0–4)	1 (Range: 0–3)	1.4±0.7	1.4±0.7	1.3±0.7	[redacted]	[redacted]	[redacted]	[redacted]
In previous 2 years	-	-	-	2.2±1.0	2.3±1.2	2.2±1.0	[redacted]	[redacted]	[redacted]	[redacted]
In previous 3 years	3 (1–9)	2 (2–5)	3 (2–6)	-	-	-	-	-	-	-
MS subtype — no. (%)										
Relapsing–remitting	53 (86.9)	54 (88.5)	50 (87.7)	329 (90.6)	333 (91.0)	333 (92.8)	[redacted]	[redacted]	[redacted]	[redacted]
Secondary progressive	8 (13.1)	7 (11.5)	7 (12.3)	22 (6.1)	17 (4.6)	12 (3.3)	[redacted]	[redacted]	[redacted]	[redacted]
Progressive relapsing	-	-	-	12 (3.3)	16 (4.4)	14 (3.9)	[redacted]	[redacted]	[redacted]	[redacted]
Use of disease-modifying therapy in previous 2 years — no. (%)	50 (82%)	51 (83.6)	41 (71.9)	90 (24.8)	102 (27.9)	102 (28.4)	25 (24.0%)	23 (21.1%)	13 (11.7%)	61 (18.8%)
Interferon beta (not otherwise specified)	8 (13.1)	9 (14.8)	7 (12.3)	-	-	-	-	-	-	-
Interferon beta-1a	-	-	-	58 (16.0)	74 (20.2)	62 (17.3)	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	-	-	-	18 (5.0)	22 (6.0)	27 (7.5)	[redacted]	[redacted]	[redacted]	[redacted]

Trial	**Phase II** [O'Connor et al. 2006; CSR] NB. slightly lower values were noted for most MRI variables reported in the low-dose teriflunomide group, although these differences were not considered to be clinically important			**TEMSO*** [O'Connor et al. 2011]			**EFC10891/ TENERE** [CSR Dec 2011]			
beta-1b										
Glatiramer acetate	5 (8.2)	6 (9.8)	7 (12.3)	36 (9.9)	23 (6.3)	43 (12.0)	[redacted]	[redacted]	[redacted]	[redacted]
EDSS score ‡	2.5 (0–6)	2.5 (0–6)	2.0 (0–6.5)	2.68± 1.34	2.68±1.34	2.67±1.24	2.04 (1.19)	2.04 (1.22)	2.33 (1.35)	2.14 (1.26)
FIS score (mean, SD) §	-	-	-	53.2± 37.9	50.4±35.6	50.3±35.9	[redacted]	[redacted]	[redacted]	[redacted]
MRI assessments							[redacted]			
Total lesion volume —ml	-	-	-	19.34± 18.94	20.37±20.59	18.08±17.49	-	-	-	-
Gadolinium-enhancing lesions ¶										
No. of patients (%)	-	-	-	137 (38.2)	127 (35.3)	125 (35.2)	-	-	-	-
No. of lesions on T1-weighted images	-	-	-	1.66± 3.55	1.50±3.96	1.81±5.17	-	-	-	-
No. (%) of patients with T1 enhancing lesions	36 (59.0)	29 (47.5)	31 (54.4)	-	-	-	-	-	-	-
No. (%) of patients with combined	38 (62.3)	29 (47.5)	35 (61.4)	-	-	-	-	-	-	-

Trial	**Phase II** [O'Connor et al. 2006; CSR] NB. slightly lower values were noted for most MRI variables reported in the low-dose teriflunomide group, although these differences were not considered to be clinically important			**TEMSO*** [O'Connor et al. 2011]			**EFC10891/ TENERE** [CSR Dec 2011]			
unique active lesions										
No. (%) of patients with new or enlarging T2 lesions	22 (36.1)	16 (26.2)	24 (42.1)	-	-	-	-	-	-	-
No. of combined unique active lesions/scan										
Mean+/- SE	2.16 ± 0.63	1.30 ± 0.60	2.48 ± 0.62	-	-	-	-	-	-	-
Median	0.5	0.0	0.5	-	-	-	-	-	-	-
No. of T1 enhancing lesions/scan										
Mean+/- SE	2.10 ± 0.62	1.23 ± 0.60	2.32 ± 0.61	-	-	-	-	-	-	-
Median	0.5	0.0	0.5	-	-	-	-	-	-	-
No. of new or enlarging T2 lesions/scan										
Mean+/- SE	0.66 ± 0.27	0.77 ± 0.26	0.80 ± 0.26	-	-	-	-	-	-	-
Median	0.0	0.0	0.0	-	-	-	-	-	-	-
T2 lesion										

Trial	**Phase II** [O'Connor et al. 2006; CSR] NB. slightly lower values were noted for most MRI variables reported in the low-dose teriflunomide group, although these differences were not considered to be clinically important			**TEMSO*** [O'Connor et al. 2011]			**EFC10891/ TENERE** [CSR Dec 2011]			
volume, mm3										
Mean	9,119	10,338	8,475	-	-	-	-	-	-	-
Median	5,774	6,294	6,224	-	-	-	-	-	-	-
Volume of hypo intense lesions on T1-weighted images —ml	-	-	-	3.26±3.64	3.35±3.96	2.91±3.25	-	-	-	-
Brain parenchymal fraction‖	-	-	-	0.76±0.02	0.76±0.02	0.76±0.02	-	-	-	-

* Data are presented for the randomised population. Plus–minus values are means ±SD. All baseline characteristics were well matched among the three groups (P>0.05). MS denotes multiple sclerosis.
† Data on race were missing for one person in each study group. Race was self-reported.
‡ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10, with higher scores indicating greater disability.
§ Scores on the Fatigue Impact Scale (FIS) range from 0 to 160, with higher scores indicating greater fatigue.
¶ Data on gadolinium-enhancing lesions were missing for four patients in the placebo group, six patients in the lower dose teriflunomide group, and four patients in the higher-dose teriflunomide group.
|| The brain parenchymal fraction was calculated as the inverse of the normalized cerebrospinal fluid volume segmented as described previously.
¦ TENERE: One patient from Tunisia, Source: [Sanofi 2011]

Table B6.3.5 Characteristics of participants in the RCTs across randomised groups (TOWER)

Trial	**TOWER** [Miller et al. 2013; Kappos et al 2012; CSR]		
Baseline characteristics	Placebo	Teriflunomide 7mg	Teriflunomide 14 mg
Number	389	408	372
Mean Age (years)	38.1 (9.1)	37.4 (9.4)	38.2 (9.4)
Male	116 (29.8%)	108 (26.5%)	114 (30.6%)
Females (%)	273 (70.2%)	300 (73.5%)	258 (69.4%)
White (%) †	318 (81.7%)	329 (80.6%)	313 (84.1%)
Region (%)			
Western Europe and Africa ¦	-	-	-
Eastern Europe	-	-	-
Americas	-	-	-
Black	7 (1.8)	8 (2.0)	7 (1.9)
Asian	60 (15.4)	60 (14.7)	49 (13.2)
Time from first symptom of MS — yr mean (SD)	7.6 (6.7)	8.2 (6.8)	8.2 (6.7)
Time Since diagnosis	[redacted]	[redacted]	[redacted]
Disease duration, yr Mean (SD)	-	-	-
Relapses — no.			
In previous year	1.4 (0.8)	1.4 (0.7)	1.4 (0.7)
In previous 2 years	2.1 (1.1)	2.1 (1.1)	2.1(1.2)
In previous 3 years	-	-	-
MS subtype — no. (%)			
Relapsing–remitting	[redacted]	[redacted]	[redacted]
Secondary progressive	[redacted]	[redacted]	[redacted]
Progressive relapsing	[redacted]	[redacted]	[redacted]
Use of disease-modifying therapy in previous 2 years — no. (%)	135 (34.7)	123 (30.1)	126 (33.9)
Interferon beta (not otherwise specified)			
Interferon beta-1a	[redacted]	[redacted]	[redacted]
Interferon beta-1b	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]
EDSS score ‡	2.7 (1.4)	2.7 (1.4)	2.7 (1.4)
FIS score (mean, SD) §	-	-	-
MRI assessments			
Total lesion volume —ml	-	-	-
Gadolinium-enhancing lesions ¶			
No. of patients (%)	-	-	-
No. of lesions on T1-weighted images	-	-	-
No. (%) of patients with T1 enhancing lesions	-	-	-
No. (%) of patients with combined unique active	-	-	-

Trial	TOWER [Miller et al. 2013; Kappos et al 2012; CSR]		
lesions			
No. (%) of patients with new or enlarging T2 lesions	-	-	-
No. of combined unique active lesions/scan			
Mean+/- SE	-	-	-
Median	-	-	-
No. of T1 enhancing lesions/scan			
Mean+/- SE	-	-	-
Median	-	-	-
No. of new or enlarging T2 lesions/scan			
Mean+/- SE	-	-	-
Median	-	-	-
T2 lesion volume, mm3			
Mean	-	-	-
Median	-	-	-
Volume of hypo intense lesions on T1-weighted images —ml	-	-	-
Brain parenchymal fraction‖	-	-	-

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), 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.

We believe all the trial outcomes reported below to be relevant to the decision problem.

Table B6.3.6 Primary and secondary outcomes of the RCTs

Trial no. (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
Phase II "Proof of Concept" Study 2001 [O'Connor et al. 2006]	• *The primary efficacy variable was the number of combined unique (CU) active (new and persisting) lesions per MRI scan during the 36-week, double-blind treatment phase.* • See Table B6.3.1 for details of measurements	Magnetic resonance imaging (MRI) is a highly sensitive technique used for the detection of brain tissue changes in patients with MS. As a result, MRI has been valuable to monitor disease activity in clinical trials. T2-weighted MRI identifies a broad spectrum of pathological changes, including inflammation, edema, demyelination, gliosis, and axonal loss. New areas of gadolinium (Gd) enhancement on T1-weighted MRI suggest recent inflammatory demyelination with disruption of the blood-brain barrier. Chronic hypo intense lesions on T1-weighted images ("black holes") are indicators of persistent damage. The extent of central nervous system atrophy involving both the brain and spinal cord is a clinically relevant measure of disease progression and highly relevant to current clinical practice.	Other **MRI outcome measures** included the number of T1 enhancing lesions, number of T2 active lesions, number of patients with CU active, T1 enhancing, and T2 active lesions, and percentage change from baseline to endpoint in the burden of disease (T2 lesion volume). **Clinical measures** included the number of patients experiencing an MS relapse, annualised relapse rate, and number of relapsing patients requiring a course of steroids. A relapse was defined as the appearance of a new symptom or worsening of an old symptom due to MS lasting 48 hours in the absence of fever, preceded by period of stability of at least 30 days and accompanied by appropriate changes on neurologic examination. **Disability** was assessed over time by measuring between-visit changes in EDSS score at visit 1 (screening) and visit 3 (baseline) and then every 12 weeks thereafter. **Disability: Additional assessments** included the number of patients in whom disability increased (defined as an	For **MRI** information see previous column. **Clinical measures: measuring relapse rate** Relapses are a defining feature of RRMS. Relapses may require admission to hospital, and are associated with a level of disability and incapacity that disrupts working, family and social life. Relapses can have a significant impact on quality of life [Orme et al. 2007]. In addition, studies have demonstrated a significant effect of relapses in producing disability early in the disease course [Lublin, 2011]. A higher relapse rate has been shown to be associated with a shorter time to fixed disability (EDSS 6) and to onset of secondary progressive disease [Lublin, 2011]. In the teriflunomide clinical trials a relapse was defined as the appearance of a new clinical sign or symptom, or clinical worsening of a previous sign or symptom that had been stable for at least 30 days and that persisted for a minimum of 24-48 hours in the absence of fever. Confirmed relapses required an increase of 1 point in each of two EDSS functional-system scores or of 2 points in one EDSS functional-system score (excluding bowel

			increase in EDSS score of ≥1.0 in patients with a baseline EDSS score of ≤5.5 or an increase in EDSS score of ≥0.5 in patients with a baseline EDSS score of ≤5.5). **Treatment emergent adverse events** were reported in all patients. Both relapse and disability assessments were made by the treating (blinded) neurologist	and bladder function and cerebral function) or an increase of 0.5 points in the EDSS score from the previous clinically stable assessment; if the EDSS score was previously 0, an increase in EDSS score of 1 point was required. **Disability** The EDSS is the most accepted tool to measure disability and is a 10-point instrument that measures different areas of functional disability in the lower half of the scale and focuses on hard ambulatory disability in the latter half [Kurtzke, 1983]. A score of 6 on the EDSS is considered an important milestone as it represents the onset of walking disability and has implications for the suitability of treatment with DMTs [ABN, 2009]. Recording **treatment emergent adverse events** is routine during clinical trials of new therapeutic agents.

Trial no. (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
LTS6048, HMR1726D/2002 **Phase 2 extension** (Confavreaux)	• The primary objective was to assess the long-term safety of teriflunomide in patients with RMS.	Long-term monitoring and assessment of safety and tolerability for a new therapeutic product is standard practice.	• Secondary objectives were to assess the long-term efficacy of teriflunomide in terms of relapse rate, disability accumulation, magnetic resonance imaging (MRI) outcomes and quality of life.	See detail above for Study 2001 Phase 2 trial **Quality of life (QoL)** assessments are not routine in clinical practice however form an integral part of assessing therapeutic interventions for cost effectiveness analyses. Validated instruments (Multiple Sclerosis Quality of Life-54 (MSQoL-54) and Fatigue Impact Scale (FIS)) were used to perform QoL assessments every 24 weeks.
EFC6049/ TEMSO [O'Connor et al. 2011]	Annualised relapse rate; a relapse was defined as the appearance of a new clinical sign or symptom, or clinical worsening of a previous sign or symptom that had been stable for at least 30 days and that persisted for a minimum of 24 hours in the absence of fever. Confirmed relapses required an increase of 1 point in each of two EDSS functional-system scores or of 2	See details above for Study 2001 Phase 2 trial **(Clinical measures: measuring relapse rate)**	Change in EDSS scores to assess progression of disability. The key prespecified MRI end point was total lesion volume. Other MRI end points included the number of gadolinium-enhancing lesions on T1-weighted images, the volume of hypo intense lesion components on T1-weighted images, the number of unique active lesions (defined as the number of gadolinium-enhancing lesions on T1-weighted images or new or enlarged lesions on T2-weighted images, without double counting), and brain atrophy. Patient-reported fatigue, assessed with the use of the Fatigue Impact Scale (FIS)	See detail above for Study 2001 Phase 2 trial See detail above for Study 2001 Phase 2 trial See detail above for LTS6048 Phase 2 extension

	points in one EDSS functional-system score (excluding bowel and bladder function and cerebral function) or an increase of 0.5 points in the EDSS score from the previous clinically stable assessment.			

Trial no. (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
LTS6050, 2006-003361-14 **Phase 3 extension to TEMSO** [CSR]	• To document the long-term safety and tolerability of two doses of teriflunomide in MS patients with relapses • See Table B6.3.1 for details of measurements	Long-term monitoring and assessment of safety and tolerability for a new therapeutic product is standard practice.	• To document the long-term effect on disability progression (key secondary endpoint), annual relapse rate, and MRI variables	See detail above for Study 2001 Phase 2 trial
EFC10891/ TENERE [CSR]	• Time to failure, with failure being defined as either relapse or permanent study treatment discontinuation for any cause whichever comes first. • See Table B6.3.1 for details of measurements	See details above for Study 2001 Phase 2 trial **(Clinical measures: measuring relapse rate)** In practice patients may discontinue treatment for a number of reasons: lack of efficacy, tolerability problems, adverse events or lack of concordance which may be multi-factorial. Ideally, therapy with a DMT will delay or prevent relapse; in TENERE 'failure' was therefore a definition applied to relapse OR any other reason for permanently discontinuing therapy.	• Frequency of relapses • FIS (fatigue) • Patient's satisfaction with treatment (using TSQM) • See table B6.3.1 for details on measurements • Safety and tolerability	See details above for Study 2001 Phase 2 trial **(Clinical measures: measuring relapse rate)** Although completion of the FIS and TSQM are not part of routine practice they are validated instruments allowing for reliable assessment of patient fatigue and treatment satisfaction; the latter becomes especially important when considering treatment adherence. Monitoring and assessment of safety and tolerability for a new therapeutic product is standard practice.
EFC10531/ TOWER [CSR;	• Annualised relapse rate • See Table B6.3.1	See details above for Study 2001 Phase 2 trial **(Clinical measures: measuring relapse**	• Disability progression • Other secondary outcome measures included:	See detail above for Study 2001 Phase 2 trial

clinicaltrials.gov]	for details of measurements	**rate)**	○ FIS (fatigue) ○ Health-related quality of life, a measure of the impact of a patient's health on his or her overall well being (using SF-36) • Safety and tolerability of teriflunomide • See Table B6.3.1 for details of measurements	**Quality of life (QoL)** assessments are not routine in clinical practice however form an integral part of assessing therapeutic interventions for cost effectiveness analyses. For details on FIS and SF-36 see table B6.3.1. Long-term monitoring and assessment of safety and tolerability for a new therapeutic product is standard practice.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B6.3.7 Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Study 2001, HMR1726D/2001 **"Proof of Concept"** **Phase 2** [O'Connor et al. 2006]	To determine the safety, efficacy and optimal oral administration dose of teriflunomide in patients with multiple sclerosis with relapses.	For the primary efficacy variable (mean number of CU active lesions per MRI scan), active treatment groups were compared with placebo using rank analysis of covariance (ANCOVA) with treatment, stratum (EDSS at baseline ≤3.5 vs. >3.5), and pooled center as fixed effects and the ranked mean pre-randomization number of CU active lesions as the covariate. Other MRI and change from baseline variables (EDSS) were assessed by ANCOVA with treatment, stratum, and pooled center as fixed effects and baseline score as the covariate. Progression and relapse rates were tested with the Cochran–Mantel–Haenszel procedure. For the secondary variables, unadjusted probabilities were presented. Safety variables were analyzed using descriptive statistics. In addition, for the cumulative number of unique active lesions, a last observation- carried-forward (LOCF) analysis was undertaken such that when a result for a scan was not available at a visit, the result from the previous visit could then be used.	207 patients enrolled 179 patients randomised Fifty-four evaluable patients per treatment group were considered sufficient to detect with 90% power an effect size of 0.32 using a two-sided Wilcoxon rank sum test and an α level of 0.05. This effect size for the Wilcoxon rank sum test corresponds to a parametric effect size (i.e., difference in means divided by the SD) of 0.67. Anticipating a 10% dropout rate, it was considered necessary to randomize 60 patients per treatment group for a total of 180 patients.	The primary analysis populations were the intent-to-treat (ITT) population (all randomised patients) and the safety evaluable population (all randomised patients who received one or more doses of study medication). The secondary analysis population was the efficacy evaluable (all randomised patients for whom there was at least one on-treatment MRI assessment and including all data collected during the period from baseline to the last day of study medication +14 days inclusively). Burden of disease, as measured by T2 lesion volume, was assessed in the completer population, which consisted of efficacy-evaluable patients who completed 231 days of treatment (i.e., the earliest day for visit 10 [36 weeks]) and who had an MRI scan at visit 10. Results in the efficacy-evaluable population were consistent with the ITT results reported. Data management and statistical analyses were conducted by sanofi-aventis and Accovion GmbH (Eschborn, Germany). An independent Data Safety Monitoring Board was responsible for overseeing the data and the safety of patients participating in the study.

				Withdrawals: in all cases, the reason for withdrawal was to be recorded in the case report form and in the subject's medical record. The subject was to be followed up to establish whether the reason was an adverse event, and if so, this was to be reported. As far as possible, all examinations scheduled for the final study day were to be performed on all subjects who received study medication but who did not complete the study according to protocol. Subjects who stopped taking study medication but did not withdraw their consent were encouraged to continue the efficacy and safety assessments as if they were on study medication. Data from these subjects were to be included in the intent-to-treat analyses.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
LTS6048, HMR1726D/2002 **Phase 2 extension** [Confavreux et al. 2012]	To assess the long-term safety and efficacy of teriflunomide in patients with RMS.	Results are based on an interim analysis with an arbitrary cut-off of January 8 2010. The duration of teriflunomide exposure for each patient during both the core study and extension was evaluated. In accordance with the statistical analysis plan, **no formal statistical tests were performed on the efficacy data**. Efficacy evaluations were performed on the intention-to-treat population, defined as all randomised patients who were exposed to the study drug in the extension. Efficacy data are presented as four treatment groups according to treatment allocation at randomisation and re-allocation at the start of the extension (i.e. placebo/7 mg, placebo/14 mg, 7 mg/7 mg or 14 mg/14 mg Continuous data are summarised using the mean and standard deviation, and categorical data by number and percentage. ARR was calculated as the ratio of the total number of relapses observed and the total patient-years of treatment during the extension.	n=147 (continued from main study) As this was a continuation study, power calculations were not part of the planning/design process.	Efficacy evaluations were performed on the intention-to-treat population, defined as all randomised patients who were exposed to the study drug in the extension. Withdrawals: For early withdrawals, the endpoint value was defined as the value collected at the last day/time of the last dose of study drug. If this value was missing, this endpoint value was the closest one prior to the last dose intake. The worst value was defined as the nadir and/or the peak post baseline (up to last dose) according to the direction (minimum or maximum) of the abnormality as defined in the potentially clinically significant abnormality list.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
EFC6049, HMR1726D/3001, 2004-000555-42 **TEMSO Phase 3** [O'Connor et al. 2011]	To evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients with relapsing multiple sclerosis	All analyses were performed according to a modified intention-to-treat principle. The modified intention-to-treat population comprised patients who underwent randomization and were exposed to study medication for at least 1 day. All inferential analyses were performed at the two sided 5% level of significance.	n=1088 A sample of 360 randomly assigned patients per group was required to provide 95% statistical power to detect relative risk reductions of 25% in the annualised relapse rate after 2 years, assuming an annualised relapse rate of 0.74 for the group receiving placebo and a standard deviation of 0.626.	The study protocol was developed by the sponsor (Sanofi-Aventis), with guidance from a steering committee of international experts on multiple sclerosis. The study was overseen by an independent data-monitoring committee. Data were collected by the investigators and analyzed by the sponsor. The authors were assisted by an independent medical-writing-services agency paid by the sponsor. The first draft of the manuscript was developed by the two lead academic authors, with input from the sponsor. The two lead academic authors made the decision to submit the manuscript for publication, in concert with the other authors. All authors vouch for the accuracy and completeness of the data, the statistical analysis, and the fidelity of the study to the trial protocol. During the study, the investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data. All analyses were performed according to a modified intention-to-treat principle. The modified intention-to-treat population comprised patients who underwent randomization and were exposed to study

				medication for at least 1 day. Withdrawals: For early withdrawals, the endpoint value was defined as the value collected at the day/time of the last dose of investigational product. If this value was missing, the endpoint value was the closest one prior to the last dose intake.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
LTS6050, 2006-003361-14 **TEMSO Phase 3 extension** [CSR]	To document the long-term safety and tolerability of two doses of teriflunomide (7 and 14 mg) in MS patients with relapses.	The Kaplan-Meier method was used to estimate median time (if estimable) to disability progression, disability progression rate over time and proportion of patients free of disability specific to each treatment group, based on ITT (EFC6049+LTS6050) population. Kaplan-Meier graphs were generated; quartiles and point probabilities were calculated. Interval estimates were calculated using 95% point wise confidence intervals (CIs). The main analysis was time to disability progression sustained at least for 12 weeks. A supportive analysis was done using time to disability progression sustained at least for 24 weeks. These analyses were based on the combined data of EFC6049/TEMSO and LTS6050. The analysis for the ARR was performed using a Poisson regression model with robust error variance to accommodate the potential over-dispersed data appropriately. The time to first confirmed relapse was analyzed using log-rank with time to first relapse as the dependent variable, treatment group as test variable, and region and baseline EDSS strata as covariates. Hazard ratios were estimated using Cox regression model with treatment group, region and baseline	n=742 (continued from main study) (54 patients who completed TEMSO did not continue to the extension study (placebo n=22; 7mg n=22; 14mg n=10)) As this was a continuation study, power calculations were not part of the planning/design process.	Regular site monitoring ensured the quality of trial conduct. Management of clinical trial data was performed according to the following rules and procedures. Data entry, verification, and validation were carried out using standard computer software (Clintrial version 4.5.3). Data were stored in an Oracle database on a secure server. A double-entry method was used to ensure that the data (except comments) were transferred accurately from the CRFs to the database. Moreover, every modification in the database could be traced using an audit trail. A data validation plan was established to define all automatic validation checks as well as supplemental manual checks to ensure data quality. All discrepancies were researched until resolution. The sanofi-aventis cross-functional clinical trial team devised a Data Review Plan which defined data tables and listings for review. Trial data was reviewed for quality, serious Good Clinical Practice noncompliance, and deviations. Specific medical review was performed on selected patients to address any safety or efficacy concerns and identify any signals of potential scientific misconduct. Sanofi-aventis conducted Investigator meetings and training sessions for clinical research associates as well as individual site initiation meetings to develop a

		EDSS strata as covariates. The analysis was based on LTS6050 data only. Estimates of the proportion of patients free of relapse at selected time points were derived using Kaplan-Meier method (as described for time to disability progression). The analysis was based on LTS6050 data only. Descriptive statistics were used to report analysis of MRI variables and changes from baseline in other measureable variables		common understanding of the clinical study protocol, CRF, and study procedures. The randomised patients were all patients for whom a patient number and a treatment kit number were allocated according to the randomization process and recorded in the IVRS database. The patients treated without being randomised were not to be considered as randomised and therefore were not included in any efficacy or safety population. Efficacy populations - Intent-to-treat (ITT) populations The ITT (EFC6049+LTS6050) population was defined as all patients randomised in both EFC6049/TEMSO and LTS6050 studies that had at least 1-day IP exposure during both EFC6049/TEMSO and LTS6050 studies. All patients were analyzed in the treatment group to which they were randomised. The ITT (EFC6049+LTS6050) population was the primary analysis population for disability progression and EDSS. The ITT (LTS6050) population was defined as all patients randomised in the LTS6050 study that had at least 1-day IP exposure during the LTS6050 study. All patients were summarised in the treatment group to which they were randomised. Withdrawals: handled as per TEMSO study.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
EFC10891, 2008-006226-34, **TENERE** **Phase 3** [CSR]	To assess the efficacy and safety of 2 doses of teriflunomide in comparison to interferon beta-1a in patients with patients with relapsing multiple sclerosis.	Continuous data were summarized using number of available data, mean, standard deviation (SD), minimum, median, and maximum for each treatment group. Categorical and ordinal data were summarised using number and percentage of patients in each treatment group. Parameters were summarized on the ITT and safety population and analyzed in the treatment group to which they were randomised. Demographic characteristics were summarized by treatment group and overall using descriptive statistics. Other baseline safety and efficacy parameters, described in efficacy and safety sections, along with the summary statistics were presented. Medical and surgical history was summarized by primary system organ class (SOC) and preferred term (PT) for each treatment group. No statistical test was performed on	N=324 (321 treated) The sample size estimation was based on the comparison between teriflunomide and interferon beta 1a with regard to the primary endpoint: time to failure, defined as relapse or permanent study treatment discontinuation for any cause. Patients were randomised using a 1:1:1 randomization ratio for teriflunomide 14 mg: teriflunomide 7 mg: interferon-beta 1a. With 100 randomised patients per arm, the study had 81% power to detect a difference between teriflunomide and interferon-beta 1a in time to failure at the 2-tailed significance level of α=0.025, assuming that the hazard rate was 0.4186 and 0.7440 for teriflunomide and interferon-beta 1a, respectively, and that the recruitment duration was approximately 1.5 years. The significance level was specified for the multiplicity consideration. The calculation of hazard ratios was based on the prior experience with teriflunomide and interferon-beta 1a showing proportions of patients with relapse at 1 year of 30% and 46% for teriflunomide and interferon-beta 1a, respectively and with premature	Regular site monitoring ensured the quality of trial conduct. Management of clinical trial data was performed according to the following rules and procedures. Data entry, verification, and validation were carried out using standard computer software (Oracle® Clinical 4.5); data were stored in an Oracle database. A double-entry method was used to ensure that the data (except comments) were transferred accurately from the CRFs to the database. Moreover, every modification in the database could be traced using an audit trail. A data checking plan was established to define all automatic validation checks, as well as supplemental manual checks, to ensure data quality. All discrepancies were researched until resolved. Sanofi-aventis conducted Investigator meetings to develop a common understanding of the clinical study protocol, CRF, and study procedures as well as individual site initiation meetings. Intent-to-treat (ITT) population was defined as all randomised patients. Patients were analyzed in the treatment group to which they were randomised. Safety population was defined as all randomised patients exposed to the study medication, regardless of the amount of treatment administered. Randomized patients for whom it was unclear whether they took the study medication were included in the safety population. Withdrawals: All study withdrawals were recorded by

		demographic and baseline characteristic data.	treatment discontinuation rate at 1 year of 6% and 12% for teriflunomide and interferon-beta 1a, respectively. These ratios were also extrapolated with respect to the treatment duration and conditions of study. Other assumptions included that the time-to-event was exponentially distributed with a constant hazard rate and that the relapse and discontinuation were competing risks. The power was calculated by using nQuery Advisor® 6.01.	the Investigator in the appropriate pages when considered as confirmed. The Investigator made every effort to re-contact the patient, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including at least his/her vital status, and last treatment date if applicable. Patients who did not complete the study and for whom no end of treatment data were available were considered as lost to follow-up.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
EFC10531, 2007-004452-36, **TOWER** **Phase 3** [CSR]	To evaluate the effect of two doses of teriflunomide on the frequency of relapses in patients with relapsing multiple sclerosis.	All inferential statistical analyses were performed at the 2-sided 5% level of significance, except when noted otherwise. Analyses were performed on both an ITT and per protocol population.	N=1169 The sample size calculations were based on a 1:1:1 randomization ratio for teriflunomide 14 mg, teriflunomide 7 mg, and placebo and the primary and key secondary efficacy variables of ARR and time to (first) sustained disability progression, respectively, with the following assumptions: • Placebo ARR of 0.74 (based on recently available MS data, where the placebo 2-year relapse rate was estimated to be 1.48) • A 25% relative risk reduction in ARR, (i.e., ARR of 0.55, for teriflunomide) • Number of relapses follows approximately Poisson distribution with over dispersion parameter of 1.3 (estimated with recently available data on Tysabri® trials and protocol for Study 2001) • A 1.5-year recruitment period with linear recruitment rate, thus the average exposure duration for ongoing patients is 1.75 years • A 2-tailed 5% significance level • Expected drop-out rate = 20%	Regular site monitoring ensured the quality of trial conduct. Management of clinical trial data for this paper-based study was performed according to the following rules and procedures. Data entry (double-entry method) and validation were contracted to pharmanet/I3 and were carried out using standard validated data capture computer software (Oracle Clinical version 4.5). Every modification in the database was traced using an audit trail. Sanofi conducted Investigator meetings and training sessions for clinical research associates as well as individual site initiation meetings to develop a common understanding of the clinical study protocol, CRF, and study procedures, in compliance with good clinical practices. Four analysis populations were defined for this study: ITT, per protocol (PP), safety, and pharmacokinetic (PK). The ITT population comprised all randomised patients who had at least one dose of study treatment. The ITT population was used for the analyses of all efficacy variables. Patients were analyzed in the treatment group to which they were randomised. The PP population comprised a subset of the ITT population that contained patients without a major efficacy related protocol deviation. The PP population was only used for the analysis of the primary efficacy and key secondary variables. The criteria for major protocol deviations were non-exposure to drug, patients not meeting inclusion criteria, irregularities in randomisation / treatment allocation, poor

			Based on the assumptions above, a total of 1110 patients (370 per treatment group) were needed for the study and had 94% power to detect a 25% relative risk reduction in ARR. Calculations were made using internally-developed statistical programs. In addition, the study had 75% power to detect a 37% hazard ratio reduction in time to disability progression using log-rank test. The sample size and power estimate was computed using EAST 4.0 with the assumptions of a hazard rate of 0.1783 in the placebo group, and 0.1116 in the teriflunomide group (i.e. 30% probability of disability progression for placebo patients by the end of 2 years, and 20% for teriflunomide patients). The sample size was also adjusted for a 20% drop out rate.	compliance, prohibited concomitant medication. The safety population was a subset of all randomised patients who received at least 1 dose or partial dose of investigational product. The PK population was a subset of the safety population and comprised patients who had at least one PK sample taken. Withdrawals: All study withdrawals were recorded by the Investigator in the appropriate pages when considered as confirmed. The Investigator made every effort to re-contact the patient, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including at least his/her vital status, and last treatment date if applicable. Patients who did not complete the study and for whom no end of treatment data were available were considered as lost to follow-up.

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

Re: TEMSO: subgroup analyses were performed for annualised relapse rate (ARR) and disability progression by baseline demographics (gender, race and age), disease characteristics (Expanded Disability Status Scale (EDSS) strata, relapse history, multiple sclerosis (MS) subtype), MRI parameters (gadolinium-enhancing lesions, total lesion volume) and prior use of MS drugs [Miller et al. 2012].

A generalised estimating equation method and Cox regression model were used to assess consistency of the treatment effect across subgroups, utilising a treatment-by-subgroup interaction test for each factor separately. Reductions in ARR and disability progression were consistent across subgroups in favor of teriflunomide, with no treatment-by-subgroup interaction test reaching statistical significance [Miller et al. 2012].

Additionally, post-hoc subgroup analyses beyond the scope of the original clinical trial protocols were performed for patients with rapidly evolving severe disease (RES) and highly active (HA) disease. These analyses were performed in response to the scope of the decision problem proposed by NICE. The RCT trial programme did not specify these groups at trial inception for separate analyses.

The sub-group analyses were performed on data from the Phase III TEMSO population as this most closely represents the respective population definitions from previous NICE guidance (i.e. RES: defined by two or more disabling relapses in one year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with previous MRI; HA: defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial MRI or at least one gadolinium-enhancing lesion. A "nonresponder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year) [NICE, 2007(a); NICE, 2012(a)]

Participant flow

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

Please note: throughout the clinical trial programme for teriflunomide, two doses 7mg and 14mg were trialled. Ultimately, teriflunomide 14mg daily has been approved by the CHMP for use in practice. Therefore, although CONSORT diagrams are shown including the 7mg dose, the clinical data discussed within this submission relates to the 14mg dose only.

Phase II "proof of concept"

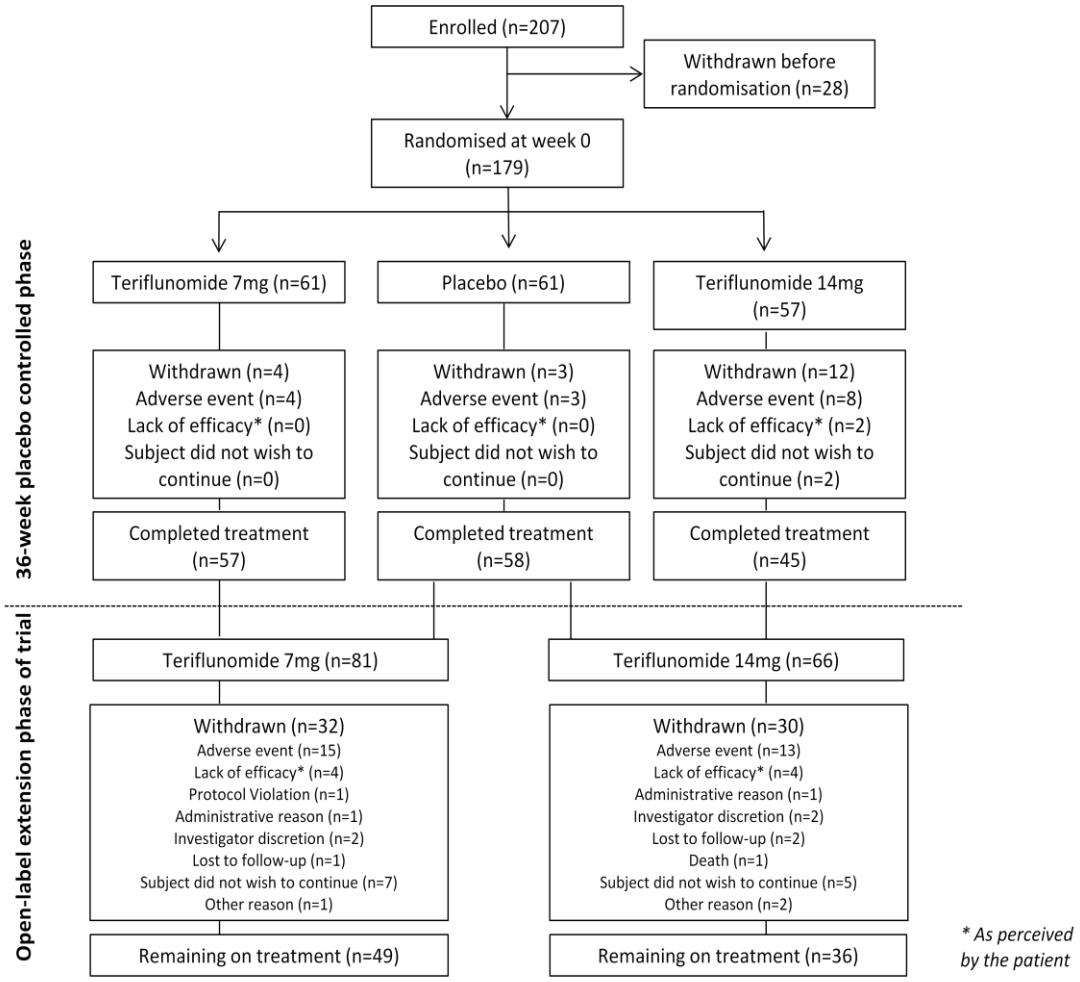
Patients were not permitted to cross to another treatment group during the course of the study.

A higher proportion of patients withdrew (largely due to adverse events) from the teriflunomide 14mg arm vs. teriflunomide 7mg or placebo, however there were no significant between group differences in TEAEs and no permanent morbidity was observed for any patients withdrawing from treatment due to adverse events [O'Connor et al. 2006].

At the point of entering the optional extension of the Phase II study, patients previously receiving placebo were randomised (according to a pre-defined schedule) to active treatment with teriflunomide 7mg or 14mg. Patients who received active treatment during the main trial continued at the same dose [Confavreux et al. 2012].

During the extension phase, rate of withdrawal has been similar across both teriflunomide groups. TEAEs were similar in both groups.

Figure 6.3.1 Phase II "proof of concept" participant flow

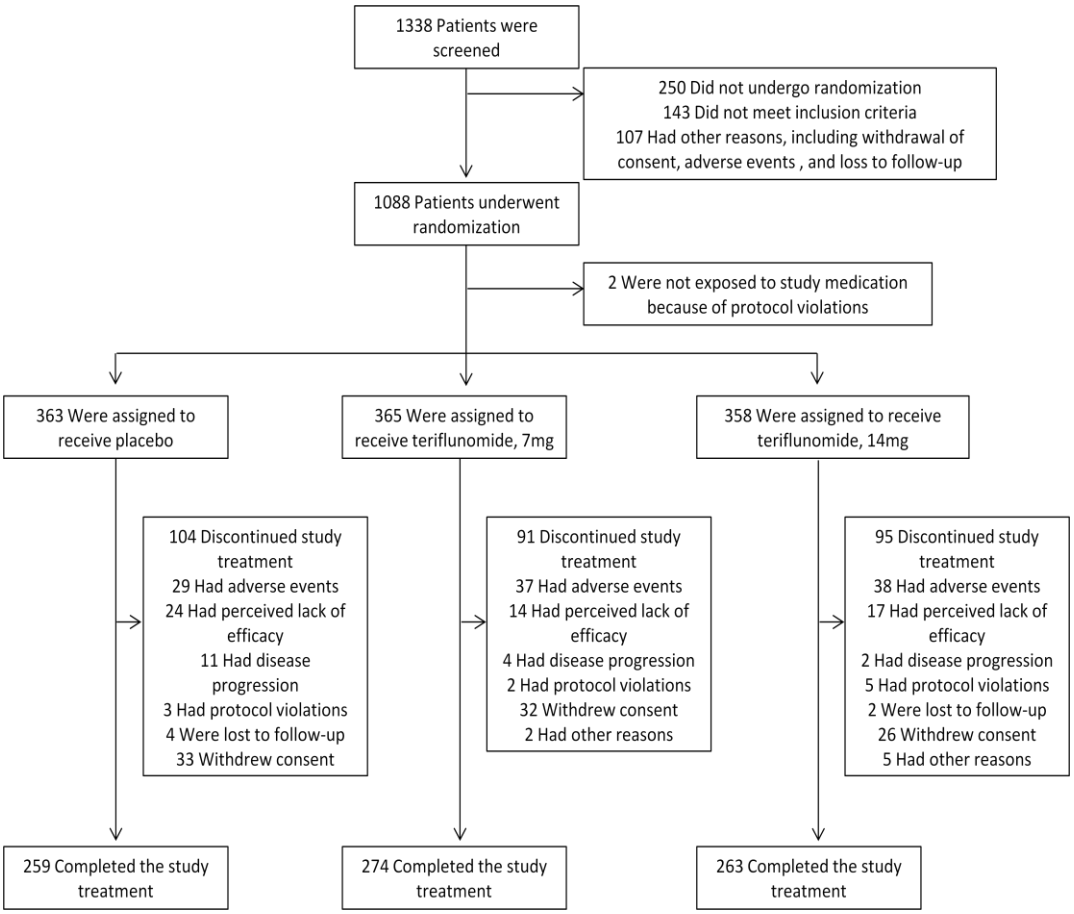


TEMSO [O'Connor et al. 2011]

Patients were not permitted to cross to another treatment group during the course of the study.

Similar proportions of patients withdrew from treatment during the course of the study; withdrawal due to adverse events was non-significantly higher in the active arms and withdrawal due to disease progression was significantly lower in the teriflunomide 14mg arm vs. placebo (p=0.02). Of the patients who discontinued the study medication prematurely, 31, 22, and 20 patients in the placebo, lower-dose teriflunomide, and higher-dose teriflunomide groups, respectively, completed the planned follow-up.

Figure 6.3.2 TESMO participant flow

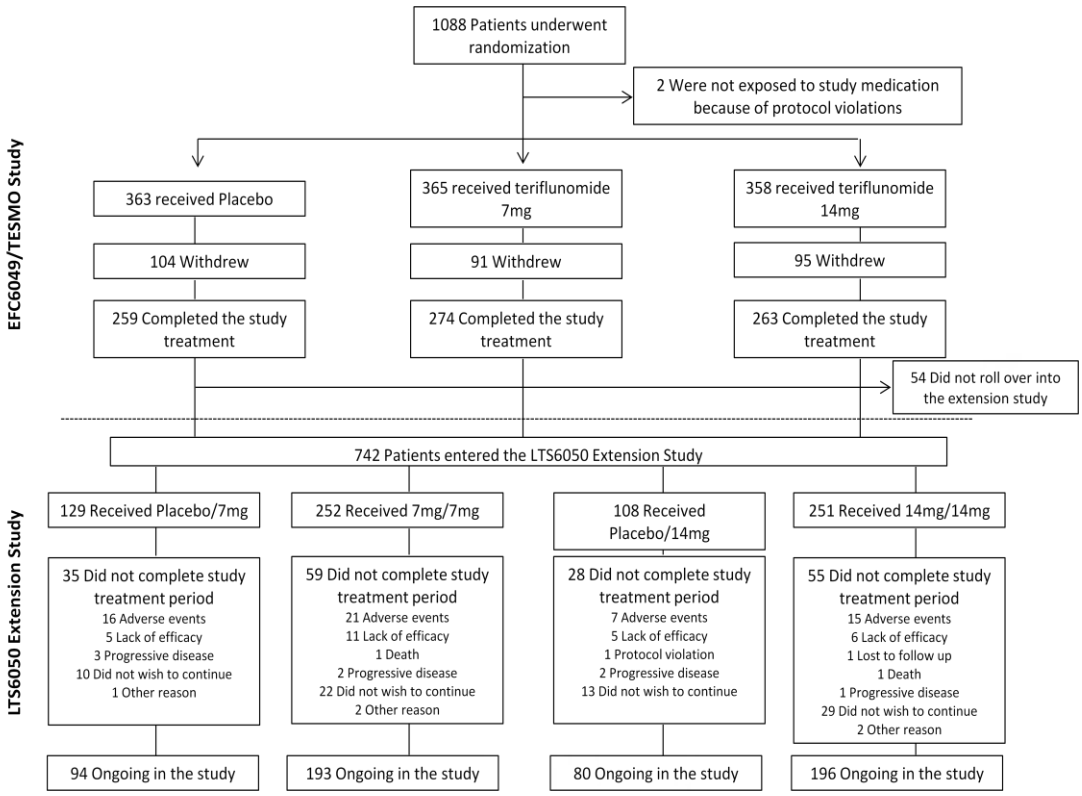


TEMSO extension (adapted from the TEMSO extension Clinical Study Report)

At the point of entering the optional extension of the TEMSO study, patients previously receiving placebo were randomised to active treatment with teriflunomide 7mg or 14mg. Patients who received active treatment during the main trial continued at the same dose. Treatment administration remained double-blind.

Similar proportions of patients withdrew from study treatment across the four arms, with adverse events the most common reason for treatment discontinuation. Adverse events were less common in the teriflunomide 14mg groups than the 7mg groups.

Figure 6.3.3 TESMO extension participant flow



TENERE [adapted from the TENERE Clinical Study Report]

Patients were not permitted to cross to another treatment group during the course of the study.

TENERE participant flow

TOWER [adapted from the TOWER Clinical Study Report]

Patients were not permitted to cross to another treatment group during the course of the study.

TOWER participant flow

6.4 Critical appraisal of relevant RCTs

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

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

6.4.3 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 B6.4.1 Quality assessment results for RCTs

Trial no. (acronym)	Phase II "Proof of Concept" Study 2001 [O'Connor et al. 2006]	TEMSO	TENERE	TOWER
Was randomisation carried out appropriately?	Yes	Yes	[redacted]	[redacted]
Was the concealment of treatment allocation adequate?	Yes. The investigator randomised eligible subjects at visit 3 after completion of all baseline assessments Each subject entering the study at screening (visit 1) was assigned a 5-digit number that was used to identify the subject throughout the study. The first 2 digits represented the investigator (center) number; the last 3 digits represented the consecutive subject number within the respective center. The investigator documented the randomization number in the case report form and the subject's records. Each subject was only to be given the medication carrying his or her randomization number. A randomization schedule was generated by the sponsor. The schedule linked sequential numbers to treatment codes allocated at random. The schedule was prepared on a 1:1:1 basis with blocks of 6	Yes, patients were centrally randomised at visit 3 via an interactive voice response system (IVRS). Study medication was dispensed by treatment kits with pre-printed 5-digit medication kit numbers randomly assigned by the IVRS. Every 12 weeks during the study, the investigational site was to contact the IVRS to allocate a new medication kit number to a patient that corresponded to the treatment designated by the randomization number; each patient received a total of 9 medication kits.	[redacted]	[redacted]

Trial no. (acronym)	Phase II "Proof of Concept" Study 2001 [O'Connor et al. 2006]	TEMSO	TENERE	TOWER
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	[redacted]	[redacted]
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, the trial was double-blind. Patients and the treating neurologists were blinded to treatment allocation. A blinded neurologist assessed relapses and disability measures. MRI scans were evaluated by blinded physicians.	Yes, the trial was double-blind. Patients, treating neurologists, and examining neurologists were unaware of treatment assignments. MRI scans were examined at a central location.	[redacted]	[redacted]
Were there any unexpected imbalances in drop-outs between groups?	Yes, there were more discontinuations in the teriflunomide 14-mg/day group than in the other groups (12 for 14mg vs. 4 for 7mg and 3 for placebo)	No	[redacted]	[redacted]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	[redacted]	[redacted]
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: ITT was used for the primary analysis population and missing data was accounted for	Yes: ITT was used for patients who underwent randomisation and received study medication for at least 1-day. Missing data was accounted for.	[redacted]	[redacted]

	Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

6.5 Results of the relevant RCTs

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

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

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

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio 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.

Table B6.5.1 (Comparative) summary of results of the Phase II and Phase III RCTs

Please note: Expanded trial results reporting primary and secondary outcomes of all trials are available in Additional Appendix 1.

Presented results are for the licensed dose of teriflunomide (14mg o.d.) unless otherwise stated. Teriflunomide 7mg o.d. though used within the clinical trial setting is not licensed for use. Severity of relapse data was not collected during the teriflunomide Phase II/III trials and therefore cannot be reported in response to the decision problem.

For the outcome entitled "Freedom of Disease Activity"- there is no clear clinical consensus on the definition of this. In practice, we understand it to be a relapse-free period where evidence of disease progression is also absent. In practical measurement terms, MRI results can be included in this composite as a practical demonstration of stable or improved disease as assessed by MRI scan. Since relapse rates and disability measures are captured as discrete outcomes, we have reported MRI data available from the Phase II/III trial program to support the concept of freedom of disease activity.

Outcomes of relevance to the decision problem	**Phase II "Proof of Concept"** Study 2001 [O'Conner et al. 2006]	**Phase II extension** Phase 2 extension to LTS6048 [Confavreux et al. 2012] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TEMSO extension** Phase 3 extension to TEMSO [CSR analysis cut-off January 2011] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TENERE** EFC10891 [Vermersch et al. 2012; CSR Dec 2011]	**TOWER** EFC10531 [CSR, Kappos et al. 2012]
Patient numbers	Teriflunomide 14mg o.d. n=57 Placebo n= 61	Teriflunomide 14mg/14mg o.d. n=40 Placebo/Teriflunomide 14mg o.d. n= 26	Teriflunomide 14mg o.d. n=358 Placebo n= 363	Teriflunomide 14mg/14mg o.d. n=251 Placebo/Teriflunomide 14mg o.d. n= 108	Teriflunomide 14mg o.d. n=111 IFNβ-1a n=104	Teriflunomide 14mg o.d. n=370 Placebo n= 388
Analyses	ITT population over 36 weeks	372 week open-label evaluation period	Modified ITT population 108 week study period	ITT	ITT analysis Study had a fixed end; range of treatment duration for completers = 49-114 weeks [Vermersch et al. 2012]	ITT analysis Study had a fixed end; range of treatment duration for completers = 48-152 weeks [Kappos et al. 2012]

Outcomes of relevance to the decision problem	**Phase II "Proof of Concept"** Study 2001 [O'Conner et al. 2006]	**Phase II extension** Phase 2 extension to LTS6048 [Confavreux et al. 2012] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TEMSO extension** Phase 3 extension to TEMSO [CSR analysis cut-off January 2011] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TENERE** EFC10891 [Vermersch et al. 2012; CSR Dec 2011]	**TOWER** EFC10531 [CSR, Kappos et al. 2012]
Primary trial outcome	MRI results – see Freedom of disease below	Safety and tolerability: see below Discontinuations due to TEAEs occurred for 19.7% of patients in the 14mg teriflunomide group. 13.6% of patients discontinued study treatment due to SAEs.	ARR see below	Safety and tolerability: see also below. [redacted]	Time to failure (confirmed relapse or permanent study discontinuation): 42 (37.8%) patients with failure vs. IFNβ-1a 44µg 3xweek 44 (42.4%); [redacted]	ARR see below

Outcomes of relevance to the decision problem	**Phase II "Proof of Concept"** Study 2001 [O'Conner et al. 2006]	**Phase II extension** Phase 2 extension to LTS6048 [Confavreux et al. 2012] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TEMSO extension** Phase 3 extension to TEMSO [CSR analysis cut-off January 2011] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TENERE** EFC10891 [Vermersch et al. 2012; CSR Dec 2011]	**TOWER** EFC10531 [CSR, Kappos et al. 2012]
Relapse rate	ARR (mean ±SD) = 0.55 ± 1.12 (vs. 0.81 ±1.22 for placebo; NS) = 32% reduction in ARR	ARR for patients on teriflunomide 14mg throughout the study and extension = 0.181	Adjusted ARR (95% CI) = 0.37 (0.31-0.44) vs. 0.54 for placebo (0.47-0.62) 31.5% relative reduction vs. placebo (p<0.001)	[redacted]	Adjusted ARR (95% CI) = 0.259 (0.153, 0.438) vs. IFNβ-1a 44µg, 0.216 (0.113, 0.415) Relative risk (95% CI) = 1.197 (0.623, 2.299) vs. IFNβ-1a , p=0.5896	Adjusted ARR (95% CI) =0.319 (0.267, 0.381) Relative risk (95% CI) = 0.637 (0.512, 0.793) vs. placebo, p=0.0001
Severity of relapse	Not reported	Not reported	Teriflunomide 14mg significantly reduced the annualised rate of relapse leading to hospitalisation by 59%, p<0.0001 vs. placebo [Miller A et al. 2012]	Not reported	Not reported	Patients treated with teriflunomide 14 mg spent significantly fewer nights in hospital for relapse (1.7 nights/pt) compared with those patients receiving placebo (3.4 nights/pt; p=0.0285) [O'Connor et al. 2013]

Outcomes of relevance to the decision problem	**Phase II "Proof of Concept"** Study 2001 [O'Conner et al. 2006]	**Phase II extension** Phase 2 extension to LTS6048 [Confavreux et al. 2012] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TEMSO extension** Phase 3 extension to TEMSO [CSR analysis cut-off January 2011] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TENERE** EFC10891 [Vermersch et al. 2012; CSR Dec 2011]	**TOWER** EFC10531 [CSR, Kappos et al. 2012]
Disability (e.g. EDSS, sustained accumulation of disability for at least 12 weeks (SAD))	7.4% of patients showed an increase in EDSS at 36 weeks vs. baseline compared to 21.3% on placebo; p<0.04 =69% relative reduction No data re: SAD	Mean (SD) change in EDSS from baseline for patients on teriflunomide 14mg throughout the study and extension = 0.61 (1.11); median (min:max) change from baseline = 0.50 (–1.5:3.0) No data re: SAD	Change in EDSS scores not reported. SAD for at least 12 weeks = 20.2% (95% CI 15.6-24.7), vs. placebo 27.3% (22.3-32.3); p=0.03 Hazard ratio vs. placebo = 0.70 (95% CI 0.51-0.97)	[redacted]	[redacted]	[redacted] The estimated percentage of patients with 12-week SAD at Week 48 using the Kaplan-Meier method was 7.8% in the teriflunomide 14 mg group and 14.2% in the placebo group; at 132 weeks = 15.8% and 21.0% respectively. HR vs. placebo = 0.685 (0.467, 1.004), p=0.0442 [redacted]

				[redacted]	[redacted]	[redacted]

Outcomes of relevance to the decision problem	**Phase II "Proof of Concept"** Study 2001 [O'Conner et al. 2006]	**Phase II extension** Phase 2 extension to LTS6048 [Confavreux et al. 2012] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TEMSO extension** Phase 3 extension to TEMSO [CSR analysis cut-off January 2011] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TENERE** EFC10891 [Vermersch et al. 2012, CSR Dec 2011]	**TOWER** EFC10531 [CSR, Kappos et al. 2012]
Symptoms of MS (e.g. fatigue, cognition and visual disturbance)	Not reported	Not reported	Patients reported only small changes from baseline in fatigue as reflected by FIS scores, with no significant differences between teriflunomide 14mg and placebo, (3.8±1.7 vs. 4.3±1.7; p=0.83)	[redacted]	FIS at 48 weeks Numerically lower change from baseline in LS mean for teriflunomide 14mg = 4.096 vs.9.099 for IFNβ-1a 44µg, 0.1789.	MMRM analysis of FIS scores numerically favoured teriflunomide (1.915 vs. 4.669 for placebo, no statistical significance). [redacted]

Outcomes of relevance to the decision problem	**Phase II "Proof of Concept"** Study 2001 [O'Conner et al. 2006]	**Phase II extension** Phase 2 extension to LTS6048 [Confavreux et al. 2012] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TEMSO extension** Phase 3 extension to TEMSO [CSR analysis cut-off January 2011] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TENERE** EFC10891 [Vermersch et al. 2012, CSR Dec 2011]	**TOWER** EFC10531 [CSR, Kappos et al. 2012]
Freedom of disease activity	There was a trend toward a greater proportion of relapse-free patients in the teriflunomide 14mg/day group compared with placebo (77 vs. 62%; p=0.098) at study end. Number of CU active lesions/scan (adjusted for baseline activity, EDSS strata and study site): Mean reduction vs. placebo -1.62 (95% CI -2.68 – 0.56) 61.3% relative reduction vs. placebo (p<0.01)	55.0% of patients (who had received teriflunomide 14mg throughout the study) were relapse-free at study reporting. New MRI lesion activity (new and newly enlarging T2 lesions, and newly active lesions) was higher in the placebo groups compared with the teriflunomide treatment groups at the end of the core study. This activity was reduced with teriflunomide treatment during the extension, where the number of newly active lesions appeared lower in the	60.6% of patients remained free of relapse at the end of study (vs. 49.3% of patients on placebo) (no p-value). Change in total lesion volume from baseline was significantly lower with teriflunomide (0.72ml±7.59) vs. placebo (2.21ml± 7.00); p<0.001. Patients on teriflunomide had significantly fewer gadolinium-enhancing lesions per T_1-weighted scan than those on placebo: 0.26 (95% CI 0.17–0.41) and 1.33 (95%	[redacted]	76.6% of patients remained relapse free at the end of the study period (vs. 84.6% for IFNβ-1a). MRI results were not reported.	[redacted] HR 0.631 (0.502, 0.794); p<0.0001 MRI results were not reported.

	Also – significant reductions in the median number of T1 enhancing lesions per scan and the median number of new or enlarging T2 lesions per scan over the 36-week treatment period (p<0.02 and p<0.03 respectively).	14-mg groups compared with the 7-mg groups; a similar pattern was observed for newly active T2 lesions.	CI1.06–1.67) respectively; relative risk 0.20 (95% CI 0.12–0.32) p<0.001. Fewer unique active lesions per scan were observed in the teriflunomide group vs. placebo: 0.75 (95% CI 0.58–0.99) and 2.46 (95% CI 2.10–2.89) respectively; p<0.001; relative risk 0.31 (95% CI 0.23–0.41) A post-hoc analysis of 'freedom from disease activity' (composite of relapse-free, disease progression free and MRI-activity free) showed 22.9% of patients on teriflunomide 14mg to be disease-activity free vs. 14.3% on placebo (no p-values reported)			

Outcomes of relevance to the decision problem	**Phase II "Proof of Concept"** Study 2001 [O'Conner et al. 2006]	**Phase II extension** Phase 2 extension to LTS6048 [Confavreux et al. 2012] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TEMSO extension** Phase 3 extension to TEMSO [CSR analysis cut-off January 2011] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TENERE** EFC10891 [Vermersch et al. 2012, CSR Dec 2011]	**TOWER** EFC10531 [CSR, Kappos et al. 2012]
Mortality	No deaths occurred.	One death reported over the study period in the teriflunomide 14mg group (underlying disease conditions and concomitant medications may have been contributory)	No deaths occurred.	[redacted]	No deaths occurred.	There were 2 deaths in the 14mg teriflunomide group. One patient committed suicide the other died of septicaemia. Neither case was considered related to the drug.

Outcomes of relevance to the decision problem	**Phase II "Proof of Concept"** Study 2001 [O'Conner et al. 2006]	**Phase II extension** Phase 2 extension to LTS6048 [Confavreux et al. 2012] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TEMSO extension** Phase 3 extension to TEMSO [CSR analysis cut-off January 2011] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TENERE** EFC10891 [Vermersch et al. 2012; CSR Dec 2011]	**TOWER** EFC10531 [CSR, Kappos et al. 2012]
Adverse effects	No significant between-group differences noted	The number of episodes of any TEAE and all types of SAE reported per patient over the study period was similar in both teriflunomide treatment groups (7mg and 14mg)	Similar proportions of patients in the placebo and 14mg teriflunomide groups had adverse events (87.5%, and 90.8% respectively) and serious adverse events (12.8%, and 15.9%) adverse events leading to discontinuation of the study medication (8.1% and 10.9%)	[redacted]	92.7% of patients reported an adverse event (vs. 96.0% for IFNβ-1a 44µg). 5.5% of patients had a SAE. (6.9% for IFNβ-1a 44µg)	86.3% of patients reported an adverse event (vs. 83.1% for placebo) 11.9% of patients had an SAE (12.2% for placebo)

Outcomes of relevance to the decision problem	**Phase II "Proof of Concept"** Study 2001 [O'Conner et al. 2006]	**Phase II extension** Phase 2 extension to LTS6048 [Confavreux et al. 2012] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TEMSO extension** Phase 3 extension to TEMSO [CSR analysis cut-off January 2011] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TENERE** EFC10891 [Vermersch et al. 2012; CSR Dec 2011]	**TOWER** EFC10531 [CSR; Kappos et al. 2012]
Discontinuation rate	Rate of discontinuation was12/57 (21.0%) (vs. 4/61, 7.0% for placebo). 8/56 (14.2%) discontinued treatment due to an adverse event (4/61, 7.0% for placebo)	Rate of discontinuation in the open label extension phase was 45.4%. 19.7% of patients discontinued treatment due to an adverse event.	95 patients (26.5%) discontinued treatment. 10.9% of patients had adverse events leading to discontinuation of the study medication (8.1% for placebo).	[redacted]	Rate of treatment discontinuation was 19.8% (28.8% for IFNβ-1a 44µg). 10.9% of patients discontinued treatment due to adverse events. (21.8% for IFNβ-1a 44µg)	Rate of treatment discontinuation was 33.9% (placebo 32.1%). 15.6% of patients discontinued treatment due to adverse events (6.7% for placebo).

Outcomes of relevance to the decision problem	**Phase II "Proof of Concept"** Study 2001 [O'Conner et al. 2006]	**Phase II extension** Phase 2 extension to LTS6048 [Confavreux et al. 2012] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TEMSO** EFC6049 [O'Connor et al. 2011]	**TEMSO extension** Phase 3 extension to TEMSO [CSR analysis cut-off January 2011] – Interim data. This trial extension remains open until teriflunomide is licensed.	**TENERE** EFC10891 [Vermersch et al. 2012; CSR Dec 2011]	**TOWER** EFC10531 [CSR; Kappos et al. 2012]
Health-related quality of life	Not reported	Not reported	No statistically significant treatment differences were observed in SF-36 or EQ-5D scores [CSR].	[redacted]	TSQM LS-mean global satisfaction score at Week 48 (higher score indicating better satisfaction) of 68.818 (SE 2.782) vs. IFNβ-1a (score = 60.975,(SE 2.942)), p=0.0162 This global satisfaction was related to a better satisfaction on each of the dimensions used in that instrument (effectiveness, side effect, and convenience)	For many of the SF-36 scores, the data numerically favoured the teriflunomide dose groups compared with placebo. However, for most analyses, differences did not reach statistical significance. [redacted]

6.6 Meta-analysis

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

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for 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).

There are three studies that can be considered for meta-analysis:

- STUDY 2001 Proof of Concept Phase II
- TEMSO
- TOWER

The following outcome measures are presented for the relevant studies where similar outcomes measures are available:

- Annualised relapse rate (ARR)
- Proportion of ratients relapse-free
- Three-month sustained accumulation disability (SAD) progression (TEMSO and TOWER only)
- All-cause discontinuations
- Discontinuations due to adverse events

This was a random-effects meta-analyses, and employed an empirical Bayes estimator of the random-effects variance. These meta-analyses were conducted in R, using package *metafor* version 1.6.

In general, very few signs of heterogeneity were found using informal classical meta-analyses of direct and one-bridge-indirect evidence (see notes following). A manual check of the demographic details of patients included in these trials did not flag any warning signs regarding differences in clinical aspects i.e. age, gender, EDSS at entry, time since diagnosis or number of previous relapses (see Table B6.3.3). Of note however the majority (>75%) of patients in the Phase II study had received previous DMTs vs. a quarter to a third of patients in TEMSO and TOWER respectively; this is to be expected due to the phase of the trial work.

- ARR: sqrt(tau) = 0.06

There were very few signs of inconsistency or heterogeneity, resulting in an extremely low estimate of random-effects variance. The estimate was so low that there were occasionally convergence problems in sensitivity analyses, caused by the MCMC estimation locking into extremely tiny (~<10^{-8}) estimates of tau.

- Discontinuation: sqrt(tau) = 0.07

There were very few signs of inconsistency or heterogeneity, resulting in a low estimate of random-effects variance. There was some inconsistency between the teriflunomide vs. placebo results in phase II study (O'Connor 2006), in which there were more discontinuations on teriflunomide and the TOWER and TEMSO trials, in which teriflunomide and placebo had roughly equal rates. However, the Phase II trial was quite small (<= 61 patients per arm), so the signal was not strong and no reason was found for why the trial found a relatively greater number of discontinuations with active treatment.

- SAD3HR: sqrt(tau) = 0.07

There were very few signs of inconsistency or heterogeneity, resulting in a low estimate of random-effects variance.

- Relapse-Free: sqrt(tau) = 0.15

Comparisons of teriflunomide versus other drugs showed little to no sign of heterogeneity.

- DAE: sqrt(tau) = 0.33

The estimate of random-effects variation was substantively significant for DAEs; however, power was low to detect any particular signals as many studies had very few events; the overall event rate was less than 10%, and most studies had fewer than 100 patients per arm. However, this result does suggest that care should be taken with generalizing the results regarding relative effects between treatments.

Please note we are not presenting Forest Plots for the meta-analysis data. Please see Forest Plots within the mixed-treatment analysis section 6.7.

Summary of Direct Evidence (Base Case Dataset: ≥2000 Recruitment Year and ≥80% RRMS Patients)

Table B6.6.1 ARR direct evidence

Comparison	Trials	Relative Risk (95% CI)
Teriflunomide (14 mg) vs. placebo	O'Connor et al. 2006	0.68 [0.36, 1.27]
	TEMSO	0.69 [0.58, 0.81]
	TOWER	0.64 [0.53, 0.77]
	Direct Meta-Analysis	0.664 [0.589, 0.749]

Table B6.6.2 Proportion relapse-free direct evidence

Comparison	Trials	Relative Risk (95% CI)
Teriflunomide (14 mg) vs. placebo	O'Connor et al. 2006	2.05 [0.91, 4.59]
	TEMSO	1.54 [1.15, 2.06]
	TOWER	1.87 [1.39, 2.51]
	Direct Meta-Analysis	[redacted]

Table B6.6.3 Three-month sustained accumulation disability progression

Comparison	Trials	Relative Risk (95% CI)
Teriflunomide (14 mg) vs. placebo	TEMSO	0.7 [0.51, 0.96]
	TOWER	0.68 [0.47, 1]
	Direct Meta-Analysis	0.694 [0.544, 0.886]

NB. Phase II trial results were excluded from the meta-analysis of three-month sustained accumulation of disability progression because this was a 6-month trial and therefore viewed as not being long enough to capture this outcome in a meaningful way.

Table B6.6.4 All-cause discontinuation

Comparison	Trials	Relative Risk (95% CI)
Teriflunomide (14 mg) vs. placebo	O'Connor et al. 2006	3.8 [1.15, 12.58]
	TEMSO	0.9 [0.65, 1.25]
	TOWER	1.07 [0.79, 1.45]
	Direct Meta-Analysis	[redacted]

Table B6.6.5 Discontinuation due to adverse events

Comparison	Trials	Relative Risk (95% CI)
Teriflunomide (14 mg) vs.	O'Connor et al. 2006	2.33 [0.66, 8.2]

placebo	TEMSO	1.37 [0.82, 2.27]
	TOWER	2.56 [1.57, 4.16]
	Direct Meta-Analysis	[redacted]

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

N/A

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

The study of teriflunomide vs. interferon-beta (TENERE) has not been included (apart from in all-cause discontinuations) as there was no placebo arm via which to allow meta-analysis.

Phase II trial results were excluded from the meta-analysis of sustained accumulation of disability progression (3 months) because this was a 6-month trial and therefore viewed as not being long enough to capture this outcome in a meaningful way.

6.7 Indirect and mixed treatment comparisons

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

Systematic Literature Search

A systematic literature search was conducted to identify studies which could potentially be used for direct and indirect comparison.

Search Strategy

MEDLINE-, EMBASE-, and Cochrane Collaboration Central Register of Clinical Trials (CENTRAL)-indexed literature were systematically searched for articles published in the last 30 years (January 1, 1980–May 20, 2011) relating to the safety and/or efficacy of DMTs for the treatment of RRMS or progressive MS (SPMS or PRMS) . Section 10.2 Appendix 2 details the search algorithms used for EMBASE, MEDLINE, and CENTRAL.

Inclusion Criteria

Articles on the following topics were selected for further review:

1. Adults with either RRMS or progressive MS (including SPMS or PRMS), of which 80% have RRMS. The choice of 80% RRMS is discussed below and was also to ensure the MTC closely aligned with the marketing authorisation of teriflunomide.
   - Trials with mixed MS patient populations with less than 20% PPMS or clinically isolated syndrome (CIS) patients also were included.
2. Single- or double-blind randomised controlled trials (RCTs) of at least six months duration and open-label extensions of these trials.
   - Trials were considered single-blind if either the patient or the examining physician was blinded to treatment.
3. Patients in at least one arm of the trial received one of the following DMTs (including pooled doses of the same drug). Comparators included placebo or any of these same selected DMTs (including the same drug

at a different dose or formulation). In the case of beta interferon, comparators were split by brand and dose. The choice of comparators was to include all possible MS DMTs.

- Alemtuzumab
- BG00012
- Daclizumab
- Fingolimod
- Glatiramer acetate
- Interferon-1a
- Interferon-1b
- Laquinimod
- Mitoxantrone
- Natalizumab
- Rituximab
- Teriflunomide

Study-reported relapse, disability progression, magnetic resonance imaging (MRI), or safety outcomes of interest

4. Several recent studies have suggested that the ARR observed in clinical trials has declined over time. In a 2010 publication by Inusah et al., a downward trend in ARR was observed in trials for MS published between 1980 and 2008; in some later trials, ARR was three times lower than in earlier trials. In a review of RCTs in RRMS conducted by Nicholas et al., the ARR for placebo was found to decrease by 6.2% per year.

Patient recruitment from the year 2000 generally coincided with the widespread introduction of the McDonald diagnostic criteria in MS clinical trials, whereas prior to this the Poser criteria were used in clinical trials. Compared with the Poser criteria, the McDonald criteria generally identify patients much earlier in the disease course, and with less frequent or severe symptoms; therefore, a change in MS diagnostic criteria may have considerable impact on the baseline disease activity of the patient population under study.

Two Key Opinion Leaders (KOLs) (Prof Patrick Vermersch neurologist from France and Prof Gary Cutter methodologist from the US) were consulted about the feasibility of performing mixed treatment comparison (MTC) analyses for DMTs in MS based on the available evidence. To account for the evidence of decreased relapse rates over time, the KOLs recommended excluding studies with patient recruitment before 2000, taking into consideration: [Cutter et al. 2013]

- New MS diagnostic criteria (McDonald)
- Earlier treatment following the publication of the CHAMPS study [Galetta, 2001]
- Timeframe for the development of the different DMTs
- For studies where the year(s) of recruitment were not reported, year of publication was used as a proxy.

The ≥80% RRMS threshold was suggested following an Advisory Board meeting after reviewing the distribution of the proportion of RRMS patients in the included trials. Based on this review, the vast majority of trials in this analysis seem to cluster into two groups: greater than or equal to 80% RRMS patients, or considerably <80% RRMS patients. As such, 80% was selected as the 'cut-off' for analysis.

Therefore, trials in the network were restricted to studies with patient recruitment after 2000 and with ≥80% RRMS patients. Sensitivity analyses were run on datasets without these restrictions. Among the trials identified in the SLR, 30 were deemed suitable for mixed MTC analyses

In order to support the validity of this approach further, data from trials conducted prior to 2000 were compared to the data identified in the base case systematic review. This analysis suggests relapses prior to study entry, and within the study placebo arms, ARR and disability progression were higher in the studies > 2000 compared to those < 2000. Specifically:

- Relapse rate prior to study entry over two year period: 2.1-2.8 studies >2000 and ≤ 2000 2.5-3.9 (Additional Appendix 2 Table AA2.1)
- ARR range during study in placebo arms: 0.36-0.99 studies >2000 and ≤ 2000 0.84-1.27 (Additional Appendix 2 Table AA2.2)
- Disability progression in placebo arms: 13%-28% studies >2000 and ≤ 2000 24.6%-52.65% (Additional Appendix 2 Table AA2.3)

Exclusion Criteria

In addition to excluding studies with patient enrolment prior to the year 2000 and with <80% RRMS in the patient population, articles based on expert opinion, commentary, letters, editorials, non-randomised studies, reviews, studies reporting results from more than one RCT, studies with no abstracts, and articles written in a language other than English were excluded from this review. Papers that reported the methods and baseline characteristics, but not the results of an RCT were excluded, as were studies that used RCT data to validate outcome measures or diagnostic criteria. Single-arm studies or studies that did not compare an intervention to one of the selected DMTs or placebo and studies that examined combination therapies were excluded from this report. Also excluded were animal, *in vitro*, foetal, molecular, genetic, pharmacodynamic, or pharmacokinetic

studies. Additionally, open-label studies (i.e., trials in which both the patients and the examining physician were not blinded) that were not extensions of blinded RCTs, studies where the number of patients in a specific treatment arm or population could not be determined, studies with fewer than 10 patients in a treatment arm, and studies that continued to recruit patients after study initiation were excluded.

Grey Literature Search

The "grey" literature (material that can be referenced but is not published in peer-reviewed, MEDLINE-, EMBASE-, or CENTRAL-indexed medical journals) were also searched for any information pertaining to the safety and efficacy of DMTs for RRMS or progressive MS. Proceedings and abstracts from professional and scientific meetings were considered only if presented within the last two years (i.e., May 2009−May 2011) or the most recent two conferences. Sources that were searched included:

- Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS)
- European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)
- European Medicines Agency (EMA)
- US Food and Drug Administration (FDA)
- American Academy of Neurology (AAN)
- American Neurological Society (ANS)
- European Neurological Society (ENS)
- European Federation of Neurological Societies (EFNS)

Documents and meeting abstracts were included if they met the study inclusion/exclusion criteria described above. Finally, a manual check of bibliographies of articles was performed to identify any additional relevant studies; one trial was identified.

Study Selection

Using the aforementioned inclusion/exclusion criteria, abstracts of all selected MEDLINE-, EMBASE-, and CENTRAL-indexed publications were manually reviewed by two independent reviewers to determine their relevance to the aims of our systematic review. For abstracts that were deemed pertinent during this first level of review, full-text articles were retrieved. After retrieval, full-text articles of all selected MEDLINE-, EMBASE-, and CENTRAL-indexed publications and grey literature sources were manually reviewed by two independent reviewers to determine their relevance to the systematic review. Discrepancies in abstract or full-text screening between the two independent reviewers were resolved through discussion with a third independent reviewer.

Supplemental Targeted Literature Search

In addition to the narrow and deep systematic search of the literature on the clinical efficacy and safety of DMTs for RRMS and progressive MS, one trial of natalizumab and one trial of teriflunomide in relapsing MS were also included [O'Connor et al. 2011; Rudick et al. 2006] as part of a supplemental targeted review of the literature. The SENTINEL trial [Rudick et al. 2006] did not meet the inclusion criteria for this systematic review because it investigated natalizumab and IFNβ-1a combination therapy. It was included in a targeted fashion because of the critical data the study provided regarding the safety of natalizumab although excluded from the MTC analysis.

MTC feasibility assessment

A feasibility assessment was performed to determine which trials should be included in the MTC analyses and to account for the evidence of decreased relapse rates over time. As part of the feasibility assessment, clinical and statistical experts in the field of MS were consulted regarding methodology and identified clinical heterogeneity. Two KOLs (Prof Patrick Vermersch, neurologist from France and Prof Gary Cutter, methodologist from the US) were consulted about the feasibility of performing MTC analyses for DMTs in MS based on the available evidence. Among the trials identified in the SLR, 30 were deemed suitable for MTC analyses. In addition, a sensitivity analysis was considered which included trials from all years, without the restriction of post 2000 publication, however, as discussed this analysis would lead to more studies using older diagnostic criteria (Poser) for MS.

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

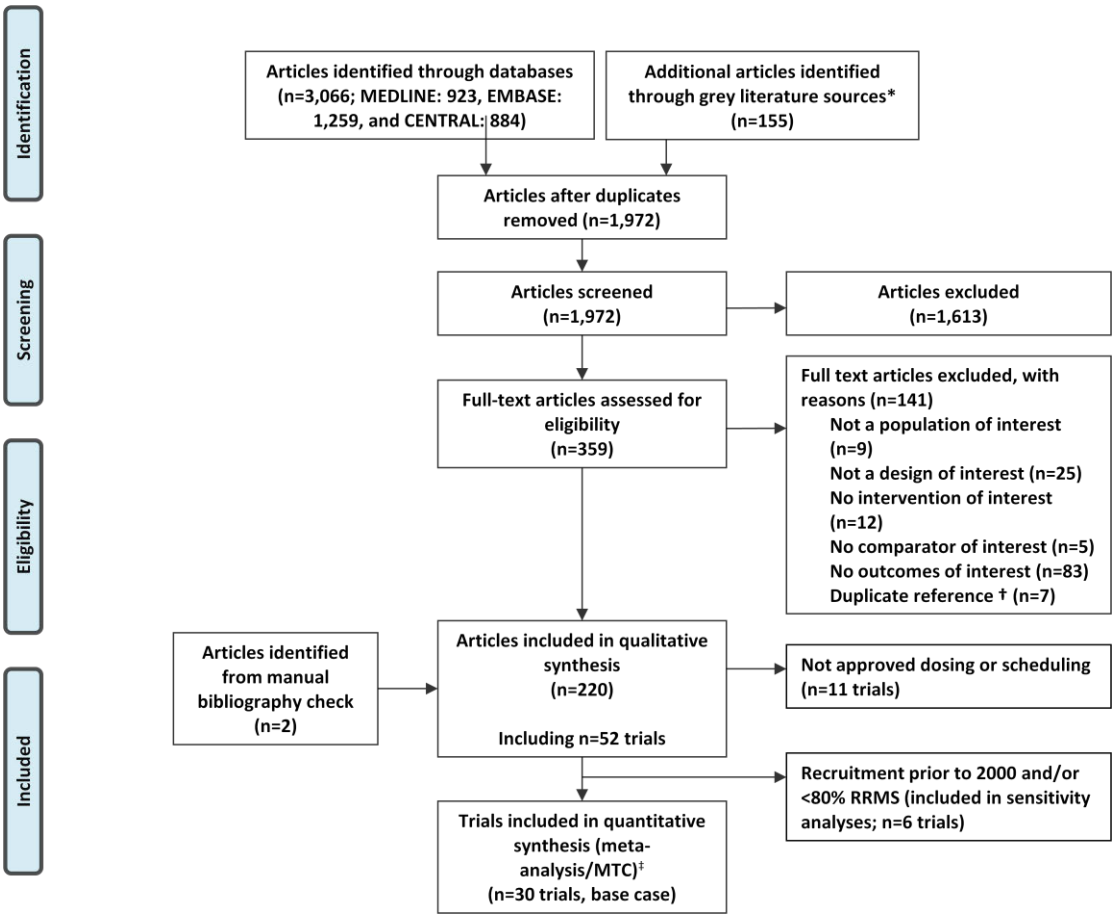
The base-case MTC included 30 clinical trials with patient recruitment 2000 and onward, and ≥80% RRMS patient population. Among 21 of these trials, patient recruitment took place after 2000; for the remaining nine trials, recruitment was assumed to be after 2000 on the basis of publication year. Most (25) of the included trials utilised the McDonald diagnostic criteria. See Additional Appendix 3 for clinical trial data extraction table.

All the relevant comparators were identified in the MTC in studies post 2000 *with the exception* of Rebif 22µg (IFNβ-1a), which is a dose used in UK practice. Studies were identified pre-2000 including IFNβ-1a 22µg and are presented in Additional Appendix 2 as part of a sensitivity analysis which considered all years from 1980 and with a ≥80% RRMS patient population. As previously discussed it was not appropriate to use the all-years analysis for the base case analysis and therefore in order to obtain data for IFNβ-1a 22µg, the ratios of results between 44µg and IFNβ-1a 22µg in the all-years sensitivity analysis were calculated and applied to the IFNβ-1a 44µg data in the base case analysis for SAD (3 months) and overall discontinuation, as these data are used in

the cost-effectiveness analysis (see Section 7.3). No data were identified for IFNβ-1a 22µg for ARR in the all-years analysis.

In the Laquinimod RMS trial, which was used in the base case for overall discontinuation and discontinuation due to adverse events, one treatment arm (laquinimod 0.1 mg) reported zero events for the discontinuation for adverse events (DAE) outcome and was subsequently removed from that analysis due to lack of ability to estimate an OR vs. placebo (as the estimate would technically be infinite, given the lack of events).

Figure B6.7.1 PRISMA diagram



*Includes the FDA and EMA websites, as well as proceedings from the following key conferences in the past two years: AAN, ACTRIMS, ANA, ECTRIMS, EFNS, ENS, and LACTRIMS.
† These seven citations were duplicates of abstracts from the grey literature that were also brought in through the MEDLINE, EMBASE, and CENTRAL searches.
‡Following the feasibility assessment and key opinion leader (KOL) recommendations, quantitative analyses were restricted to trials with recruitment from 2000 onward (16 trials were excluded) and with at least 80% RRMS patients (10 trials were excluded). These two restrictions combined (with some overlap) reduced the number of trials suitable for quantitative analyses from 52 to 30.

Table B6.7.1 List of RCTs included in the MTC base case analysis

Trial	Treatment Arm	Dose	Number Randomized	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
1. CAMMS223 [Coles et al. 2008]	Alemtuzumab	12 mg IV annually	112	McDonald	100% RRMS	2002–2004	31.9±8.0	35.7%	1.9±0.7	NR	0%	NR	0.11
	Alemtuzumab	24 mg IV annually	110	McDonald	100% RRMS	2002–2004	32.2±8.8	35.5%	2.0±0.7	NR	0%	NR	0.08
	IFNβ-1a	44 µg SC 3 times weekly	111	McDonald	100% RRMS	2002–2004	32.8±8.8	36.0%	1.9±0.8	NR	0%	NR	0.36
2. CARE-MS I [Cohen et al. 2012]	IFNβ-1a	44 µg SC 3 times weekly	187	McDonald	100% RRMS	2007–2009	33.2±8.5	35.0%	2±0.8	1 yr: 1.8	0%	2.0±1.3	0.39
	Alemtuzumab	12 mg IV daily for 5 days at 0 months, daily for 3 days at 12 months	376	McDonald	100% RRMS	2007–2009	33.0±8	35.0%	±0.8	1 yr: 1.8	0%	2.1±1.4	0.18
3.CARE-MS II [Coles et al. 2012]	Alemtuzumab	12 mg IV daily for 5 days at 0 months, daily for 3 days at 12 months	426	McDonald	100% RRMS	2007–2009	34.8± 8.36	34%	2.7±1.26	1 yr: 1.7	DMT: 100%	4.5±2.68	0.26
	IFNβ-1a	44 µg SC 3 times weekly	202	McDonald	100% RRMS	2007–2009	35.8± 8.77	35%	2.7±1.21	1 yr: 1.5	DMT: 100%	4.7±2.86	0.52

Trial	Treatment Arm	Dose	Number Randomized	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
4. SELECT [Giovannoni et al. 2011]	Daclizumab	300 mg SC injection once every 4 weeks	203	McDonald (Polman)	100% RRMS	NR	35±9	NR	2.6±1.2	1 yr: 1.3	NR	3±NR	0.23
	Daclizumab	150 mg SC injection once every 4 weeks	201	McDonald (Polman)	100% RRMS	NR	35±9	NR	2.8±1.2	1 yr: 1.4	NR	3±NR	0.21
	Placebo		196	McDonald (Polman)	100% RRMS	NR	37±9	NR	2.7±1.2	1 yr: 1.3	NR	2±NR	0.46
5.FREEDOMS [Kappos et al. 2010]	Fingolimod	1.25 mg oral daily	429	McDonald	100% RRMS	2006–2007	37.4±8.9	31.2%	2.4±1.4	2 yr: 2.1	DMT history: 39.6%	8.4±6.9	0.16
	Fingolimod	0.5 mg oral daily	425	McDonald	100% RRMS	2006–2007	36.6±8.8	30.4%	2.3±1.3	2 yr: 2.1	DMT history: 42.6%	8.0±6.6	0.18
	Placebo		418	McDonald	100% RRMS	2006–2007	37.2±8.6	28.7%	2.5±1.3	2 yr: 2.2	DMT history: 40.4%	8.1±6.4	0.40
6.FREEDOMS II [Calabresi et al. 2012]	Fingolimod	1.25 mg once daily	370	NR	100% RRMS	NR	40.9±8.9	24%	2.5±1.3	1 yr: 1.5 2 yr: 2.3	DMT: 77.6%	10.8±8.2	0.20
	Fingolimod	0.5 mg once daily	358	NR	100% RRMS	NR	40.6±8.4	23%	2.4±1.3	1 yr: 1.4 2 yr: 2.2	DMT: 73.7%	10.4±8.0	0.21
	Placebo		355	NR	100% RRMS	NR	40.1±8.4	19%	2.4±1.3	1 yr: 1.5 2 yr: 2.2	DMT: 73.0%	10.6±7.9	0.40

Trial	Treatment Arm	Dose	Number Randomized	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years	Male	Baseline EDSS	Previous Relapse Rate	Prev. Treated	Disease Duration, Years*	ARR at End of Trial
							(Mean ± SD)	(%)	(Mean ± SD)		(%)	(Mean ± SD)	
7. FTY720 D2201 Study Group [Kappos et al. 2006]	Fingolimod	1.25 mg oral daily	94	McDonald	89% RRMS, 11% SPMS	2003–2004	38.0±NR	24.7%	2.7±NR	2 yr: 1.9	NR	NR	0.35
	Fingolimod	5.0 mg oral daily	94	McDonald	87% RRMS, 13% SPMS	2003–2004	38.3±NR	29.3%	2.5±NR	2 yr: 1.9	NR	NR	0.36
	Placebo		93	McDonald	90% RRMS, 10% SPMS	2003–2004	37.1±NR	33.7%	2.6±NR	2 yr: 1.8	NR	NR	0.77
8. Saida et al. 2012 [Saida et al. 2012]	Placebo		57	McDonald	100% RRMS	2007–2010	35±8.9	32%	2.1±1.7	1 yr: 1.7 2 yr: 2.8	NR	NR	0.99
	Fingolimod	0.5 mg oral daily	57	McDonald	94.7% RRMS 5.3% SPMS	2007–2010	35±9	30%	2.3±1.9	1 yr: 1.4 2 yr: 2.2	NR	NR	0.50
	Fingolimod	1.25 mg oral daily	57	McDonald	98.2% RRMS 1.8% SPMS	2007–2010	36±9.3	32%	1.8±1.7	1 yr: 1.5 2 yr: 2.3	NR	NR	0.41

Trial	Treatment Arm	Dose	Number Randomized	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
9. TRANSFORMS [Cohen et al. 2010]	Fingolimod	1.25 mg oral daily	426	McDonald/ Polman	100% RRMS	2006–2007	35.8±8.4	31.2%	2.2±1.3	2 yr: 2.2	Any therapy: 58.5%; Any IFN: 49.1%; GA: 15.7%	7.3±6.0	0.20
	Fingolimod	0.5 mg oral daily	431	McDonald/ Polman	100% RRMS	2006–2007	36.7±8.8	34.6%	2.2±1.3	2 yr: 2.3	Any therapy: 55.2%; Any IFN: 50.8%; GA: 13.2%	7.5±6.2	0.16
	IFNβ-1a	30 µg IM weekly	435	McDonald/ Polman	100% RRMS	2006–2007	36.0±8.3	32.2%	2.2±1.3	2 yr: 2.3	Any therapy: 56.3%; Any IFN: 47.6%; GA: 15.4%	7.4±6.3	0.33
10. BG-12 Phase IIb Study [Kappos et al. 2008]	BG-12	120 mg oral daily	64	McDonald	100% RRMS	2004–2005	34.8± 10.2	34.4%	2.5±1.1	NR	NR	NR	0.29
	BG-12	120 mg oral 3 times daily	64	McDonald	100% RRMS	2004–2005	36.3±9.5	31.3%	2.5±1.0	NR	NR	NR	0.60
	BG-12	240 mg oral 3 times daily	64	McDonald	100% RRMS	2004–2005	37.3±9.1	33.3%	2.9±1.3	NR	NR	NR	0.28
	Placebo		65	McDonald	100% RRMS	2004–2005	35.6±8.2	44.6%	2.7±1.2	NR	NR	NR	0.41

Trial	Treatment Arm	Dose	Number Randomized	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
11. CONFIRM [Fox et al. 2012]	Placebo		363	McDonald	100% RRMS	NR	36.9±9.2	31%	2.6±1.2	1 yr: 1.4	DMT: 31%	4.8±5.0	0.40
	BG-12	240 mg oral twice daily	359	McDonald	100% RRMS	NR	37.8±9.4	32%	2.6±1.2	1 yr: 1.3	DMT: 28%	4.9±5.1	0.22
	BG-12	240 mg oral 3 times daily	345	McDonald	100% RRMS	NR	37.8±9.4	28%	2.5±1.2	1 yr: 1.4	DMT: 29%	4.6±5.2	0.20
	GA	20 mg SC daily	350	McDonald	100% RRMS	NR	36.7±9.1	29%	2.6±1.2	1 yr: 1.4	DMT: 29%	4.4±4.7	0.29
12. DEFINE [Gold et al. 2012]	Placebo		408	McDonald	100% RRMS	NR	38.5± 9.14	25%	2.48±1.24	1 yr: 1.3	55.6%	5.8±5.78	0.36
	BG-12	240 mg oral twice daily	410	McDonald	100% RRMS	NR	38.1± 9.11	28%	2.40±1.29	1 yr: 1.3	54.4%	5.6±5.39	0.17
	BG-12	240 mg oral 3 times daily	416	McDonald	100% RRMS	NR	38.8± 8.85	26%	2.36±1.19	1 yr: 1.3	55.3%	5.1±5.29	0.19
13. FORTE Study Group [Comi et al. 2011]	GA	20 mg SC daily	586	McDonald/ Polman	100% RRMS	2006–2007	36.3±9.0	28.2%	2.2±1.2	1yr: 1.5	NR	6.3±6.5	0.33
	GA	40 mg SC daily	569	McDonald/ Polman	100% RRMS	2006–2007	36.3±9.0	28.5%	2.1±1.1	1yr: 1.4	NR	6.5±6.7	0.35

Trial	Treatment Arm	Dose	Number Randomized	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
14. Dose-Comparison 9006 Study Group [Cohen et al. 2007]	GA	20 mg SC daily	44	Poser	100% RRMS	2003–2005	37.1±7.0	29.5%	2.0±1.2	1 yr: 1.5	NR	7.4±6.2	NR
	GA	40 mg SC daily	46	Poser	100% RRMS	2003–2005	37.4±6.5	19.6%	2.1±1.0	1 yr: 1.5	NR	6.7±6.4	NR
15. BEYOND [O'Connor et al. 2009]	IFNβ-1b	500 µg SC every other day	899	McDonald	100% RRMS	2003–2005	35.9±NR	30.0%	2.3±NR	1 yr: 1.6	NR	5.4±NR	0.33
	IFNβ-1b	250 µg SC every other day	897	McDonald	100% RRMS	2003–2005	35.8±NR	30.1%	2.4±NR	1 yr: 1.6	NR	5.3±NR	0.36
	GA	20 mg SC daily	448	McDonald	100% RRMS	2003–2005	35.2±NR	31.7%	2.3±NR	1 yr: 1.6	NR	5.1±NR	0.34
16. BECOME [Cadavid et al. 2009]	IFNβ-1b	250 µg SC every other day	36	NR	86% RRMS, 14% CIS	NR	36.0±NR	25.0%	NR	1 yr: 1.8	NR	NR	0.37
	GA	20 mg SC daily	39	NR	77% RRMS, 23% CIS	NR	36.0±NR	36.0%	NR	1 yr: 1.9	NR	NR	0.33
17. REGARD [Mikol et al. 2008]	IFNβ-1a	44 µg SC 3 times weekly	386	McDonald	100% RRMS	2004	36.7±9.8	31.0%	2.3±1.3	NR	NR	5.9±3.0	0.30
	GA	20 mg SC daily	378	McDonald	100% RRMS	2004	36.8±9.5	28.0%	2.3±1.3	NR	NR	6.5±7.1	0.29

Trial	Treatment Arm	Dose	Number Randomized	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
18. CombiRx [The CombiRx trial 2012]	IFNβ-1a plus GA	30 µg IM weekly plus 20 mg SC daily	499	Poser/McDonald	100% RRMS	2005–2009	37.1±9.4	25.4%	1.9±1.2	1 yr: 1.7	NR	4.2±5.4	0.12
	IFNβ-1a	30 µg IM weekly	250	Poser/McDonald	100% RRMS	2005–2009	37.6± 10.2	30.8%	2.0±1.2	1 yr: 1.7	NR	4.7±6.4	0.16
	GA	20 mg SC daily	259	Poser/McDonald	100% RRMS	2005–2009	39.0±9.5	28.6%	2.0±1.1	1 yr: 1.6	NR	4.3±5.5	0.11
19. Etemadifar, 2006 [Etemadifar et al. 2006]	IFNβ-1a	30 µg IM weekly	30	Poser	100% RRMS	2002–2004	NR	20.0%	1.9±1.1	1 yr: 2.0	NR	2.9±2.3	NR
	IFNβ-1a	44 µg SC 3 times weekly	30	Poser	100% RRMS	2002–2004	NR	23.3%	2.1±1.0	1 yr: 2.4	NR	3.0±2.2	NR
	IFNβ-1b	250 µg SC every other day	30	Poser	100% RRMS	2002–2004	NR	30.0%	1.9±0.7	1 yr: 2.2	NR	3.7±2.3	NR
20. EVIDENCE [Panitch et al. 2002]	IFNβ-1a	44 µg SC 3 times weekly	339	Poser	100% RRMS	NR	38.3±NR	25.1%	2.3±NR	2 yr: 2.6	NR	6.5±NR	0.54
	IFNβ-1a	30 µg IM weekly	338	Poser	100% RRMS	NR	37.4±NR	25.4%	2.3±NR	2 yr: 2.6	NR	6.7±NR	0.65
21. BRAVO [Vollmer et al. 2011]	Placebo		450	McDonald	100% RRMS	NR	NR	NR	NR	NR	NR	NR	0.37
	Laquinimod	0.6 mg oral daily	434	McDonald	100% RRMS	NR	NR	NR	NR	NR	NR	NR	0.29
	IFNβ-1a	30 µg IM once weekly	447	McDonald	100% RRMS	NR	NR	NR	NR	NR	NR	NR	0.27

Trial	Treatment Arm	Dose	Number Randomized	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
22. LAQ/5062 [Comi et al. 2008]	Laquinimod	0.3 mg oral daily	98	McDonald	100% RRMS	2005	NR	NR	2.3±1.1	1 yr: 1.46	0%	NR	0.76
	Laquinimod	0.6 mg oral daily	106	McDonald	100% RRMS	2005	NR	NR	2.3±1.0	1 yr: 1.51	0%	NR	0.52
	Placebo		102	McDonald	100% RRMS	2005	NR	NR	2.5±1.1	1 yr: 1.37	0%	NR	0.77
23. Laquinimod in Relapsing MS [Polman et al. 2005]	Laquinimod	0.1 mg oral daily	68	McDonald	84% RRMS, 16% SPMS	2002	42.4±NR	20.6%	3.2±NR	NR	NR	5.8±NR	NR
	Laquinimod	0.3 mg oral daily	74	McDonald	79% RRMS, 21% SPMS	2002	39.6±NR	29.7%	3.2±NR	NR	NR	5.5±NR	NR
	Placebo		67	McDonald	91% RRMS, 9% SPMS	2002	38.7±NR	26.9%	3.0±NR	NR	NR	5.3±NR	NR
24. ALLEGRO [Comi et al. 2012]	Laquinimod	0.6 mg oral daily	550	McDonald	100% RRMS	2007–2008	38.9±9.2	29%	2.6±1.3	1 yr: 1.2 2 yr: 1.9	38.2%	8.7±6.9	0.30
	Placebo		556	McDonald	100% RRMS	2007–2008	38.5±9.1	34%	2.6±1.3	1 yr: 1.3 2 yr: 1.9	39.7%	8.7±6.7	0.39
25. AFFIRM [Polman et al. 2006]	Natalizumab	300 mg IV per 4 weeks	627	McDonald	100% RRMS	2001	35.6±8.5	28.4%	2.3±1.2	1 yr: 1.5	NR	NR	0.23
	Placebo		315	McDonald	100% RRMS	2001	36.7±7.8	33.0%	2.3±1.2	1 yr: 1.5	NR	NR	0.73
26. HERMES [Hauser et al. 2008]	Rituximab	1,000 mg IV at days 1 and 15	69	McDonald	100% RRMS	NR	39.6±8.7	24.6%	NR	NR	78.3%	9.6±6.4	0.37
	Placebo		35	McDonald	100% RRMS	NR	41.5±8.5	17.1%	NR	NR	77.1%	9.6±7.1	0.72
27. Teriflunomide in Relapsing MS [O'Connor et al.	Teriflunomide	7 mg oral daily	61	Poser	88.5% RRMS, 11.5% SPMS	2001–2003	40.1±9.3	24.6%	NR	1 yr: 1.0	83.6	10.3±8.1	0.58

Trial	Treatment Arm	Dose	Number Randomized	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
2006]	Teriflunomide	14 mg oral daily	57	Poser	87.7% RRMS, 12.3% SPMS	2001–2003	40.1±9.1	21.1%	NR	1 yr: 1.0	71.9	8.5±7.1	0.55
	Placebo		61	Poser	86.9% RRMS, 13.1% SPMS	2001–2003	39.2±8.7	32.8%	NR	1 yr: 1.0	82	8.6±7.9	0.81
28. TEMSO [O'Connor et al. 2011]	Teriflunomide	7 mg oral daily	366	McDonald	91% RRMS, 9% SPMS/ CPMS	2004–2008	37.4±9.0	30.3%	2.7±1.3	2 yr: 2.3	DMT: 27.9%	8.8±6.8	0.37
	Teriflunomide	14 mg oral daily	359	McDonald	92.8% RRMS, 7.2% SPMS/ CPMS	2004–2008	37.8±8.2	29.0%	2.7±1.2	2 yr: 2.2	DMT: 28.4%	8.7±6.7	0.37
	Placebo		363	McDonald	90.6% RRMS, 9.4% SPMS/ CPMS	2004–2008	38.4±9.0	24.2%	2.7±1.3	2 yr: 2.2	DMT: 24.8%	8.6±7.1	0.54
29.TENERE [Vermersch et al. 2012; CSR]	Teriflunomide	7 mg oral daily	109	McDonald	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.410
	Teriflunomide	14 mg oral daily	111	McDonald	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.259
	IFNβ-1a	44 µg SC 3 times weekly	104	McDonald	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.216
30. TOWER [Sanofi. Clinical Study Report 2012]	Teriflunomide	7 mg oral daily	408	McDonald	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Teriflunomide	14 mg oral daily	372	McDonald	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo		389	McDonald	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.7.3 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.

Table B6.7.2 Summary of the trials used to conduct the indirect comparison – part A

No. Trials	References of trials	Teriflunomide		Placebo	IM IFNβ-1a 30µg	SC IFNβ-1a 44µg	IFNB-1b			Glatiramer Acetate		Alemtuzumab		Nataluzimab	Fingolimod		
		7mg	14mg				250 µg	500 µg	12mg	20 mg	40 mg	12mg	24mg		0.5mg	1.25mg	5mg
3	Phase II Proof of Concept Study TEMSO TOWER	✓	✓	✓													
1	TENERE	✓	✓			✓											
2	Forte Study Group Dose-Comparison 9006 Study Group									✓	✓						
1	Etemadifar				✓	✓	✓										
1	EVIDENCE				✓	✓											
1	BEYOND						✓	✓		✓							
1	BECOME						✓			✓							
1	REGARD					✓				✓							
1	CombiRx*				✓					✓							
2	CARE-MS I CARE-MS II					✓						✓					
1	CAMMS223					✓						✓	✓				
1	AFFIRM			✓										✓			

No. Trials	References of trials	Teriflunomide		Placebo	IM IFNβ-1a 30µg	SC IFNβ-1a 44µg	IFNB-1b			Glatiramer Acetate		Alemtuzumab		Nataluzimab	Fingolimod		
		7mg	14mg				250 µg	500 µg	12mg	20 mg	40 mg	12mg	24mg		0.5mg	1.25mg	5mg
3	FREEDOMS FREEDOMS II Saida et al			✓											✓	✓	
1	FTY720 D2201 Study Group			✓												✓	✓
1	TRANSFORMS					✓									✓	✓	

Table B6.7.3 Summary of the trials used to conduct the indirect comparison – part B

No. Trials	References of trials	Placebo	IM IFNβ-1a 30µg	SC IFNβ-1a 44µg	IFNB-1b		Glatiramer Acetate		Daclizumab		Laquinimod			Rituximab	BG12			
					250 µg	500 µg	20 mg	40 mg	150 mg	300 mg	0.1mg	0.3 mg	0.6 mg		120mg od	120mg tds	240mg bd	240mg tds
1	SELECT	✓							✓	✓								
1	BRAVO	✓	✓										✓					
1	LAQ/5062	✓										✓	✓					
1	Laquinimod in Relapsing MS	✓									✓	✓						
1	ALLEGRO	✓											✓					
1	HERMES	✓												✓				
1	BG-12 Phase IIb	✓													✓	✓		✓
1	CONFIRM	✓					✓										✓	✓
1	DEFINE	✓															✓	✓

Figure B6.7.2 ARR Network (Base Case–Recruitment Year 2000 Onward, at least 80% RRMS)

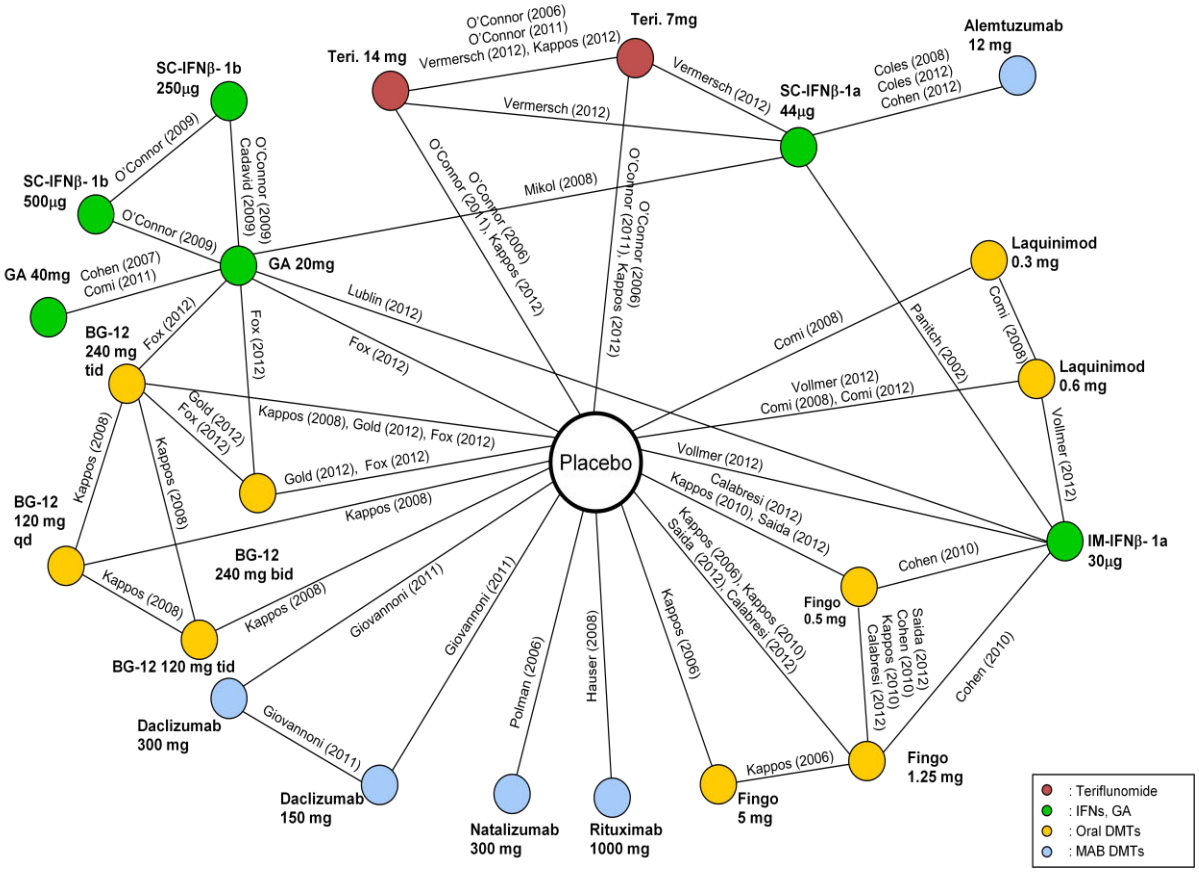


Figure B6.7.3 Relapse-free Network (Base Case –Recruitment Year 2000 Onward, at least 80% RRMS)

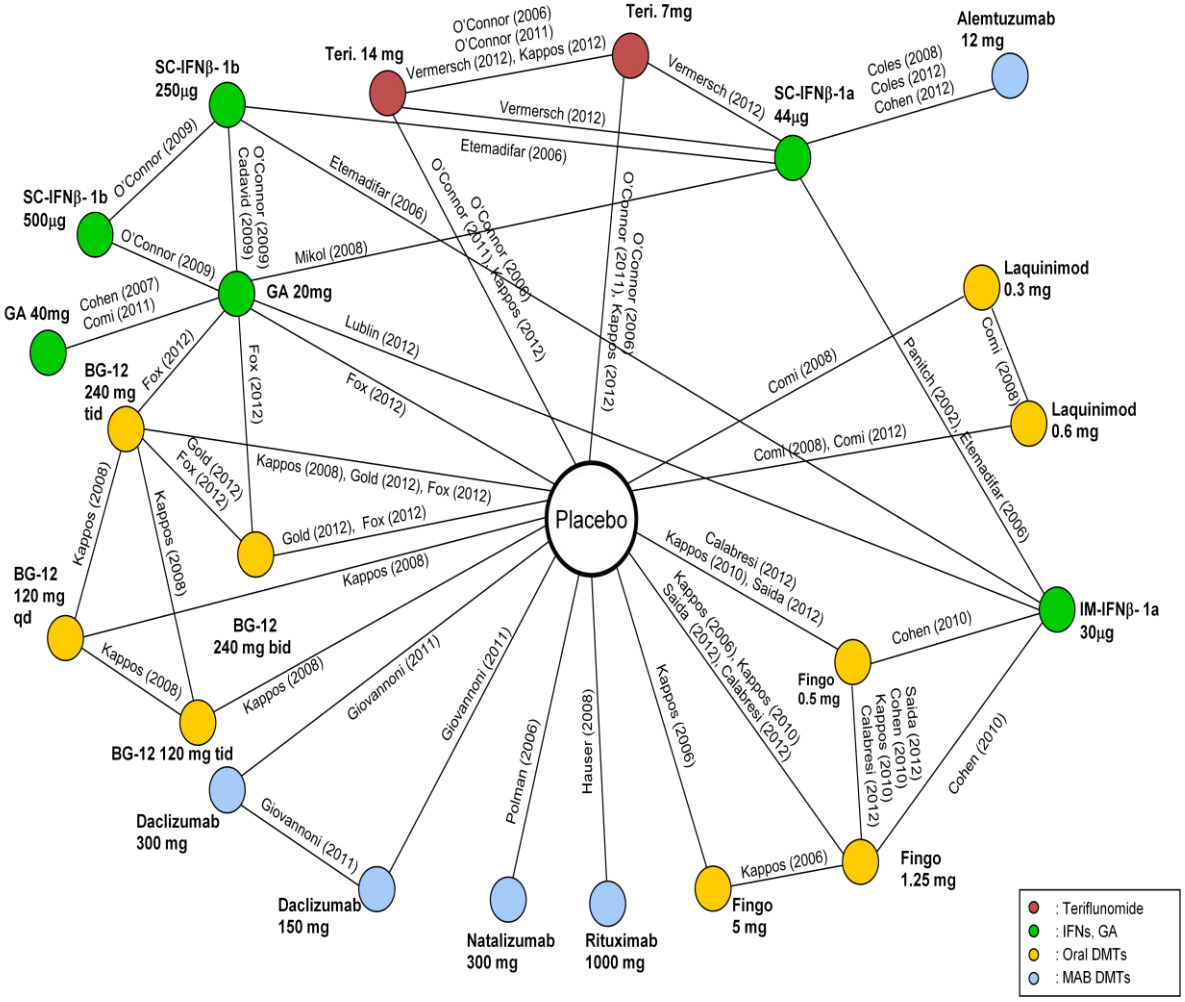


Figure B6.7.4 Three-month SAD Network (Base Case – Recruitment Year 2000 Onward, at least 80% RRMS)

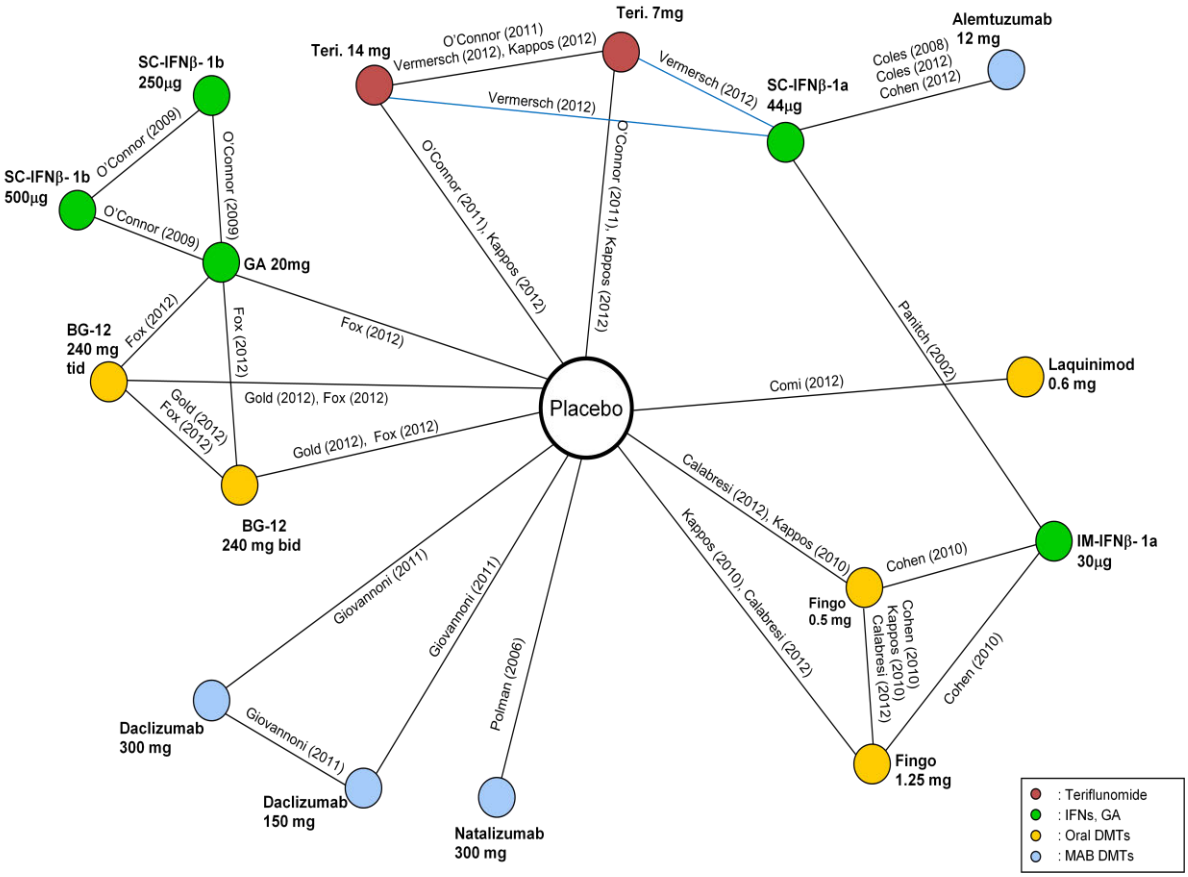


Figure B6.7.5 Overall Discontinuation Network (Base Case – Recruitment Year 2000 Onward, at least 80% RRMS)

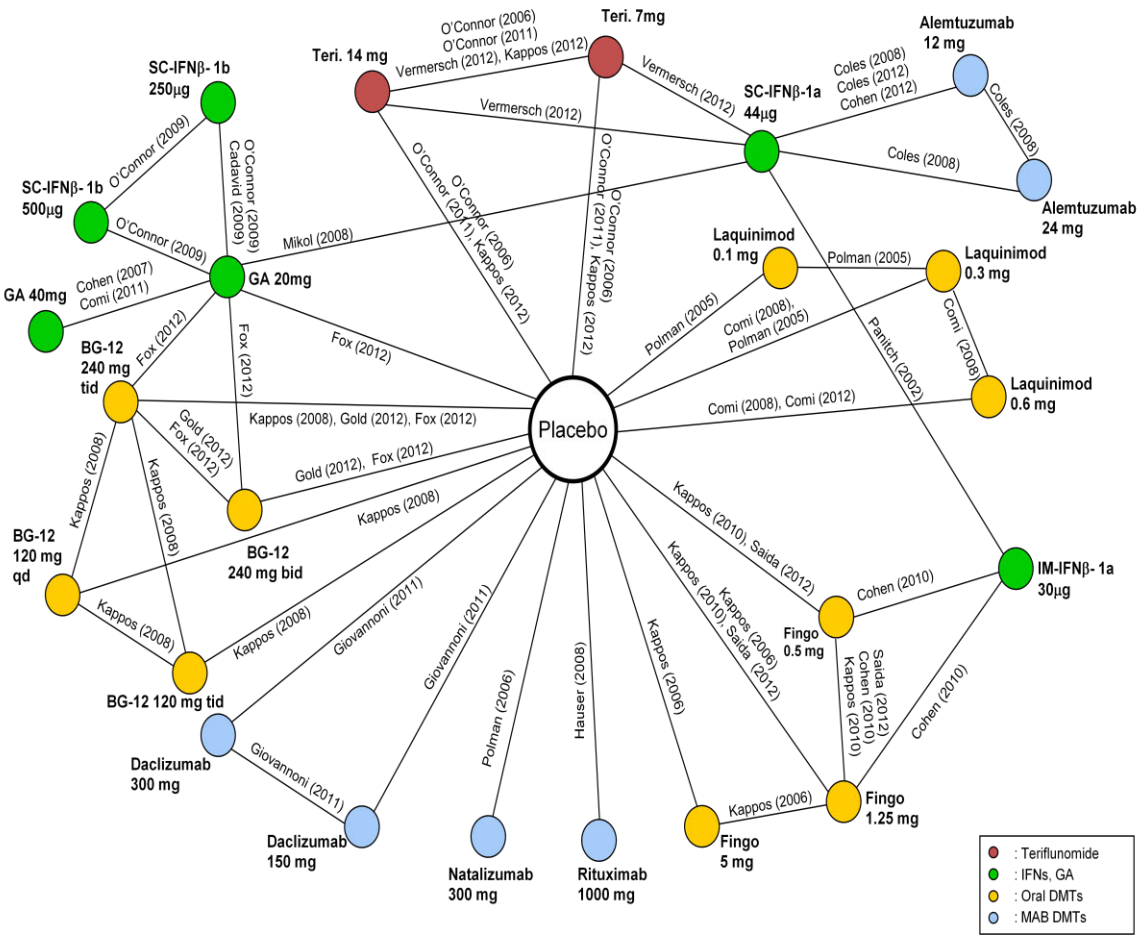
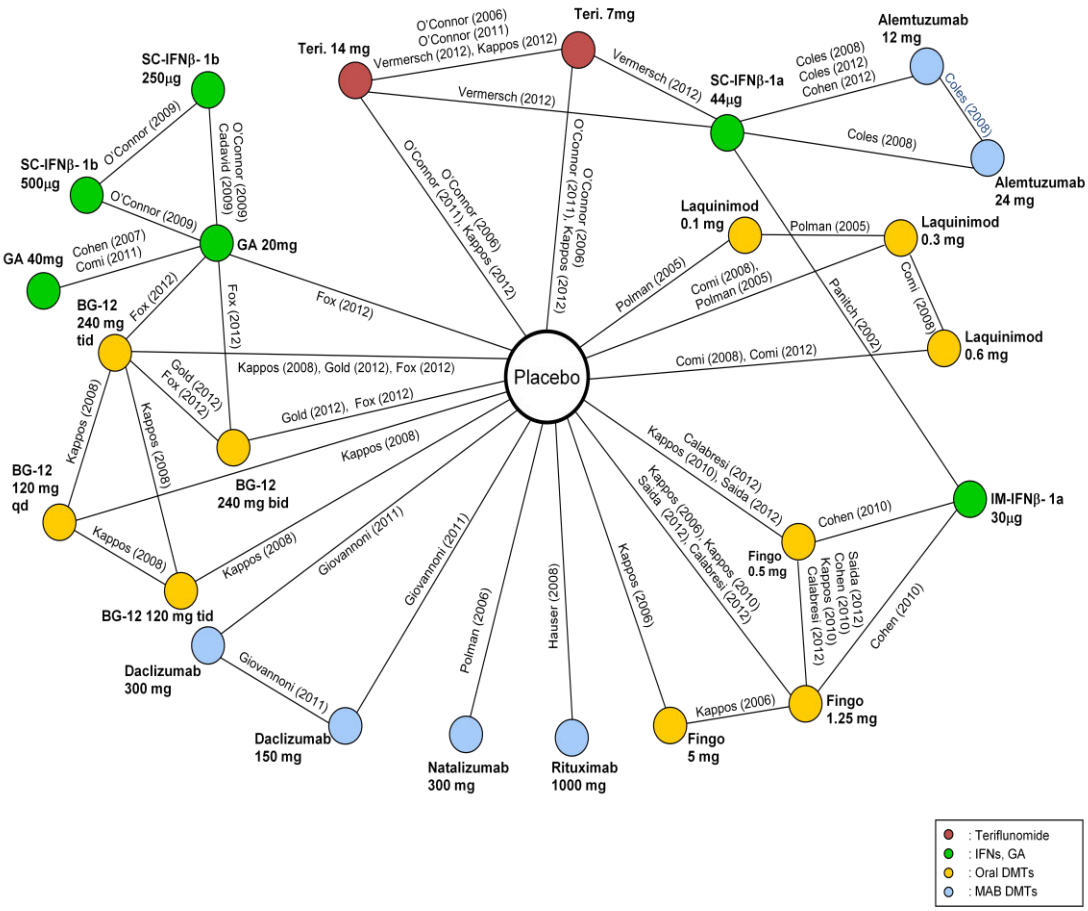


Figure B6.7.6 DAEs Network (Base Case – Recruitment Year 2000 Onward, at least 80% RRMS)



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

N.B. for All-years sensitivity analysis, please see Additional Appendix 2.

Table B6.7.4 Annualised relapse rate data for the MTC

Trial	Population	Treatment	Time point (months)	ARR
CAMMS223	All	SC IFNβ-1a 44 µg	36	0.36
		Alemtuzumab 12 mg		0.11
		Alemtuzumab 24 mg		0.08
CARE-MS I	All	SC IFNβ-1a 44 µg	24	0.39
		Alemtuzumab 12 mg		0.18
CARE-MS II	All	SC IFNβ-1a 44 µg	24	0.52
		Alemtuzumab 12 mg		0.26
SELECT	All	Placebo	12	0.46
		Daclizumab 150 mg		0.21
		Daclizumab 300 mg		0.23
FREEDOMS	All	Placebo	24	0.4
		Fingolimod 0.5 mg		0.18
		Fingolimod 1.25 mg		0.16
FREEDOMS II	All	Placebo	24	0.4
		Fingolimod 0.5 mg		0.21
		Fingolimod 1.25 mg		0.2
FTY720 D2201 Study Group	All	Placebo	6	0.77
		Fingolimod 1.25 mg		0.35
		Fingolimod 5 mg		0.36
Saida et al 20012	All	Placebo	6	0.99
		Fingolimod 0.5 mg		0.5
		Fingolimod 1.25 mg		0.41
TRANSFORMS	All	Fingolimod 1.25 mg	12	0.2
		Fingolimod 0.5 mg		0.16
		IM IFNβ-1a 30 µg		0.33
BG-12 Phase IIb Study	All	BG-12 120 mg qd	6	0.42
		BG-12 120 mg tid		0.78
		BG-12 240 mg tid		0.44
		Placebo		0.65
CONFIRM	All	Placebo	24	0.4
		BG-12 240 mg bid		0.22
		BG-12 240 mg tid		0.2

Trial	Population	Treatment	Time point (months)	ARR
		GA 20 mg		0.29
DEFINE	All	Placebo	24	0.36
		BG-12 240 mg bid		0.17
		BG-12 240 mg tid		0.19
FORTE Study Group	All	GA 20 mg	12	0.33
		GA 40 mg		0.35
Dose Comparison 9006 Study Group	All	GA 20 mg	9	0.69
		GA 40 mg		0.4
BEYOND	All	IFNβ-1b 500 µg	33	0.33
		IFNβ-1b 250 µg		0.36
		GA 20 mg		0.34
BECOME	All	GA 20 mg	24	0.33
		IFNβ-1b 250 µg		0.37
REGARD	All	GA 20 mg	24	0.29
		SC IFNβ-1a 44 µg		0.3
CombiRx	All	IM IFNβ-1a 30 µg	36	0.16
		GA 20 mg		0.11
EVIDENCE	All	SC IFNβ-1a 44 µg	12	0.585
		IM IFNβ-1a 30 µg		0.693
BRAVO	All	Placebo	24	0.37
		Laquinimod 0.6 mg		0.29
		IM IFNβ-1a 30 µg		0.27
LAQ/5062	All	Placebo	9	0.77
		Laquinimod 0.3 mg		0.76
		Laquinimod 0.6 mg		0.52
ALLEGRO	All	Placebo	24	0.39
		Laquinimod 0.6 mg		0.3
AFFIRM	All	Natalizumab 300 mg	24	0.23
		Placebo		0.73
HERMES	All	Rituximab 1000 mg	11	0.4
		Placebo		0.7
TEMSO	All	Placebo	27	0.54
		Teriflunomide 7 mg		0.37
		Teriflunomide 14 mg		0.37
TEMSO	RRMS	Placebo	27	[redacted]
		Teriflunomide 7 mg		[redacted]
		Teriflunomide 14 mg		[redacted]
TENERE	All	SC IFNβ-1a 44 µg	27	0.216

Trial	Population	Treatment	Time point (months)	ARR
		Teriflunomide 7 mg		0.41
		Teriflunomide 14 mg		0.259
Teriflunomide in MS	All	Placebo	9	0.81
		Teriflunomide 7 mg		0.58
		Teriflunomide 14 mg		0.55
TEMSO	RRMS	Placebo	ALL	[redacted]
		Teriflunomide 7 mg		[redacted]
		Teriflunomide 14 mg		[redacted]
TOWER	All	Placebo	27	0.5
		Teriflunomide 7 mg		0.39
		Teriflunomide 14 mg		0.32
TOWER	RRMS	Placebo	27	[redacted]
		Teriflunomide 7 mg		[redacted]
		Teriflunomide 14 mg		[redacted]

Abbreviations: ARR = annualised relapse rate; GA = glatiramer acetate; IFNβ-1a = interferon beta-1a; IFNβ-1b = interferon beta-1b; IM = intramuscular; mg = milligram; µg = microgram; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous

Table B6.7.5 Relapse-free data used in the MTC

Trial	Popn.	Treatment	Time point	Proportion S	Number Relapse-free	Relapse-free (denominator)
CAMMS223	All	SC IFNβ-1a 44 µg	36	59.46%	66	111
		Alemtuzumab 12 mg		78.57%	88	112
		Alemtuzumab 24 mg		84.55%	93	110
CARE-MS I	All	SC IFNβ-1a 44 µg	24	58.82%	110	187
		Alemtuzumab 12 mg		77.66%	292	376
CARE-MS II	All	SC IFNβ-1a 44 µg	24	46.53%	94	202
		Alemtuzumab 12 mg		65.49%	279	426
SELECT	All	Placebo	12	63.78%	125	196
		Daclizumab 150 mg		81.09%	163	201
		Daclizumab _300 mg		79.80%	162	203
FREEDOMS	All	Placebo	24	45.69%	191	418
		Fingolimod 0.5 mg		70.35%	299	425
		Fingolimod 1.25 mg		74.59%	320	429
FREEDOMS II	All	Placebo	24	52.68%	187	355
		Fingolimod 0.5 mg		71.51%	256	358
		Fingolomid 1.25mg		NR	NR	370
FTY720 D2201 Study Group	All	Placebo	6	65.59%	61	93
		Fingolimod 1.25 mg		85.11%	80	94
		Fingolimod 5 mg		84.04%	79	94
Saida et al	All	Placebo	6	64.91%	37	57
		Fingolimod 0.5 mg		78.95%	45	57
		Fingolimod 1.25 mg		83.33%	45	54
TRANSFORMS	All	Fingolimod 1.25 mg	12	79.76%	335	420
		Fingolimod 0.5 mg		82.52%	354	429
		IM IFNβ-1a 30 µg		69.37%	299	431
BG-12 Phase IIb Study	All	BG-12 120 mg qd	6	82.81%	53	64

Trial	Popn.	Treatment	Time point	Proportion S	Number Relapse-free	Relapse-free (denominator)
		BG-12 120 mg tid		68.75%	44	64
		BG-12 240 mg tid		80.95%	51	63
		Placebo		75.38%	49	65
CONFIRM	All	Placebo	24	58.95%	214	363
		BG-12 240 mg bid		71.03%	255	359
		BG-12 240 mg tid		75.94%	262	345
		GA 20 mg		68.00%	238	350
DEFINE	All	Placebo	24	53.92%	220	408
		BG-12 240 mg bid		72.93%	299	410
		BG-12 240 mg tid		74.04%	308	416
FORTE Study Group	All	GA 20 mg	12	77.65%	455	586
		GA 40 mg		76.98%	438	569
Dose Comparison 9006 Study Group	All	GA 20 mg	9	52.27%	23	44
		GA 40 mg		76.09%	35	46
BEYOND	All	IFNβ-1b 500 µg	33	59.96%	539	899
		IFNβ-1b 250 µg		57.97%	520	897
		GA 20 mg		58.48%	262	448
BECOME	All	GA 20 mg	24	71.79%	28	39
		IFNβ-1b 250 µg		52.78%	19	36
REGARD	All	GA 20 mg	24	61.90%	234	378
		SC IFNβ-1a 44 µg		61.92%	239	386
CombiRx	All	IM IFNβ-1a 30 µg	36	73.86%	178	241
		GA 20 mg		79.67%	196	246
Etemadifar et al.	All	IFNβ-1b 250 µg	24	43.33%	13	30
		IM IFNβ-1a 30 µg		20.00%	6	30
		SC IFNβ-1a 44 µg		56.67%	17	30
EVIDENCE	All	SC IFNβ-1a 44 µg	12	61.95%	210	339
		IM IFNβ-1a 30 µg		52.07%	176	338
LAQ/5062	All	Placebo	9	62.75%	64	102
		Laquinimod 0.3 mg		59.18%	58	98

Trial	Popn.	Treatment	Time point	Proportion S	Number Relapse-free	Relapse-free (denominator)
		Laquinimod 0.6 mg		70.75%	75	106
ALLEGRO	All	Placebo	24	52.16%	290	556
		Laquinimod 0.6 mg		62.91%	346	550
AFFIRM	All	Natalizumab 300 mg	24	66.99%	420	627
		Placebo		40.95%	129	315
HERMES	All	Rituximab 1000 mg	11	79.71%	55	69
		Placebo		60.00%	21	35
TEMSO	All	Placebo	27	45.73%	166	363
		Teriflunomide 7 mg		53.70%	196	365
		Teriflunomide 14 mg		56.42%	202	358
	RRMS	Placebo	27	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]
TENERE	All	SC IFNβ-1a 44 µg	27	84.62%	88	104
		Teriflunomide 7 mg		57.80%	63	109
		Teriflunomide 14 mg		76.58%	85	111
Teriflunomide in MS	All	Placebo	9	62.30%	38	61
		Teriflunomide 14 mg		77.19%	44	57
	RRMS	Placebo	9	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]
TOWER	All	Placebo	27	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]
	RRMS	Placebo	27	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]

Table B6.7.6 Three-month sustained accumulation of disability (SAD) (HR) data used in the MTC

Trial	Popn.	Treatment	Time point	Proportion SAD 3	Number SAD3	Denominator SAD3
CARE-MS I	All	SC IFNβ-1a 44 µg	24	[redacted]	[redacted]	[redacted]
		Alemtuzumab 12 mg	24	[redacted]	[redacted]	[redacted]
CARE-MS II	All	SC IFNβ-1a 44 µg	24	[redacted]	[redacted]	[redacted]
		Alemtuzumab 12 mg	24	[redacted]	[redacted]	[redacted]
CAMMS223	All	SC IFNβ-1a 44 µg	36	[redacted]	[redacted]	[redacted]
		Alemtuzumab 12 mg		[redacted]	[redacted]	[redacted]
		Alemtuzumab 24 mg		[redacted]	[redacted]	[redacted]
SELECT	All	Placebo	12	13.27%	26	196
		Daclizumab 150 mg		5.97%	12	201
		Daclizumab 300 mg		7.88%	16	203
FREEDOMS	All	Placebo	24	24.16%	101	418
		Fingolimod 0.5 mg		17.65%	75	425
		Fingolimod 1.25 mg		16.55%	71	429
FREEDOMS II	All	Placebo	24	29.01%	103	355
		Fingolimod 0.5 mg		25.42%	91	358
TRANSFORMS	All	Fingolimod 1.25 mg	12	6.67%	28	420
		Fingolimod 0.5 mg		5.83%	25	429
		IM IFNβ-1a 30 µg		7.89%	34	431
BEYOND	All	IFNβ-1b 500 µg	24	22%	200	899
		IFNβ-1b 250 µg		27%	244	897
		GA 20mg		21%	92	448
CONFIRM	All	Placebo	24	16.80%	61	363
		BG-12 240 mg bid		12.81%	46	359
		BG-12 240 mg tid		13.04%	45	345
		GA 20 mg		15.71%	55	350
DEFINE	All	Placebo	24	26.47%	108	408
		BG-12 240 mg bid		15.61%	64	410

Trial	Popn.	Treatment	Time point	Proportion SAD 3	Number SAD3	Denominator SAD3
		BG-12 240 mg tid		16.11%	67	416
EVIDENCE	All	SC IFNβ-1a 44 µg	11	12.68%	43	339
		IM IFNβ-1a 30 µg		14.50%	49	338
ALLEGRO	All	Placebo	24	15.65%	87	556
		Laquinimod 0.6 mg		11.09%	61	550
AFFIRM	All	Natalizumab 300 mg	24	17.07%	107	627
		Placebo		28.89%	91	315
TEMSO	All	Placebo	27	27.27%	99	363
		Teriflunomide 7 mg		21.64%	79	365
		Teriflunomide 14 mg		20.11%	72	358
TENERE	All	SC IFNβ-1a 44 µg	27	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]
TOWER	All	Placebo	27	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]

Table B6.7.7 Overall discontinuation (discont.) data used in the MTC

Trial	Popn.	Treatment	Time point	Proportion Discont.	Number Discont.	Denominator Discont.
CAMMS 223	All	SC IFNβ-1a 44 µg	36	38.32%	41	107
		Alemtuzumab 12 mg		12.96%	14	108
		Alemtuzumab 24 mg		11.11%	12	108
CARE-MS I	All	SC IFNβ-1a 44 µg	24	12.30%	23	187
		Alemtuzumab 12 mg		3.72%	14	376
CARE-MS II	All	SC IFNβ-1a 44 µg	24	21.78%	44	202
		Alemtuzumab 12 mg		6.21%	27	435
		Alemtuzumab 24mg		7.45%	12	161
SELECT	All	Placebo	12	9.18%	18	196
		Daclizumab 150 mg		7.96%	16	201
		Daclizumab _300 mg		7.88%	16	203
FREEDOMS	All	Placebo	24	27.51%	115	418
		Fingolimod 0.5 mg		18.82%	80	425
		Fingolimod 1.25 mg		30.54%	131	429
FTY720 D2201 Study Group	All	Placebo	6	6.52%	6	92
		Fingolimod 1.25 mg		5.38%	5	93
		Fingolimod 5 mg		11.96%	11	92
Saida et al	All	Placebo	6	10.53%	6	57
		Fingolimod 0.5 mg		15.79%	9	57
		Fingolimod 1.25 mg		11.11%	6	54
TRANSFORMS	All	Fingolimod 1.25 mg	12	14.76%	62	420
		Fingolimod 0.5 mg		10.26%	44	429
		IM IFNβ-1a 30 µg		11.83%	51	431
BG12 Phase IIb	All	BG12 120mg qd	6	15.63%	10	64
		BG12 120mg tid		20.31%	13	64
		BG-12 140mg tid		25.40%	16	63

Trial	Popn.	Treatment	Time point	Proportion Discont.	Number Discont.	Denominator Discont.
		Placebo		18.46%	12	65
CONFIRM	All	Placebo	24	35.54%	129	363
		BG-12 240 mg bid		29.53%	106	359
		BG-12 240 mg tid		27.91%	96	344
		GA 20 mg		24.50%	86	351
DEFINE	All	Placebo	24	34.80%	142	308
		BG-12 240 mg bid		30.73%	126	410
		BG-12 240 mg tid		30.53%	127	416
FORTE Study Group	All	GA 20 mg	12	8.87%	52	586
		GA 40 mg		13.88%	79	569
Dose Comparison 9006 Study Group	All	GA 20 mg	9	13.64%	6	44
		GA 40 mg		13.04%	6	46
BEYOND	All	IFNβ-1b 500 µg	33	18.15%	161	887
		IFNβ-1b 250 µg		11.71%	104	888
		GA 20 mg		15.96%	71	445
BECOME	All	GA 20 mg	24	10.26%	4	39
		IFNβ-1b 250 µg		11.11%	4	36
REGARD	All	GA 20 mg	24	13.60%	51	375
		SC IFNβ-1a 44 µg		20.89%	80	383
EVIDENCE	All	SC IFNβ-1a 44 µg	12	7.37%	25	339
		IM IFNβ-1a 30 µg		6.21%	21	338
Laquinimod in RMS	All	Laquinimod 0.1mg	6	4.41%	3	68
		Laquinimod 0.3mg		6.76%	5	74
		Placebo		4.48%	3	67
LAQ/5062	All	Placebo	9	10.79%	11	102
		Laquinimod 0.3 mg		6.12%	6	106
		Laquinimod 0.6 mg		5.66%	6	106
ALLEGRO	All	Placebo	24	23.20%	129	556
		Laquinimod 0.6 mg		20.55%	113	550

Trial	Popn.	Treatment	Time point	Proportion Discont.	Number Discont.	Denominator Discont.
AFFIRM	All	Natalizumab 300 mg	24	12.12%	76	627
		Placebo		14.60%	46	315
HERMES	All	Rituximab 1000 mg	11	15.94%	11	69
		Placebo		40.00%	14	35
TEMSO	All	Placebo	27	28.65%	104	363
		Teriflunomide 7 mg		24.93%	91	365
		Teriflunomide 14 mg		26.54%	95	358
	RRMS	Placebo	27	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]
TENERE	All	SC IFNβ-1a 44 µg	27	29.70%	30	101
		Teriflunomide 7 mg		18.18%	20	110
		Teriflunomide 14 mg		20.00%	22	110
Teriflunomide in MS	All	Placebo	9	6.56%	4	61
		Teriflunomide 7mg		4.92%	3	61
		Teriflunomide 14 mg		21.05%	12	57
	RRMS	Placebo	9	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]
TOWER	All	Placebo	27	32.47%	125	385
		Teriflunomide 7 mg		32.76%	134	409
		Teriflunomide 14 mg		33.96%	126	371
	RRMS	Placebo	27	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]

Table B6.7.8 Discontinuation due to adverse events used in the MTC

Trial	Popn.	Treatment	Time point	Proportion with DAE	Number with DAE	Denominator DAE
CAMMS223	All	SC IFNβ-1a 44 µg	36	12.15%	13	107
		Alemtuzumab 12 mg		1.85%	2	108
		Alemtuzumab 24 mg		0.93%	1	108
CARE-MS I	All	SC IFNβ-1a 44 µg	24	5.88%	11	187
		Alemtuzumab 12 mg		1.33%	5	376
CARE-MS II	All	SC IFNβ-1a 44 µg	24	7.43%	15	202
		Alemtuzumab 12 mg		3.22%	14	435
		Alemtuzumab 24mg		3.73%	6	161
SELECT	All	Placebo	12	0.51%	1	196
		Daclizumab 150 mg		1.00%	2	201
		Daclizumab _300 mg		1.97%	4	203
FREEDOMS	All	Placebo	24	5.74%	24	418
		Fingolimod 0.5 mg		3.53%	15	425
		Fingolimod 1.25 mg		7.23%	31	429
FTY720 D2201 Study Group	All	Placebo	6	4.35%	4	92
		Fingolimod 1.25 mg		5.38%	5	93
		Fingolimod 5 mg		8.70%	8	92
Saida et al	All	Placebo	6	5.26%	3	57
		Fingolimod 0.5 mg		10.53%	6	57
		Fingolimod 1.25 mg		11.11%	6	54
TRANSFORMS	All	Fingolimod 1.25 mg	12	7.62%	32	420
		Fingolimod 0.5 mg		3.73%	16	429
		IM IFNβ-1a 30 µg		2.78%	12	431
BG-12 Phase IIb Study	All	BG-12 120 mg qd	6	7.81%	5	64
		BG-12 120 mg tid		10.94%	7	64

Trial	Popn.	Treatment	Time point	Proportion with DAE	Number with DAE	Denominator DAE
		BG-12 240 mg tid		12.70%	8	63
		Placebo		0.00%	0	65
CONFIRM	All	Placebo	24	5.79%	21	363
		BG-12 240 mg bid		10.03%	36	359
		BG-12 240 mg tid		11.05%	38	344
		GA 20 mg		7.69%	27	351
DEFINE	All	Placebo	24	5.39%	22	408
		BG-12 240 mg bid		12.44%	51	410
		BG-12 240 mg tid		15.87%	66	416
FORTE Study Group	All	GA 20 mg	12	4.78%	28	586
		GA 40 mg		8.96%	51	569
Dose Comparison 9006 Study Group	All	GA 20 mg	9	2.27%	1	44
		GA 40 mg		8.70%	4	46
BEYOND	All	IFNβ-1b 500 µg	33	2.25%	20	887
		IFNβ-1b 250 µg		1.46%	13	888
		GA 20 mg		1.80%	8	445
BECOME	All	GA 20 mg	24	2.56%	1	39
		IFNβ-1b 250 µg		0.00%	0	36
EVIDENCE	All	SC IFNβ-1a 44 µg	11	4.72%	16	339
		IM IFNβ-1a 30 µg		4.14%	14	338
Laquinimod in RMS	All	Laquinimod 0.3mg	6	2.70%	2	74
		Placebo		1.49%	1	67
LAQ/5062	All	Placebo	9	4.90%	5	102
		Laquinimod 0.3 mg		2.04%	2	98
		Laquinimod 0.6 mg		1.89%	2	106
ALLEGRO	All	Placebo	24	5.04%	28	556
		Laquinimod 0.6 mg		7.64%	42	550
AFFIRM	All	Natalizumab 300 mg	24	6.06%	38	627
		Placebo		4.13%	13	315

Trial	Popn.	Treatment	Time point	Proportion with DAE	Number with DAE	Denominator DAE
HERMES	All	Rituximab 1000 mg	11	4.35%	3	69
		Placebo		5.71%	2	35
TEMSO	All	Placebo	27	7.99%	29	363
		Teriflunomide 7 mg		10.14%	37	365
		Teriflunomide 14 mg		10.61%	38	358
	RRMS	Placebo	27	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]
TENERE	All	SC IFNβ-1a 44 µg	27	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]
Teriflunomide in MS	All	Placebo	9	6.56%	4	61
		Teriflunomide 7mg		4.92%	3	61
		Teriflunomide 14 mg		10.04%	8	57
	RRMS	Placebo	9	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]
TOWER	All	Placebo	27	6.75%	26	385
		Teriflunomide 7 mg		13.20%	54	409
		Teriflunomide 14 mg		15.63%	58	371
	RRMS	Placebo	27	[redacted]	[redacted]	[redacted]
		Teriflunomide 7 mg		[redacted]	[redacted]	[redacted]
		Teriflunomide 14 mg		[redacted]	[redacted]	[redacted]

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix. See Additional Appendix 4.

Quantitative analyses were performed on the following outcomes:

- Rates Ratio for Annualised Relapse Rate (ARR) (modeling the number of total events in each arm as following a Poisson distribution)
- Odds Ratio for remaining relapse-free
- Hazard Ratio for three-month Sustained Accumulation of Disability (SAD)
- Odds Ratio for total discontinuations
- Odds Ratio for discontinuation due to adverse events

MTC

Random-effect MTC analyses were conducted to compare all DMTs under investigation within a single model. MTC analyses employed a vaguely informative normal prior with a uniform standard deviation (SD), the value of which was 1.0 for all outcomes.

Bayesian MTC analyses were conducted assuming the treatment effect came from a random distribution of effects. For Bayesian MTCs, a burn-in of 50,000 iterations was used for all analyses; BGR trace plots suggested this was more than enough of a burn-in to allow estimates to converge. A follow-up of 50,000 iterations was used to create the sample for the posterior, and history plots were reviewed to confirm convergence. In addition, an inspection of the ratio of the measure of convergence error to the SD of the estimates confirmed that the ratio was less than 3.5% for almost all estimates, further suggesting convergence and in keeping with published guidelines. National Institute for Health and Care Excellence (NICE) recommendations provided by the Decision Support Unit suggest that the Monte Carlo error (accounting for both the number of iterations and the extent of auto-correlation) should be ≤5% of the posterior SD for the parameters examined.

All analyses are described in Table B6.7.9 below, including the sensitivity analysis. A sensitivity analysis was included based on ≥80% RRMS and including studies for all years from 1980, rather than from 2000 used in the base case and the results are presented in Additional Appendix 2.

Table B6.7.9 Analyses conducted by outcome

Analysis	Base Case	Sensitivity Analysis
Description	**Recruitment ≥2000 and ≥80% RRMS**	**All-years and ≥80% RRMS**
ARR (rate ratio)	✓	✓
Proportion relapse-free (OR)	✓	
SAD confirmed 3 months (HR)	✓	✓
Total discontinuations (OR)	✓	✓
DAEs (OR)	✓	

Note: ✓designates analyses that were conducted.

Abbreviations: ARR = annualised relapse rate; HR = hazard ratio; OR = odds ratio

Indirect comparison for highly active disease (HAD) and rapidly evolving severe disease (RES)

The MTC did not consider subgroups of RRMS (i.e. HAD or RES) and consequently two indirect comparisons were performed which multiplied outcomes calculated for teriflunomide in these subgroups, by those observed in the respective subgroups for fingolimod (HAD only) and natalizumab (RES only). Outcomes included SAD at 3 months, ARR and overall discontinuation.

6.7.6 Please present the results of the analysis.

Results and associated Forest Plots are presented for the base-case MTC of the therapies included in the decision problem. For the all-years sensitivity analysis, see Additional Appendix 2. For expanded results including all therapies used in the MTC see Additional Appendix 5.

Results are also presented here of the indirect comparisons for teriflunomide in HAD and RES. For HAD, only the TEMSO study recorded patients who had at least one relapse within one year before randomisation, and with previous DMT intake (only interferon) for at least 12 months, gap from last DMT to randomisation lower or equal to 12 months, and at least one GAD lesion at baseline. For RES, only the TEMSO study recorded patients who had at least two relapses within one year before randomization, and at least one GAD lesion at baseline.

Table B6.7.10 Annualised relapse rate results from the MTC

	Teriflunomide 14mg	Placebo
	Rate ratio [95% CrI]	
Teriflunomide 14mg	N/A	0.67 [0.57, 0.77]
IFNβ-1b 250 µg	0.98 [0.73, 1.31]	0.68 [0.52, 0.88]
IM IFNβ-1a 30 µg	0.86 [0.69, 1.05]	0.78 [0.67, 0.91]
SC IFNβ-1a 44 µg	1.06 [0.84, 1.35]	0.62 [0.51, 0.76]
GA 20 mg	1.05 [0.83, 1.31]	0.64 [0.53, 0.76]
Fingolimod 0.5 mg	1.45 [1.17, 1.80]	0.46 [0.40, 0.54]
Natalizumab 300 mg	2.12 [1.63, 2.75]	0.31 [0.25, 0.39]

Figure B6.7.7 Forest Plot: Annualised relapse rate results from the MTC

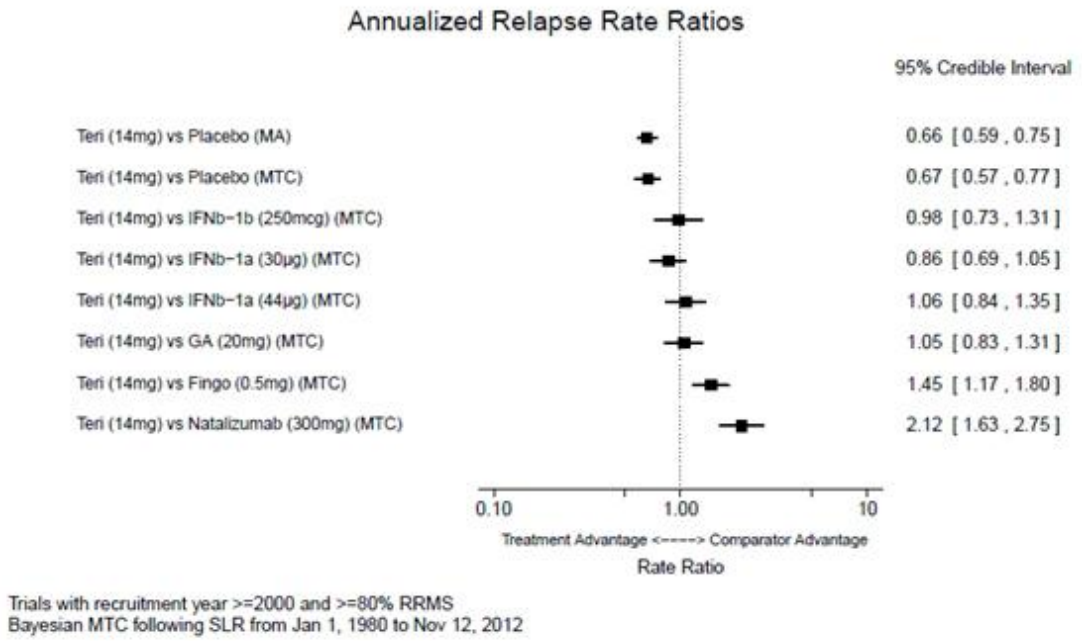


Table B6.7.11 Annualised relapse rate data for the HA-disease sub-analysis

Trial	Population	Treatment	Time point (months)	ARR [95% CI]	RR vs. placebo
TEMSO	HA disease	Placebo (n=10)	All	[redacted]	
		Teriflunomide 14 mg (n=11)		[redacted]	[redacted]

Table B6.7.12 Annualised relapse rate data for the RES-disease sub-analysis

Trial	Population	Treatment	Time point (months)	ARR [95% CI]	RR vs. placebo
TEMSO	RES disease	Placebo (n=39)	All	[redacted]	
		Teriflunomide 14 mg (n=33)		[redacted]	[redacted]

Fingolimod was associated with an ARR of 0.57 [0.28-1.16] compared to placebo based on the EPAR subgroup analysis considering patients who had at least one relapse within one year before randomization [Fingolimod EPAR, 2005]. Therefore, the indirect comparison of teriflunomide vs. fingolimod for HAD was calculated [redacted]. Natalizumab was associated with an ARR of 0.81 [0.70-0.88] compared to placebo based on the

NICE manufacturers submission [Biogen, 2006]. Therefore, the indirect comparison of teriflunomide vs. natalizumab for RES was calculated as [redacted]

Table B6.7.13 Proportion relapse-free results from the MTC

	Teriflunomide 14mg	Placebo
	Odds ratio [95% CrI]	
Teriflunomide 14mg	[redacted]	[redacted]
IFNβ-1b 250 µg	[redacted]	[redacted]
IM IFNβ-1a 30 µg	[redacted]	[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]
GA 20 mg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]

[redacted] **Forest plot: Proportion relapse-free results from the MTC**

[redacted]

Table B6.7.14 Relapse-free data for the HA-disease sub-analysis

Trial	Population	Treatment	Time point	Number (%)	Odds ratio vs. placebo
TEMSO	HA disease	Placebo (n=10)	All	[redacted]	
		Teriflunomide 14 mg (n=11)		[redacted]	[redacted]

Table B6.7.15 Relapse-free data for the RES-disease sub-analysis

Trial	Population	Treatment	Time point	Number (%)	Odds ratio vs. placebo
TEMSO	RES disease	Placebo (n=39)	All	[redacted]	
		Teriflunomide 14 mg (n=33)		[redacted]	[redacted]

No indirect comparison was performed in HAD or RES due to insufficient data for fingolimod and natalizumab from the literature.

Table B6.7.16 Three-month sustained accumulation of disability results from the MTC

	Teriflunomide 14mg	Placebo
	Hazard ratio [95% CrI]	
Teriflunomide 14mg		0.71 [0.53, 0.92]
IFNβ-1b 250 µg	0.58 [0.30, 1.12]	1.21 [0.68, 2.16]
IM IFNβ-1a 30 µg	0.77 [0.50, 1.24]	0.91 [0.61, 1.33]
SC IFNβ-1a 44 µg	0.90 [0.54, 1.45]	0.79 [0.51, 1.24]
GA 20 mg	0.76 [0.45, 1.30]	0.93 [0.59, 1.45]
Fingolimod 0.5 mg	0.95 [0.64, 1.35]	0.75 [0.58, 0.96]
Natalizumab 300 mg	1.22 [0.77, 1.94]	0.58 [0.4, 0.84]

Figure B6.7.9 Forest plot: Three-month sustained accumulation of disability results from the MTC

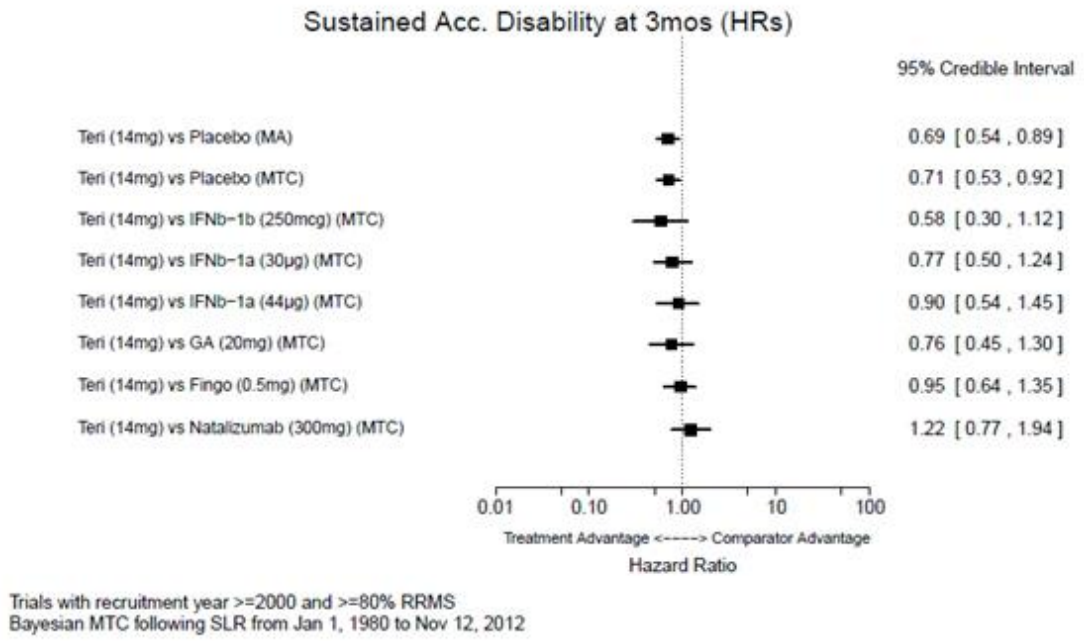


Table B6.7.17 Three-month sustained accumulation of disability (SAD) data for the HA-disease sub-analysis

Trial	Population	Treatment	Time point (months)	Number (%) with SAD	HR vs. placebo (95% CI)
TEMSO	HA disease	Placebo (n=10)	All	[redacted]	
		Teriflunomide 14 mg (n=11)		[redacted]	[redacted]

Table B6.7.18 Three Month sustained accumulation of disability (SAD) data for the RES-disease sub-analysis

Trial	Population	Treatment	Timepoint (months)	Number (%) with SAD	HR vs. placebo (95% CI)
TEMSO	RES disease	Placebo (n=39)	All	[redacted]	
		Teriflunomide 14 mg (n=33)		[redacted]	[redacted]

Fingolimod was associated with a SAD HR of 0.77 [0.31-1.921] compared to placebo based on the EPAR subgroup analysis considering patients who had at least one relapse within one year before randomisation [Fingolimod EPAR, 2005]. Therefore, the indirect comparison of teriflunomide vs. fingolimod for HAD was calculated as [redacted] Natalizumab was associated with a SAD HR of 0.47 [0.24-0.93] compared to placebo based on the NICE manufacturers submission [Biogen, 2006]. Therefore, the indirect comparison of teriflunomide vs. natalizumab for RES was calculated as [redacted]

Table B6.7.19 Total discontinuations odds ratio results from the MTC

	Teriflunomide 14mg	Placebo
	Odds ratio [95% CrI]	
Teriflunomide 14mg		[redacted]
IFNβ-1b 250 µg	[redacted]	[redacted]
IM IFNβ-1a 30 µg	[redacted]	[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]
GA 20 mg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]

[redacted] **Forest plot: Total discontinuations odds ratio results from the MTC**

[redacted]

Table B6.7.20 Overall Discontinuation data for the HA-disease sub-analysis

Trial	Population	Treatment	Time point (months)	Number (%) discontinuing	Odds ratio vs. placebo (95% CI)
TEMSO	HA disease	Placebo (n=10)	All	[redacted]	
		Teriflunomide 14 mg (n=11)		[redacted]	[redacted]

Table B6.7.21 Overall Discontinuation data for the RES-disease sub-analysis

Trial	Population	Treatment	Time point (months)	Number (%) discontinuing	Odds ratio vs. placebo (95% CI)
TEMSO	RES disease	Placebo (n=39)	All	[redacted]	
		Teriflunomide 14 mg (n=33)		[redacted]	[redacted]

No indirect comparison was performed in HAD or RES due to insufficient data for fingolimod and natalizumab from the literature.

Table B6.7.22 Discontinuations due to adverse events odds ratio results from the MTC

	Teriflunomide 14mg	Placebo
	Odds ratio [95% CrI]	
Teriflunomide 14mg		[redacted]
IFNβ-1b 250 µg	[redacted]	[redacted]
IM IFNβ-1a 30 µg	[redacted]	[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]
GA 20 mg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]

[redacted] **Forest plot: Discontinuations due to adverse events odds ratio results from the MTC**

[redacted]

Table B6.7.23 Discontinuation due to adverse events data for the HA-disease sub-analysis

Trial	Population	Treatment	Time point (months)	Number (%) discontinuing	Odds ratio vs. placebo (95% CI)
TEMSO	HA disease	Placebo (n=10)	All	[redacted]	
		Teriflunomide 14 mg (n=11)		[redacted]	[redacted]

Table B6.7.24 Discontinuation due to adverse events data for the RES-disease sub-analysis

Trial	Population	Treatment	Time point (months)	Number (%) discontinuing	Odds ratio vs. placebo (95% CI)
TEMSO	RES disease	Placebo (n=39)	All	[redacted]	
		Teriflunomide 14 mg (n=33)		[redacted]	[redacted]

No indirect comparison was performed in HAD or RES due to insufficient data for fingolimod and natalizumab from the literature.

Data for Rebif® (IFNβ-1a) 22µg

As previously discussed, data for IFNβ-1a 22µg were not available from the studies included in the base case analysis but represents a dose used routinely in UK practice. Therefore the ratio between results from the sensitivity analysis MTC (all-years, ≥80% RRMS) was applied to the base case MTC e.g. the all-cause discontinuation OR of teriflunomide versus IFNβ-1a 22µg from the sensitivity analysis MTC was [redacted], whilst teriflunomide versus IFNβ-1a 44µg was [redacted]. Therefore, the ratio of IFNβ-1a 44µg to 22µg was [redacted] in the sensitivity analysis MTC. Applying this ratio to the all-cause discontinuation OR of teriflunomide versus IFNβ-1a 44µg from the base case MTC gives an OR for teriflunomide versus IFNβ-1a 22µg of [redacted]

Table B6.7.25 Inferred rates for (IFNβ-1a) 22µg post-2000

Parameter	All-years MTC Rebif 44µg	All-years MTC Rebif 22µg	Ratio of 44 to 22	Post-2000 MTC Rebif 44µg	Inferred Post-2000 Rebif 22µg value
ARR		N/A			Assume same as Rebif 44µg
Relapse Free	N/A	N/A			
SAD3 (comparator vs. placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations (Teri 14mg vs. comparator)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations due to AE	N/A	N/A			

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

In the MTC described, there were not many trials investigating the same comparison; therefore there wasn't the power to detect heterogeneity. Informal classical meta-analyses of direct and indirect effects were examined for strong signs of heterogeneity but nothing of concern was observed.

The following areas of clinical heterogeneity were explored (see Table B6.7.1):

- Age was relatively homogenous across studies ranging from 32 years [Coles et al. 2008] to 42 years [Hauser et al. 2008]
- Percentage of male patients showed a degree of variation from 17% to 45%
- Disease duration showed a degree of variation from 2 years to 10.8 years

- Eight of the 30 studies had a certain proportion of patients without RRMS although in this regard it is noted that the study entry criteria was RRMS ≥80%
- Of the 16 studies where percentage prior use of DMT was recorded only three were treatment naïve studies. In the remaining 13 studies DMT prior use varied from 11-21% [Vermersch et al. 2012] to 77-78% [Hauser et al. 2008]
- Baseline EDSS was relatively homogenous across studies with a range of 2.1 to 3
- Relapse rate prior to study entry was relatively homogenous across studies with two year period relapse rate range of 2.1-2.8 (Table 6.7.1)
- There was a degree of variation in the ARR during study in placebo arms: 0.36-0.99 studies (Table 6.7.4)
- There was a degree of variation in disability progression in placebo arms: 13%-28% (Table 6.7.6).

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

No studies were identified within the base case MTC which it was thought appropriate to exclude on the basis of clinical or statistical heterogeneity.

As discussed in Section 6.6.1, to minimize clinical heterogeneity, the base case MTC analysis was conducted on only studies that recruited patients in or after the year 2000. As part of a sensitivity analysis, the impact of excluding studies from the MTC on the basis of the year of recruitment was tested and all studies within the systematic literature review irrespective of year of recruitment were included within an MTC (included in Additional Appendix 2)

The results of this sensitivity analysis MTC are as follows:

- Table AA2.1 in Additional Appendix 2 shows that six studies are added to the MTC as a result of including all studies identified in the literature review irrespective of year of recruitment. This includes three studies of glatiramer acetate versus placebo [Bornstein et al. 1987; Johnson et al. 1995; Comi et al. 2001], one for IFNβ-1b 250 µg versus placebo [Duquette et al. 1993], one for SC IFNβ-1a 44µg (versus SC IFNβ-1a 22µg and placebo) [Ebers et al 1998] and one for IM IFNβ-1a 30µg versus placebo [Jacobs et al. 1996].
- ARR in Table AA2.2 in Additional Appendix 2 (which when compared to the comparable results in Table B6.7.1 in the base case MTC) shows that for all the included comparators ARR rates appear to be similar. In this regard it is noted that two studies are added to the MTC in the SA compared to the base case of glatiramer acetate versus placebo [Johnson et al. 1995; Comi et al. 2001], one for IFNβ-1b

250µg versus placebo [Duquette et al. 1993] and one for IM IFNβ-1a 30µg versus placebo [Jacobs et al. 1996].

- HR for 3 month SAD versus placebo are better in the all-years sensitivity analysis MTC (see Table AA2.3, Additional Appendix 2) than in the base case MTC (see Table B6.7.1) for all comparators (with the exception of the central estimate of natalizumab which remains the same) and for teriflunomide. The most substantial differences are for IFNβ-1b 250µg, SC IFNβ-1a 44µg and for glatiramer acetate. In this regard it is noted that two studies are added to the network MTC in the sensitivity analysis compared to the base case of glatiramer acetate versus placebo, [Johnson et al. 1995; Bornstein et al. 1987] one for IFNβ-1b 250µg versus placebo [Duquette et al. 1993] and one for SC IFNβ-1a 44µg (versus SC IFNβ-1a 22µg and placebo) [Ebers et al. 1998] (as shown in Table AA2.3 in Additional Appendix 2)
- OR for total discontinuation rate versus placebo and versus teriflunomide are worse for all comparators in the all-years MTC (see Table AA2.4, Additional Appendix 2) than in the base case MTC (see Table B6.7.1). In this regard it is noted that two studies are added to the network MTC in the all-years sensitivity analysis compared to the base case of glatiramer acetate versus placebo [Johnson et al. 1995; Comi et al. 2001], one for IFNβ-1b 250µg versus placebo [Duquette et al. 1993] , one for SC IFNβ-1a 44µg (versus SC IFNβ-1a 22µg and placebo) [Ebers et al. 1991] and one for IM IFNβ-1a 30µg versus placebo [Jacobs et al. 1996] (as shown in Table AA2.4 in Additional Appendix 2).

This all-year sensitivity analysis MTC analysis needs to be considered in the context of the rationale for having exclusion criteria based on year of recruitment in the base case MTC (as outlined in Section 6.1.1). Namely, changes in diagnostic criteria and in clinical practice leading to the identification of patients much earlier in the disease course, and with less frequent or severe symptoms and a noticeable decline in ARR rates in more recent years, even across patients receiving placebo in clinical trials and definitions of outcomes. In this context the following is noted:

- Relapse rate in the two year period prior to study entry: 2.1-2.8 studies >2000 and ≤ 2000 2.5-3.9 (Additional Appendix 2 Table AA2.1)
- ARR range during study in placebo arms: 0.36-0.99 studies >2000 and ≤ 2000 0.84-1.27 (Additional Appendix 2 Table AA2.2)
- Disability progression in placebo arms: 13%-28% studies >2000 and ≤ 2000 24.6%-52.65% (Additional Appendix 2 Table AA2.3)

An analysis of the relevant publications was performed to identify heterogeneity in the definition of outcomes. It is noted that whilst this was not identified to be the case for ARR and total discontinuation rate, this was the case

for disability progression. All the studies included in the base-case MTC used the same measure of disability progression which was sustained disability progression at 3 months (i.e. a minimum increase in EDSS state of at least one point compared to baseline sustained over two measurements separated by 3 months). Given the fluctuating nature of MS symptoms, such a confirmation that disability progression is sustained is of importance. In addition the utilisation of the same measurement of disability progression (EDSS) is important to ensure that heterogeneity in outcome measurement in this regard does not occur. In relation to the four studies included in the disability progression HR all-years MTC network (see Table AA1.3, Additional Appendix 2) the following is noted:

- Three of the studies measured disability progression using EDSS: One of glatiramer acetate versus placebo [Johnson et al. 1998] (n=251), one for IFNβ-1b 250 µg versus placebo [Duquette et al. 1993] (n=147) and one for SC IFNb-1a 44 µg (versus SC IFNb-1a 22 µg and placebo) [Ebers et al. 1998] (n=560). Only one of these three studies had a measure of disability which included a repeat measure to confirm sustainability of disability. This was the study of SC IFNb-1a 44 µg (versus SC IFNb-1a 22 µg and placebo) and it used a 3 month definition of sustainability.
- One study [Bornstein et al. 1987] (n=50) did not use EDSS. This was a study of glatiramer acetate versus placebo. It used the Kurtzke Disability Status Score (DSS). The EDSS is an update of the DSS. The DSS has 10 grades or steps beyond 0 (normal), extending to status 10 (death due to MS). One of the main differences in the EDSS was that it provides, for each step from 1 through 9, two steps that together add up to the same step of the original DSS [Kurtzke, 1983]. The Bornstein study also did not include a repeat measure of sustainability within its definition of disability. The rate of disability progression in the placebo arm of this study was substantially higher than in the other three studies included in the all-years sensitivity analysis; 52.65% compared to 28%-29% (see Table AA2.3, Additional Appendix 2) and to those observed in the placebo arms in the base case MTC (13%-28%) (Table B6.7.1).

As discussed in the health economic section (Section 7.6) where a sensitivity analysis is carried out using this all-years MTC, the model is sensitive to the assumptions made in relation to the HR disability progression results. Given this and the suggestion of clinical and outcome measurement heterogeneity being substantial in one of the glatiramer acetate versus placebo studies [Bornstein et al. 1987] the SA MTC was run without the inclusion of this study. (See Table AA2.8 and Figure AA2.7, Additional Appendix 2). The key results to note in this regard are:

- HR for sustained accumulation of disability (3 months) in the all-years sensitivity analysis MTC without Bornstein et al 1987 of glatiramer acetate versus placebo is 0.8 (compared to 0.76 in the all-years MTC including Bornstein et al 1987 and 0.93 in the base case MTC)

Further analysis of the impact of running the cost effectiveness analysis with and without the Bornstein study is considered in the health economic section of the submission (Section 7.6).

6.7.9 Please discuss any heterogeneity between results of pair wise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

See section B6.7.7.

6.8 Non-RCT evidence

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

We have not considered any non-RCT data in this submission to support statements regarding the efficacy of teriflunomide or any of the comparators identified in the decision problem.

6.9 Adverse events

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 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 10.8 and 10.9, appendices 8 and 9.

Selection of trials for reporting of adverse events was via the same process as that described in section 6.1 and 6.2. In addition, a placebo-controlled, pooled safety analysis of data from the Phase II and TEMSO studies compiled for pharmacovigilance purposes during the trial programme for teriflunomide was identified [Sanofi 2001, Aubagio 2.7.4 summary-clin-safety].

Adverse event reporting was a mandatory part of all the teriflunomide studies identified in sections 6.1 and 6.2 (discussed in section 6.3). However, the primary objective of the extension arms of the Phase II (Proof of Concept) and Phase III TEMSO trials was the assessment of safety and tolerability and hence the results to date from these trial extensions are reported here. We additionally report the results of the pooled safety analysis and TOWER studies as these are presented vs. placebo and represent discrete trial populations; subsequent impact of adverse events on cost-effectiveness has been derived from this data.

The pooled safety data from the teriflunomide Phase II-III monotherapy program in relapsing MS patients considers two pools of patients:

- **Pool A:** Focused on the placebo-controlled segments of studies (2001 and EFC6049/TEMSO).
- **Pool B:** Included the non-controlled long-term treatment with teriflunomide based on Phase 2-3 studies and their extensions, including a subset of patients with more than 10 years follow-up (Studies 2001+LTS6048 and EFC6049+LTS6050) and the teriflunomide treatment arms from the active-controlled Phase 3 study (EFC10891/TENERE).

The following results are representative of Pool A data only. The rationale for not including Pool B data within this safety report includes:

- Pool B includes *non-controlled* long-term data.
- Pool B includes safety data from the extensions arms of the Phase II 2001 study and Phase III EFC6049 (TEMSO) study.
- This safety data has already been included – see above.
- Pool B includes the EFC10891 (TENERE) study, which has no placebo comparator.

Modelling of the effects of adverse events (see section 7) on cost effectiveness considers the impact of adverse events where incidence is ≥4% of that observed with placebo. Selected results from the pooled analyses are therefore represented relative to this cut-off. It should be noted that many adverse effects occurring at this level require monitoring or cessation of therapy rather than active treatment of the adverse event. Adverse effects may also incur a disutility.

Cost effectiveness modelling is influenced by discontinuations due to adverse events, monitoring of blood parameters, management of gastrointestinal disturbances (nausea and diarrhoea), alopecia (a disutility) and liver function abnormalities. All are reported below.

In summary, almost all patients on teriflunomide report at least one treatment-emergent-adverse-event (TEAE), however for the majority of events, incidence is similar to placebo.

Adverse events of note are:

- Liver function analyses – elevations of liver enzymes have been observed in patients and occur mostly within 6-months of treatment initiation; it is for this reason that close monitoring of liver enzymes is recommended during the first 6-months of treatment [Teriflunomide SmPC, 2013]
- Diarrhoea, nausea and vomiting which are mild to moderate, transient and infrequently lead to discontinuation [Teriflunomide SmPC, 2013]
- Parasthesias and dysaethesias – both have been reported at a higher rate than with placebo and tend to improve with treatment cessation [Teriflunomide SmPC, 2013]
- Infections – teriflunomide is an immunomodulatory agent therefore an effect on immune function is expected. However, no increase in serious infection has been observed [Teriflunomide SmPC, 2013]
- Alopecia – most cases are diffuse or generalised over the scalp and largely resolve as treatment continues. Few patients discontinue due to alopecia [Teriflunomide SmPC, 2013]

There have been very few deaths in patients receiving teriflunomide; of those that have occurred, none have been directly attributed to teriflunomide.

Expanded reporting of adverse event data for the TEMSO extension, pooled safety analysis and TOWER studies can be found in Additional Appendix 6.

Long-term safety of leflunomide

Teriflunomide is the active metabolite of leflunomide which has been in clinical use for arthritis and psoriatic arthritis for over a decade. It is therefore pertinent to examine the safety record of leflunomide to identify any 'red-flags' related to safety. In general the side effect profile of leflunomide is acceptable; side effects of leflunomide are relatively common but most are mild and manageable without discontinuation: diarrhoea, rash, reversible alopecia and transient rises in liver enzyme tests are reported. This is in line with the reported adverse event profile for teriflunomide. More significant health problems related to leflunomide use are rarer and include hypertension, bone marrow suppression, peripheral axonal neuropathy, interstitial pneumonitis and teratogenicity [Jones et al. 2010].

Since the launch of leflunomide, there have been reports of fatal liver injury but in arthritis patients, this has been reported to be no more likely than with methotrexate and less likely than with other disease modifying antirhematic drugs (DMARDs). The FDA placed a 'black box' warning for liver failure on the datasheet for leflunomide in 2010. In accordance with this, close monitoring is required with leflunomide therapy (and likewise, teriflunomide [Teriflunomide SmPC, 2013]) [Jones et al. 2010].

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

Phase II 'Proof of Concept' extension (on-going) [Confavreux et al. 2012]

Please note relative-risk ratios are not available for this data.

The Phase II extension study assessed the long-term safety of teriflunomide in patients with RMS. Almost every patient reported at least one treatment-emergent adverse event (TEAE) over the long study period, the most commonly reported including infections, hepatic disorders, gastrointestinal disorders, neurological disorders, psychiatric disorders and haematologic abnormalities. Other specific AEs of interest included decreased hair density, blood pressure increase, hypersensitivity reaction, malignancies and pregnancies.

Discontinuations due to TEAEs occurred for 13 (19.7%) patients. Serious adverse events (SAEs) were reported in 19 (28.8%) patients with 9 (13.6%) patients discontinuing due to serious TEAEs.

One death was reported over the study period. A 51-year-old Caucasian female patient, who had been treated with teriflunomide 14 mg for 4.8 years, died from a sudden cardiac disorder a few hours after admission to hospital for 'malaise' with anxiety, hypotension and tachycardia. The patient had a medical history of dyspnoea, anxiety disorder, depression/delusions and Hashimoto's thyroiditis with hypothyroidism. Additionally, 2 years earlier, the patient had experienced an SAE of respiratory failure in association with pneumonia and tachycardia. The patient was also concomitantly taking several medications, including propranolol, salmeterol, levothryrox, betamethasone, amantadine and oestradiol, and was given benzodiazepines at the time of the event. Therefore, underlying disease conditions and concomitant medications may have been contributory. See Table B6.9.1.

Table B6.9.1 Incidence (patients, n, %) of treatment-emergent adverse events throughout the study (≥20 % crude incidence during the core study and extension)

TEAE	Crude incidence, n (%)	Episodes of TEAEs per patient, N1 (N2/n)[a]
	Teriflunomide 14mg (N=66)	Teriflunomide 14mg (N=66)
Any TEAE	66 (100)	37.9 (2503/66)
Infections and infestations	**56 (84.8)**	**7.5 (421/56)**
Nasopharyngitis	35 (53.0)	1.9 (68/35)
Upper respiratory tract infection	29 (43.9)	2.2 (63/29)
Influenza	23 (34.8)	1.8 (41/23)
Urinary tract infection	15 (22.7)	2.9 (44/15)
Gastrointestinal disorders	**50 (75.8)**	**3.6 (180/50)**
Diarrhoea	25 (37.9)	1.6 (40/25)
Nausea	17 (25.8)	1.5 (25/17)
Investigations[a]	**53 (80.3)**	**5.5 (292/53)**
Alanine aminotransferase increased	19 (28.8)	2.1 (39/19)
Aspartate aminotransferase increased	15 (22.7)	1.5 (22/15)
Nervous system disorders	**61 (92.4)**	**8.5 (517/61)**
Hypoaesthesia	33 (50.0)	2.3 (77/33)
Headache	26 (39.4)	2.5 (64/26)
Pallanesthesia	20 (30.3)	1.3 (26/20)
Sensory disturbance	19 (28.8)	1.3 (24/19)
Contd over.		

TEAE contd.	Crude incidence, n (%)	Episodes of TEAEs per patient, NI (N2/n)[a]
	Teriflunomide 14mg (N=66)	Teriflunomide 14mg (N=66)
Dizziness	14 (21.2)	2.5 (35/14)
Hyperreflexia	14 (21.2)	1.9 (27/14)
Multiple sclerosis[b]	13 (19.7)	1.2 (15/13)
Coordination abnormal	10 (15.2)	1.4 (14/10)
Psychiatric disorders	**34 (51.5)**	**1.8 (61/34)**
Insomnia	17 (25.8)	1.3 (22/17)
Depression	10 (15.2)	1.4 (14/10)
Skin and subcutaneous	**42 (63.6)**	**2.6 (111/42)**
Hair thinning/decreased hair	18 (27.3)	1.4 (25/18)
Rash	11 (16.7)	1.9 (21/11)
Musculoskeletal and	**53 (80.3)**	**5.7 (301/53)**
Muscular weakness	25 (37.9)	2.2 (55/25)
Back pain	24 (36.4)	1.9 (37/20)
Pain in extremity	21 (31.8)	2.5 (52/21)
Paresthesia	20 (30.3)	1.9 (37/20)
Arthralgia	18 (27.3)	1.5 (27/18)
General disorders	**52 (78.8)**	**3.3 (169/52)**
Fatigue	32 (48.5)	2.2 (71/32)
Gait disturbance	11 (16.7)	1.2 (13/11)
Asthenia	8 (12.1)	1.1 (9/8)
Renal and urinary disorders	**23 (34.8)**	**2.6 (60/23)**
Micturition urgency	13 (19.7)	1.9 (25/13)
Serious TEAEs[d]		
Any serious TEAE	19 (28.8)	2.0 (38/19)
Hepatic enzyme increased	5 (7.6)	1.0 (5/5)
Alanine aminotransferase	2 (3.0)	1.5 (3/2)
Loss of consciousness	2 (3.0)	1.0 (2/2)
Neutropenia	2 (3.0)	1.5 (3/2)
Pneumonia	2 (3.0)	1.0 (2/2)
Multiple sclerosis[b]	0	0 (0/0)
Breast Cancer	0	0 (0/0)

TEAE: Treatment-emergent adverse event
Data presented by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and by decreasing order of frequency in the 14mg dose group. The number (NI) represents the number of TEAEs per patient. It is calculated as the ratio of the total number of TEAEs (N2) and the total number of patients with at least one TEAE (n).
[a]Laboratory abnormalities reported as TEAEs were based on the investigators decision and/or on the following reporting thresholds (confirmed by a re-test): alanine aminotransferase ≥2x upper limit of normal (ULN) or bilirubin ≥2xULN; serum amylase or lipase levels ≥2xULN; neutrophil counts <1000 cells/µL.
[b]MS relapse, which was classed as a MS adverse event in the safety data set.
[c]MedDRA preferred term: Alopecia.
[d]More than 1 serious TEAE (crude incidence) reported in either treatment group

TEMSO extension [TEMSO extension CSR]

Please note relative-risk ratios are not available for this data.

This Phase III extension study assessed the long-term safety of teriflunomide in patients with relapses. The overall incidence of TEAEs was [redacted] for patients receiving 14mg teriflunomide; the incidence of treatment-emergent SAEs was [redacted] and TEAEs leading to permanent treatment discontinuation was [redacted]

The most commonly reported TEAEs were [redacted]

Table B6.9.2 Overview of safety profile: treatment emergent adverse events – Safety Population

n (%)	14mg		
	Placebo/14mg (N=107)	14mg/14mg (N=250)	Total (N=357)
Patients with any TEAE	[redacted]	[redacted]	[redacted]
Patients with any treatment emergent SAE	[redacted]	[redacted]	[redacted]
Patients with any TEAE leading to death	[redacted]	[redacted]	[redacted]
Patients with any TEAE leading to permanent treatment discontinuation	[redacted]	[redacted]	[redacted]

Table B6.9.3 Number (%) of patients with TEAE by primary system organ class (SOC) and preferred term (PT) - Safety population

Primary System Organ Class (SOC) Preferred Term (PT) n (%)	14mg		
	Placebo/14mg (n=107)	14mg/14mg (n=250)	Total (n=357)
Hepatic disorder any class	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Hematopoietic cytopenias any	[redacted]	[redacted]	[redacted]
Blood and lymphatic system	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Pancreatic disorder any class	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]

Investigations	[redacted]	[redacted]	[redacted]
Malignancy any class	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]
Anaphylactic reaction (hypersensitivity) any class	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Alopecia any class	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue	[redacted]	[redacted]	[redacted]
Hypertension any class	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Interstitial lung disease any class	2 (1.9%)	0	2 (0.6%)
Infections and infestations	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and	[redacted]	[redacted]	[redacted]
Peripheral neuropathy any class	4 (3.7%)	4 (1.6%)	8 (2.2%)
Nervous system disorders	[redacted]	[redacted]	[redacted]

Pooled analysis of placebo-controlled Phase II/III data [Sanofi 2011, Aubagio 2.7.4 summary-clin-safety]

Relative risk data available from the pooled analysis

In line with the other adverse event data presented, the pooled analysis indicates gastrointestinal symptoms (diarrhoea, nausea, vomiting), urinary tract and other infections, alopecias, paraesthesias/dysaethesias and other pain, neutropenias and some dermal effects to be of note.

Table B6.9.4 Incidence rate and relative risk ratio of common treatment-emergent adverse events (TEAEs) with (HLT ≥ 2% in any group) – Safety population – Pool A

HLT: High Level Term	Placebo (N=421)	Teriflunomide 14mg (N=415)	Relative risk ratio (95% CI)
Upper respiratory tract infections	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue pain and discomfort	[redacted]	[redacted]	[redacted]
Headaches NEC	[redacted]	[redacted]	[redacted]
Liver function analyses	[redacted]	[redacted]	[redacted]
Asthenic conditions	[redacted]	[redacted]	[redacted]
Diarrhoea (excl infective)	[redacted]	[redacted]	[redacted]
Nausea and vomiting symptoms	[redacted]	[redacted]	[redacted]
Urinary tract infections	[redacted]	[redacted]	[redacted]
Alopecias	[redacted]	[redacted]	[redacted]
Paraesthesias and dysaethesias	[redacted]	[redacted]	[redacted]
Sensory abnormalities NEC	[redacted]	[redacted]	[redacted]
Gastrointestinal and abdominal pains (excl oral and throat)	[redacted]	[redacted]	[redacted]
Influenza viral infections	[redacted]	[redacted]	[redacted]
Lower respiratory tract and lung infections	[redacted]	[redacted]	[redacted]
Depressive disorders	[redacted]	[redacted]	[redacted]
Joint related signs and symptoms	[redacted]	[redacted]	[redacted]
Non-site specific injuries NEC	[redacted]	[redacted]	[redacted]
Bladder and urethral symptoms	[redacted]	[redacted]	[redacted]
Pain and discomfort NEC	[redacted]	[redacted]	[redacted]
Neurological signs and symptoms NEC	[redacted]	[redacted]	[redacted]
Viral infections NEC	[redacted]	[redacted]	[redacted]
Abdominal and gastrointestinal infections	[redacted]	[redacted]	[redacted]
Herpes viral infections	[redacted]	[redacted]	[redacted]
Inner ear signs and symptoms	[redacted]	[redacted]	[redacted]
Rashes, eruptions and exanthems NEC	[redacted]	[redacted]	[redacted]

HLT: High Level Term	Placebo (N=421)	Teriflunomide 14mg (N=415)	Relative risk ratio (95% CI)
Dermatitis and eczema	[redacted]	[redacted]	[redacted]
Muscle weakness conditions	[redacted]	[redacted]	[redacted]
Coughing and associated symptoms	[redacted]	[redacted]	[redacted]
Disturbances in initiating and maintaining sleep	[redacted]	[redacted]	[redacted]
Muscle related signs and symptoms NEC	[redacted]	[redacted]	[redacted]
Upper respiratory tract signs and symptoms	[redacted]	[redacted]	[redacted]
Neutropenias	[redacted]	[redacted]	[redacted]
Vascular hypertensive disorders NEC	[redacted]	[redacted]	[redacted]
Dental pain and sensation disorders	[redacted]	[redacted]	[redacted]
Dyspeptic signs and symptoms	[redacted]	[redacted]	[redacted]
Visual disorders NEC	[redacted]	[redacted]	[redacted]
White blood cell analyses	[redacted]	[redacted]	[redacted]
Anxiety symptoms	[redacted]	[redacted]	[redacted]
Dermal and epidermal conditions NEC	[redacted]	[redacted]	[redacted]
Pruritus NEC	[redacted]	[redacted]	[redacted]
Skin injuries NEC	[redacted]	[redacted]	[redacted]
Gastrointestinal signs and symptoms NEC	[redacted]	[redacted]	[redacted]
Dental and oral soft tissue infections	[redacted]	[redacted]	[redacted]
Infections NEC	[redacted]	[redacted]	[redacted]
Atopic disorders	[redacted]	[redacted]	[redacted]
Gastrointestinal atonic and hypomotility disorders NEC	[redacted]	[redacted]	[redacted]
Menstruation with increased bleeding	[redacted]	[redacted]	[redacted]
Muscle pains	[redacted]	[redacted]	[redacted]
Acnes	[redacted]	[redacted]	[redacted]
Febrile disorders	[redacted]	[redacted]	[redacted]
General signs and symptoms NEC	[redacted]	[redacted]	[redacted]
Lumbar spinal cord and nerve root disorders	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue signs and symptoms NEC	[redacted]	[redacted]	[redacted]
Physical examination procedures	[redacted]	[redacted]	[redacted]
Ear infections	[redacted]	[redacted]	[redacted]
Limb injuries NEC (incl traumatic amputation)	[redacted]	[redacted]	[redacted]
Menstruation and uterine bleeding	[redacted]	[redacted]	[redacted]

HLT: High Level Term	Placebo (N=421)	Teriflunomide 14mg (N=415)	Relative risk ratio (95% CI)
NEC			
Migraine headaches	[redacted]	[redacted]	[redacted]
Mononeuropathies	[redacted]	[redacted]	[redacted]
Anaemias NEC	[redacted]	[redacted]	[redacted]
Female reproductive tract infections	[redacted]	[redacted]	[redacted]
Tinea infections	[redacted]	[redacted]	[redacted]
Digestive enzymes	[redacted]	[redacted]	[redacted]
Flatulence, bloating and distens	[redacted]	[redacted]	[redacted]
Multiple sclerosis acute and progressive	[redacted]	[redacted]	[redacted]
Skin structures and soft tissue infections	[redacted]	[redacted]	[redacted]
Bacterial infections NEC	[redacted]	[redacted]	[redacted]
Cardiac signs and symptoms NEC	[redacted]	[redacted]	[redacted]
Fungal infections NEC	[redacted]	[redacted]	[redacted]
Lymphatic system disorders NEC	[redacted]	[redacted]	[redacted]
Feelings and sensations NEC	[redacted]	[redacted]	[redacted]
Leukopenias NEC	[redacted]	[redacted]	[redacted]
Ovarian and fallopian tube cysts and neoplasms	[redacted]	[redacted]	[redacted]
Cholecystitis and cholelithiasis	[redacted]	[redacted]	[redacted]
Coagulation and bleeding analyses	[redacted]	[redacted]	[redacted]
Erythemas	[redacted]	[redacted]	[redacted]
Neuromuscular disorders NEC	[redacted]	[redacted]	[redacted]
Oedema NEC	[redacted]	[redacted]	[redacted]
Cerebellar coordination and balance disturbances	[redacted]	[redacted]	[redacted]
Conjunctival infections, irritations and inflammations	[redacted]	[redacted]	[redacted]
Nasal congestion and inflammations	[redacted]	[redacted]	[redacted]
Ocular disorders NEC	[redacted]	[redacted]	[redacted]
Dental and gingival therapeutic procedures	[redacted]	[redacted]	[redacted]
Muscle, tendon and ligament injuries	[redacted]	[redacted]	[redacted]
Partial vision loss	[redacted]	[redacted]	[redacted]
Urinary abnormalities	[redacted]	[redacted]	[redacted]
Gait disturbances	[redacted]	[redacted]	[redacted]

See appendices for further adverse event detail.

Phase III TOWER study [TOWER CSR]

The TOWER study represents the largest phase III trial available reporting teriflunomide vs. placebo. The overall incidence of patients with TEAEs was similar between treatment groups: placebo: 83.1%; and teriflunomide 14 mg: 86.3%. This was also the case for treatment-emergent SAEs: placebo: 12.2%; teriflunomide 14 mg: 11.9%. The percentage of patients with TEAEs leading to permanent treatment discontinuation was 15.6% in the teriflunomide treatment arm compared with the placebo group (6.2%). Increased rates for ALT increased, neutropenia, and alopecia in particular were also seen. See Tables B6.9.5-B6.9.6.

There were 4 deaths reported during the study. One patient in the placebo group died due to respiratory infection, (1 patient in the teriflunomide 7 mg group died due to a motor vehicle accident), and 2 patients died in the teriflunomide 14 mg group, 1 from suicide and the other from septicemia due to a gram-negative organism.

Table B6.9.5 Overview of adverse event profile: treatment-emergent adverse events – safety population

n (%) number and percentage of patients with at least one TEAE	**Placebo (N=385)**	**Teriflunomide 14mg (N=371)**
Patients with any TEAE	320 (83.1%)	320 (86.3%)
Patients with any treatment emergent SAE	47 (12.2%)	44 (11.9%)
Patients with any TEAE leading to death	1 (0.3%)	2 (0.5%)
Patients with any TEAE leading to permanent treatment discontinuation	24 (6.2%)	58 (15.6%)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

Among the most common TEAEs (≥ 8%) presenting with an increased incidence in the teriflunomide group compared with the placebo group and with an apparent dose effect were ALT increased, alopecia, and neutropenia. Diarrhoea occurred at an increased incidence with teriflunomide compared with the placebo group.

Please note – relative risks calculated from final percentage incidence values. 95% confidence intervals are not available.

Table B6.9.6 Number (%) of patients with TEAE(s) with a frequency ≥2% in any treatment group by PT - Safety population

Preferred Term n (%)	Placebo (N=385)	Teriflunomide 14mg (N=371)	Relative Risk
Any class	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	32 (8.3%)	52 (14.0%)	[redacted]
Alopecia	17 (4.4%)	50 (13.5%)	[redacted]
Headache	42 (10.9%)	46 (12.4%)	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Diarrhoea	28 (7.3%)	41 (11.1%)	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Nausea	34 (8.8%)	38 (10.2%)	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Pain in extremity / Limb Pain	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]

Dyspepsia	[redacted]	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]
Micturition urgency	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]
Migraine	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Hepatic steatosis	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]
Sensory disturbance	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]	[redacted]
Ovarian cyst	[redacted]	[redacted]	[redacted]
TEAE: Treatment emergent adverse event, PT: Preferred term MedDRA version: 15.0 n (%) = number and percentage of patients with at least one TEAE Note: Table sorted by decreasing frequency of PT in teriflunomide 14mg group.			

6.10 Interpretation of clinical evidence

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

Results from the randomised clinical trials presented provide a strong clinical evidence base for the benefit of teriflunomide in treating patients with RRMS.

In two double blind, placebo-controlled studies teriflunomide has demonstrated consistent efficacy in reducing relapse frequency and disability accumulation with significantly better results than placebo. The data from extension studies indicates that this efficacy is maintained with minimal safety concerns.

Key outcomes teriflunomide vs. placebo (please refer to Table B6.3.6 for full outcomes):

In **TEMSO and TOWER:**

- Results were consistent between the two trials
- Adjusted ARR results were: 0.37 [redacted]; teriflunomide significantly reduced the adjusted ARR with reported relative risk reductions compared to placebo of 0.685 (p<0.001) [redacted] (p=0.0001) respectively
    - In addition to reducing the ARR, in the TEMSO study teriflunomide significantly reduced relapses leading to hospitalisation (59%; *P*<0.0001 versus placebo). Teriflunomide reduced relapses with investigator-assessed sequelae by 53% p<0.0001
    - During TOWER, patients treated with teriflunomide 14 mg spent significantly fewer nights in hospital for relapse (1.7 nights/patient) compared with those patients receiving placebo (3.4 nights/patient; p=0.0285) [O'Connor et al. 2013].

[redacted] n TEMSO, sustained accumulation of disability for at least 12 weeks (SAD) was significantly reduced for teriflunomide vs. placebo, HR= 0.70 (95% CI 0.51-0.97) (n=358 and 363 respectively) but [redacted]

- In the Direct Meta-Analysis of TEMSO and TOWER HR = 0.694 [0.544, 0.886]

[redacted]With regards to the symptoms of MS, neither trial revealed major changes from baseline in FIS score, with no significant difference to placebo in TEMSO but [redacted]

- Similarly, health-related quality of life showed no significant differences in SF-36 or EQ-5D scores however, [redacted]

- 60.6% [redacted] respectively of patients remained relapse-free at study end (vs. 49.3% and [redacted] for placebo)
    - MRI data within TEMSO revealed significantly fewer gadolinium –enhancing lesions per T_1-weighted scan (relative risk 0.20, p<0.001) and fewer unique active lesions per scan (relative risk 0.31, p<0.001) for teriflunomide vs. placebo.
- The rate of discontinuation (all causes) was 26.5% and [redacted] respectively. 10.9% (note this result is reported as 10.61% in the MTC due to differing methodologies in determining the figure) and [redacted] were due to adverse events
    - There were no deaths in TEMSO. [redacted]

Key outcomes: long-term efficacy and safety (please refer to Table B6.3.6 for full outcomes):

Phase II extension and TEMSO extension studies

The long-term efficacy of teriflunomide is supported by the Phase II long-term extension study and the interim results from the ongoing long-term extension of TEMSO. The Phase II results were reported at a median follow up of 7.1 years, patients in the TEMSO extension at interim cut-off had received up to 5 years of treatment. The primary outcome of these studies was safety and tolerability; however secondary efficacy endpoints demonstrate continued activity of teriflunomide**:**

- The ARR was reduced in comparison to the core studies: in the Phase II study ARR was 0.181; in the TEMSO extension it was [redacted]
    - However patients had minimal disability accumulation during the periods; EDSS scores increased by a median of 0.5 in the Phase II study, no obvious changes were observed in the [redacted]
    - SAD was collected in the TEMSO extension and showed [redacted]

[redacted] With regards to symptoms of MS, [redacted]

    - [redacted]
- 55.0% and [redacted] of patients who took teriflunomide 14mg throughout the core and extension study periods remained relapse free.
    - MRI data for patients who swapped from placebo to teriflunomide in the TEMSO extension demonstrated [redacted]

- The rate of discontinuation was 45.4% and [redacted] respectively; 19.7% and [redacted] discontinued due to adverse events
    - There was one death in the Phase II extension – underlying disease conditions and concomitant medications may have been contributory. [redacted]

Key outcomes teriflunomide vs. interferonβ-1a (IFNβ-1a) (please refer to Table B6.3.6 for full outcomes):

IFNβ-1a represents one of the current standards of care in the management of RRMS. In the phase III TENERE study, teriflunomide demonstrated comparable efficacy to IFNβ-1a (Rebif), whilst improving patient satisfaction.

In **TENERE**:

[redacted]

- The discontinuation rate was [redacted]% for teriflunomide vs [redacted] for IFNβ-1a
    - [redacted] discontinued treatment with teriflunomide due to adverse events vs. [redacted] for IFNβ-1a. [redacted]
- Using the TSQM, [redacted].
    - FSI scores were [redacted]) for teriflunomide vs. IFNβ-1a .

Meta-analysis

- Results from the meta-analysis indicate teriflunomide is better than placebo for all measures of efficacy, using relative risks (95% CI):
    - ARR = 0.664 (0.589, 0.749)
    - Proportion relapse free = [redacted]
    - SAD = 0.694 (0.544, 0.886)
- i.e. patients relapse less frequently, have an improved chance of remaining relapse-free and are less likely to achieve sustained accumulation of disability for 3 months.

- Patients on teriflunomide versus placebo are more likely to discontinue medication for any reason including adverse events – this is to be expected (relative risk – all cause [redacted], relative risk – adverse events [redacted]).

MTC

- In the base case (≥2000 and ≥80% RRMS):
  - [redacted]For ARR and proportion relapse-free outcomes, results for teriflunomide [redacted]However, fingolimod and natalizumab demonstrate [redacted]vs. teriflunomide / interferons / glatiramer[redacted]
    - Teriflunomide, fingolimod and natalizumab have significantly improved results for SAD (3 months) vs. placebo (unlike the interferons or glatiramer).
  - [redacted]All-cause discontinuations [redacted]
    - [redacted]Discontinuations due to adverse events [redacted]
    - [redacted]Application of the all-years MTC sensitivity analysis (see Additional Appendix 2) results to the base case implies that [redacted]
- In the RES / HA sensitivity analyses:
  - [redacted]Teriflunomide shows [redacted]
  - [redacted]Teriflunomide shows [redacted]
    - [redacted]for teriflunomide on SAD (3 months) vs. placebo in HA or RES.
    - [redacted]
- In the all-years sensitivity analysis:
  - Results largely mirror those of the base-case.

Adverse Events

- From the clinical trial programme, teriflunomide was found to be well tolerated when compared to placebo. Similar proportions of patients in the placebo and teriflunomide groups had TEAEs, SAEs and AEs leading to discontinuation of the study medication.
- When compared to IFNβ-1a the proportion of patients with at least one TEAE and with serious TEAEs was similar across both treatment groups. In addition more patients discontinued treatment with IFNβ-1a due to TEAEs compared to teriflunomide.
- Of particular concern to patients is alopecia – often reported as hair thinning or decreased hair density. In the long-term follow-up of the Phase II trial, these cases were reported to be mild or moderate and transient in nature and did not lead to treatment discontinuation [Confavreux et al. 2012]
    - In a pooled analysis of the core Phase II study with TEMSO, hair loss/thinning was shown to be more common with teriflunomide 14mg vs. placebo but in the majority was mild (73%) and recovered without sequelae (90.5%) whilst on therapy [Freedman et al. 2012]

Safety of Teriflunomide vs. Placebo:

- We have reported safety data from a pooled analysis of the phase II study and TEMSO [Sanofi 2001, Aubagio 2.7.4 summary-clin-safety].

[redacted]Among the most common TEAEs (≥ 8% and where incidence was at least 4% higher in the teriflunomide arm) were [redacted]Rate of TEAEs leading to permanent treatment discontinuation was [redacted]

- These data are further supported by results from the TOWER study, where the overall incidence of patients with TEAEs was [redacted]This was also the case for treatment-emergent SAEs ([redacted]However the percentage of patients with TEAEs leading to permanent treatment discontinuation with teriflunomide was [redacted]compared with [redacted]the placebo group.
- Among the most common TEAEs (≥ 8%) presenting with an increased incidence in the teriflunomide groups compared with the placebo group and with an apparent dose effect were [redacted]

Phase II and Phase III Long-term Safety Data

- In the phase III extension study assessing the long-term safety of teriflunomide in patients with relapses the overall incidence of TEAEs was [redacted] for patients receiving teriflunomide; the incidence of treatment-emergent SAEs was [redacted] and TEAEs leading to permanent treatment discontinuation was [redacted]
- The most commonly reported TEAEs were [redacted]
- [redacted] the most frequent finding among hepatic PCSAs (potentially clinically significant abnormalities). [redacted] is a possible contributor to the events.

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

Strengths of the Clinical Evidence Base

Three large randomised multi-centre, multi-country phase III clinical trials including both placebo and comparator studies have been conducted in addition to a phase II randomised multi centre study in comparison to placebo. All studies were well designed, randomised studies:

- All three of the placebo controlled studies (Phase II, TEMSO and TOWER) were double-blind; in the comparative study vs. injectable IFNβ-1a (TENERE), although it was administered open-label, the study was rater-blinded. In total across the three placebo-controlled studies 788 patients received teriflunomide 14mg and 813 patients received placebo.
    - N.B. A teriflunomide 7mg arm was also included in all of the studies but does not form part of the European license and has therefore not been discussed as part of this submission.
- Both the Phase II and Phase III TEMSO studies have on-going long-term extension arms, which have generated follow-up data out as far as 8.5 years; this provides additional reassurance about the manageable safety profile of teriflunomide. Ongoing efficacy analyses have also demonstrated the continued efficacy of teriflunomide in those patients who remain on treatment.
- For all three of the phase III studies, patients with relapsing multiple sclerosis (RMS) had to meet the McDonald criteria for MS diagnosis (which are now considered the standard criteria for diagnosis in clinical practice) and also had to have an EDSS score of 5.5 or less at study entry. In TEMSO and

TOWER, patients were also required to have RMS as specifically defined by at least 1 relapse over the 1 year preceding the trial or at least 2 relapses in the 2 years preceding the trial.

- Missing values were accounted for during all trials. For example, the last-observation-carried-forward principle was used for missing data points (unless the previous was baseline) with rules applied for missing dates. Missing categorical variables led to exclusion of patients from percentage calculations in TEMSO and TENERE. In TOWER, no imputation was made for missing or incomplete data.
- Primary efficacy population across all studies was the intention-to- treat (ITT) population which was all randomised patients, with the safety population being all randomised patients that received at least one dose of study medication.
- The primary end point of the two phase III placebo controlled studies was annualised relapse rate (ARR); this was a secondary end point in the TENERE (phase III vs. IFNβ-1a) study. Relapses are a defining feature of RRMS and reduction in relapse is a key clinical end point when treating RRMS.
- A secondary end point in each study was sustained accumulation of disability (SAD) maintained for at least 12 weeks which was measured using EDSS. The progression to a score of 6 on the EDSS is considered an important milestone as it represents the onset of walking disability and has implications for the suitability of treatment with DMTs [ABN, 2009]. For patients, this remains an outcome of high importance as this outcome most closely conveys how RMS incrementally reduces the ability to function 'normally' with accumulation of associated disabilities.
- Outcomes for teriflunomide 14mg/day have been consistent across the Phase II and Phase III trials, lending weight to the evidence base in support of teriflunomide. None of the trial data available to date has inferred questionability of previously reported efficacy results.

Limitations of the clinical evidence base

- It has not been possible to supply full answers to some elements of the decision problem, namely 'freedom of disease activity' and 'severity of relapse' as these were not defined endpoints in the trial program for teriflunomide. For freedom of disease we have supplied MRI data as this is an accepted method of assessing disease activity in clinical practice and is reported within the Phase II and TEMSO studies; one post-hoc analysis of the TEMSO trial provides data on a composite endpoint of "free of disease activity". For severity of relapse we have been able to report the post-hoc sub-analysis of TEMSO relating to hospitalisation – i.e relapses severe enough to require admission.
- Prior to 2000 the accepted criteria for diagnosing MS was the Poser criteria and this was therefore used as an entry criteria for the teriflunomide phase II, "proof of concept" placebo-controlled study (see Section 6.6.1 for detailed discussion). From discussions with clinical experts when looking at the feasibility of undertaking the MTC, the POSER criteria would identify patients much later in their disease course and therefore the more sensitive McDonald criteria were used, as these identify patients earlier

in the disease course, and with less frequent or severe symptoms. In practical terms this means that after the introduction of McDonald criteria into clinical and trial practice, baseline disease activity has appeared to change (i.e. disease appears 'less' active at study entry). In support of this theory, it has been observed in several recent studies that the ARR recorded in clinical trials has declined over time. In a 2010 publication by Inusah et al., a downward trend in ARR was observed in trials for MS published between 1980 and 2008; in some later trials, ARR was three times lower than in earlier trials. In a review of RCTs in RRMS conducted by Nicholas et al., the ARR for placebo was found to decrease by 6.2% per year.

- No head to head comparisons with glatiramer acetate, interferons other than IFNβ-1a, natalizumab or fingolimod are available for teriflunomide. Therefore a mixed treatment comparison was performed in order to compare to these treatments.
- The teriflunomide studies recruited a general population of patients with RRMS, there was no emphasis or planned sub-analysis of the effect of teriflunomide in RES or HA disease, therefore these have been analysed post-hoc and the resultant patient numbers are too small to draw firm conclusions from.
- Rebif (IFNβ-1a) is used in practice at a dose of 22µg for patients who cannot tolerate the higher dose in view of the treating specialist [Rebif SmPC]. It is therefore a limitation of the base-case MTC that primary reference sources are unavailable to include this dose in the base-case treatment networks. This has been compensated for in the results presented in the MTC by applying the ratios of results in the all-years sensitivity analysis to the results for IFNβ-1a 44µg in the base case to provide inferred results for SAD and discontinuation rates.
- MTC analysis can sometimes produce results that are questionable e.g. in this MTC, SAD results for IFNβ-1b 250µg appear worse than those for placebo.

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

Population

The evidence base presented is for patients with RRMS only and does not include patients with SPMS or PRMS. The rationale for not including these populations is that teriflunomide has a CHMP positive opinion for RRMS only and these other types of MS are outside of the license.

Comparator

Direct evidence is presented for teriflunomide vs. IFNβ-1a from the TENERE study. For other interferons and glatiramer acetate evidence is presented from a mixed treatment comparison as head-to-head data are absent. Evidence has also been presented in the MTC for the other comparators natalizumab and fingolimod for the entire RRMS patient population however this is not in line with the current NICE recommendations for these agents. Therefore in addition, a sub-group analysis of the phase III TEMSO study of teriflunomide has been carried out for both the RES and HAD RRMS populations. TEMSO data was used as the populations involved most closely that match those defined by NICE as RES or HA-disease.

Rapidly evolving severe (RES) disease is defined in the NICE natalizumab guidance [NICE, 2007(a)] as two or more disabling relapses in one year and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI. The TEMSO population could be analysed for those patients with RES and at least one gadolinium-enhancing lesion at baseline. The ITT population of the study were patients with at least two relapses within one year before randomisation.

Highly active (HA) disease is defined in the NICE fingolimod guidance [NICE, 2012(a)] as those patients failing to respond to a full and adequate course of beta-interferon defined as at least 1 relapse in the last year and at least nine T2 hyper intense lesions or at least one gadolinium enhancing lesion. The TEMSO population could be analysed for those with HA disease, having had interferon therapy for at least 12 months prior to randomisation (with a gap no longer than 12 months between prior therapy and randomisation) with at least one gadolinium-enhancing lesion at baseline. The ITT population of the study had experienced at least one relapse within one year before randomisation.

Subgroups

The following sub-groups have not been presented as these data are not available from the phase III studies:

- Patients with RRMS whose disease has inadequately responded to treatment with disease modifying therapy
- Patients with RRMS intolerant to treatment with disease modifying therapy

The following subgroups have been presented, but please see discussion in Section B6.10.2 see discussion around the limitations of these analyses:

- Patients with HAD RRMS
- Patients with RES RRMS

Outcomes

Evidence is presented for the majority of outcomes listed in the decision problem alongside primary outcomes of the individual trials where these were additional to those identified in the decision problem. Evidence is also presented for resource utilisation with regard to hospitalisation (for relapse or any cause) and emergency medical visits.

The course of MS may be looked upon as the interaction between the two clinical phenomena of relapses and disability progression although the contribution of the former to the latter is not clear [Confavreux et al. 2006]. Relapses may require admission to hospital, and are associated with a level of disability and incapacity that disrupts working, family and social life. Accumulation of disability clearly presents a challenge to patients and their carers, alongside the very real representation of worsening disease. Relapses can have a significant impact on quality of life [Orme et al. 2007].

The most accepted tool to measure disability is the Expanded Disability Status Scale (EDSS), which is a 10-point instrument that measures different areas of functional disability in the lower half of the scale and focuses on hard ambulatory disability in the latter half. A score of 6 on the EDSS is considered an important milestone as it represents the onset of walking disability and has implications for the suitability of treatment with disease-modifying treatments (DMTs) [Kurtze, 1983]. Frequent and prolonged relapses with incomplete recovery at onset and a short interval between the initial episode and first relapse are adverse prognostic features but the main determinant of disability is onset of the progressive phase [Compston et al. 2002]

As shown in cost effectiveness section 7, the cost effectiveness model is most sensitive to the HR associated with disability progression. As stated above, the following results are of relevance in relation to the teriflunomide clinical trial programme and cost effectiveness:

- In TEMSO, sustained accumulation of disability for at least 12 weeks (SAD) was significantly reduced vs. placebo: HR 0.70 (95% CI 0.51-0.97) (n=358 and 363) but not in TOWER HR vs. placebo = 0.685 [redacted] p=0.0442 (n=370 and 388).
- In the Direct Meta-Analysis of TEMSO and TOWER, HR = 0.694 [0.544, 0.886]

Given the importance of this variable to the health economic model it is important to place these results in the context of the main comparators (SC IFNβ-1a 44µg and 22µg, im IFNβ-1a 30µg, SC IFNβ-1b 8MIU and glatiramer acetate 20mg) and the disability outcomes associated with the relevant placebo-controlled studies. The details of such a consideration are provided below, but the overarching conclusion drawn from these data is that of these five potential comparators and teriflunomide, only teriflunomide and SC IFNβ-1a 44 µg, have placebo controlled studies in which they demonstrate a statistically significant difference to placebo in relation to reducing disability progression.

In the base case MTC one placebo controlled study for the main comparators was identified (Additional Appendix 3 Table AA3.13):

- Glatiramer acetate 20mg versus placebo HR 0.93 [0.63, 1.37] [Fox et al. 2012] (n=350 and 363)
- In all the studies with RRMS patients ≥ 80% (including those <2000 and ≥2000) only SC IFNβ-1a 44µg showed statistical significance for SAD (3 months) versus placebo, HR = 0.65 (0.45, 0.94) (n=184 and 187) [Ebers et al. 1998]. (Additional Appendix 2, Table AA2.3)
- Specifically in addition to the CONFIRM study [Fox et al. 2012] outlined above, results for SAD (3 months) were: (see Additional Appendix 2, Table AA2.3):
    - No relevant studies were found for IM IFNβ-1a 30µg
    - SC IFNβ-1a 22 µg versus placebo, HR= 0.76 [0.53, 1.08] (n=185 and 187) [Ebers et al. 1998]
    - SC IFNβ-1b 8 MIU versus placebo, HR= 0.68 [0.4, 1.17] (n=125 and 123) [Duquette et al. 1993]
    - Glatiramer acetate 20mg versus placebo, HR= 0.32 [0.09, 1.09] [Bornstein et al. 1987] (n=25 and 25) and 0.86 [0.51, 1.45] [Johnson et al. 1996] (n= 126 and 126)
    - As noted in Section 6.7.7 there is great deal of heterogeneity in the outcome measures used to capture disability progression in these studies

There are some key elements of MS as a disease process that are of high importance to a patient vs. clinical signs and symptoms. For a patient, relevant issues are: suffering relapses, becoming increasingly disabled with time and maintenance of an acceptable quality of life on both a daily and long-term basis. The end points in the teriflunomide clinical trial program are highly relevant to clinical practice:

- Annualised relapse rate provides a measure of the number of relapses suffered by patients in the studies.
- Sustained accumulation of disability maintained for at least 12 weeks is a measure of disability progression and uses EDSS, a scale used to measure disability in clinical practice.
- Measuring symptoms of MS such as fatigue is relevant to clinical practice as fatigue has a profound effect on the daily activities of patients with MS.

The decision problem identified severity of relapse as an outcome of interest. This was not formally captured as an outcome during the teriflunomide clinical trial program however post-hoc hospitalisation data is reported from the TEMSO and TOWER trials (i.e. where relapse was severe enough to require admission).

Freedom of disease activity

Freedom of disease activity is an outcome for which there is no clearly defined consensus. In practice we understand this to be a relapse-free period where evidence of disease progression is also absent. Throughout

the clinical trial program for teriflunomide, treatment with teriflunomide has consistently led to higher proportions of patients remaining free of relapse vs. placebo (see Table B6.3.6). During the largest phase III trial (TOWER) the probability of patients being relapse free at 132 weeks was significantly higher for teriflunomide (0.515, 95% CI 0.436, 0.595) vs. placebo (0.377, 95% CI 0.301, 0.452); the hazard ratio being 0.631 (95% CI 0.502, 0.794), p<0.0001.

In practical measurement terms, MRI results can be included in this composite as a practical demonstration of stable or improved disease as assessed by MRI scan. Since relapse rates and disability measures are reported as discrete outcomes themselves (see Table B6.3.6), we have reported MRI data (where available) from the Phase II/III trial program to support the concept of freedom of disease activity.

MRI outcomes were reported during the Phase II program (including extension study) and in TEMSO. During the Phase II study a 61.3% relative reduction in the number of CU active lesions per scan (adjusted for baseline activity, EDSS strata and study site) was observed for teriflunomide vs. placebo (p<0.01). There were also significant reductions in the median number of T1 enhancing lesions per scan and the median number of new or enlarging T2 lesions per scan over the 36-week treatment period (p<0.02 and p<0.03 respectively). During the extension phase of the study, the trend for decreased MRI activity once teriflunomide was introduced to patients previously receiving placebo continued to be observed (see Table B6.3.6).

During TEMSO, patients on teriflunomide had significantly fewer gadolinium-enhancing lesions per T_1-weighted scan than those on placebo: 0.26 (95% CI 0.17–0.41) and 1.33 (95% CI1.06–1.67) respectively; relative risk 0.20 (95% CI 0.12–0.32) p<0.001. In addition, fewer unique active lesions per scan were observed in the teriflunomide group vs. placebo: 0.75 (95% CI 0.58–0.99) and 2.46 (95% CI 2.10–2.89) respectively; p<0.001; relative risk 0.31 (95% CI 0.23–0.41).

Mortality

MS has been associated with an almost threefold increase in the risk for death, with excess mortality rates from other diseases such as cardiovascular disease and infectious and respiratory disease. The median time to death is around 30 years from disease onset, representing a reduction in life expectancy of approximately 10 years [Bronnum-Hansen et al. 2004]. Over the duration of the teriflunomide trials there was not the opportunity to observe any significant changes in mortality, so whilst relevant, it is difficulty to observe any change without very long follow up.

Measurement of symptoms

The symptoms of MS experienced by patients are the result of acute neurological dysfunction; this covers a wide array of clinical manifestations encompassing the motor, sensory, visual and autonomic nervous systems [Compston et al. 2008; Mallam et al. 2009]. Patients commonly experience fatigue, spasticity, bladder

dysfunction, pain and cognitive dysfunction. Less common are depression, bowel dysfunction, and paroxysmal symptoms [Crayton et al. 2006].

The *measurement* of MS symptoms is not a routine part of clinical practice, however is clearly important to the patient; during Phase III clinical trials for teriflunomide the symptoms of MS were reported upon as additional endpoints. Fatigue was measured using the Fatigue Impact Scale, a validated instrument allowing for reliable assessment of patient fatigue. In TEMSO and the associated extension study, minimal changes in FIS were observed. During TENERE changes in FIS favoured teriflunomide over IFNβ-1a (but with no significant difference). In the larger TOWER study, MMRM analysis of FIS changes showed no statistical difference between teriflunomide and placebo; conversely, ANCOVA analysis showed a moderately significant preference for teriflunomide (p=0.0429). MSFC (multiple sclerosis functional composite is a three-part, standardized, quantitative, assessment instrument for use in clinical studies of MS [Cutter et al. 1999]. This was reported upon in the TEMSO extension and showed little change in score from baseline. See Table B6.3.6.

Quality of life

Health related quality of life (HRQoL) was reported during the Phase III trial program and in general showed no deterioration in QoL whilst receiving teriflunomide. There was some indication of improved satisfaction with treatment when considered vs. IFNβ-1a during the TENERE trial; this was related to effectiveness, side effects and convenience – the latter likely to be explained by oral vs. parenteral administration. In the TOWER study ANCOVA analysis of the SF-36 mental health scores showed a nominally (p=0.0224) significant difference in favour of teriflunomide vs. placebo from baseline to last visit (see Table B6.3.6).

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

Teriflunomide was prescribed to trial populations around the world, including UK populations. The eligible patients are representative of the populations we anticipate teriflunomide to be prescribed for in clinical practice i.e. RRMS with EDSS ≤5.5, although we would anticipate patients with a previous diagnosis of RES or HA disease to be preferentially prescribed alternative DMTs (i.e. fingolimod or natalizumab as appropriate) in the UK according to NICE guidance.

We know from the UK Risk Sharing Scheme (RSS) [Pickin et al. 2009] that the mean age of patients at baseline was 39.3 years which is slightly higher than the mean age of 37.9 years in TEMSO and TOWER. Additionally the EDSS distribution in the teriflunomide trials indicated slightly milder patients than the UK RSS. A lower EDSS distribution at treatment initiation is more representative of the UK target population for teriflunomide which is early in the disease as first line treatment [Genzyme KOL interview report, 2013]. Treatment in the earlier stages of the disease is supported, to avoid accumulation of disability [Pugliatti et al. 2013].

The trial populations included patients dosed with both 7mg and 14mg teriflunomide During the placebo controlled trials, patients received 7mg:14mg:placebo into a 1:1:1 ratio. In the open-label extension studies, 7mg and 14mg were prescribed 1:1. In practice teriflunomide will only be recommended at an approved dose of 14mg, hence it is the efficacy results at this dose which have been focused upon in this submission.

During the trial programme quality of life and patient functional scales were evaluated. In practice this is not routinely assessed in such a formal fashion, although such measures would be expected to be discussed informally with patients.

We expect teriflunomide to be used in clinical practice in both pre-treated and treatment-naive patients; therefore the mixture of these two populations within the trials is representative. We perceive teriflunomide's place in the treatment pathway to be similar to the interferons and glatiramer, and as such would be prescribed prior to, as an alternative to, or after either of these therapies. Interviews with KOLs about this positioning have revealed that patients routinely swap between the interferon brands and glatiramer; teriflunomide adds to these options [Genzyme KOL interview report, 2013].

We also anticipate patients being treated reasonably early on in their disease course, with the oral presentation of teriflunomide facilitating the use of active therapy (where patients may previously have resisted parenteral therapy). As previously discussed, patients who could be diagnosed as having RES or HA disease were included in the trial, however in UK clinical practice, we would expect many of these patients to be treated preferentially, although not exclusively, with other therapies (fingolimod or natalizumab, as appropriate).

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

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

A systematic review was conducted to obtain all relevant cost-effectiveness studies in MS. Consequently, the PICOS (population, interventions, comparators, outcomes and study type) principal was applied to define the following review question:

"What modelling techniques have been used previously to conduct economic evaluations for DMTs in the treatment of multiple sclerosis?"

Searches were conducted on the 10th and 11th October 2012. Studies of interest were identified by searching electronic databases including Embase, Medline, Medline (R) In-Process, EconLIT and NHS EED. A search strategy was developed to identify studies indexed in Embase (also covers MEDLINE and MEDLINE (R) In-Process) and then modified for searches in OVIDSP (covers EconLIT) and The Cochrane Library (covers NHS EED) to account for differences in syntax and thesaurus headings. Searches included terms for free text and keywords (e.g. Medical Subject Heading (MESH) terms) with no restrictions on the date or language of publication. To find additional references to those identified during database searching a grey literature search was performed. Section 10.10, Appendix 10 details the search strategies, databases searched and subsequent results from the database sites searched.

References included for the review had to meet the pre-specified inclusion/exclusion criteria shown in Table B7.1.1.

Table B7.1.1 Eligibility criteria used in the cost-effectiveness systematic review

Selection criteria	Inclusion	Exclusion
Population	• Adults with either RRMS or progressive MS (including SPMS or PRMS)	• Primary progressive multiple sclerosis (PPMS)
Intervention/ comparator	• Teriflunomide (Aubagio) • Beta-interferon (Avonex or Rebif or Extavia or Betaferon)	• Any other interventions in multiple sclerosis

	• Glatiramer acetate (Copolymer 1 or Copaxone) • Natalizumab (Tysabri or Antegren) • Fingolimod (Gilenya) • Mitoxantrone (Mitozantrone or Novantrone) • Daclizumab (Zenapax) • Alemtuzumab (Lemtrada or Campath-1H or Campath or Mabcampath) • Rituximab (Rituxan) • Laquinimod • bg00012 (BG-12 or fumarate or dimethylfumarate or Panaclar or oral fumarate) • Best supportive care (BSC)	

Study type	• Economic evaluations:
	  ○ Cost-effectiveness analysis
	  ○ Cost-utility analysis
	  ○ Cost-benefit analysis
	  ○ Cost-minimisation analysis
	  ○ Economic evaluation alongside clinical trials (EEACT)
		• Retrospective observational studies, reviews, letters, comment articles, or any sources that discuss costs where no formal economic analysis has been undertaken

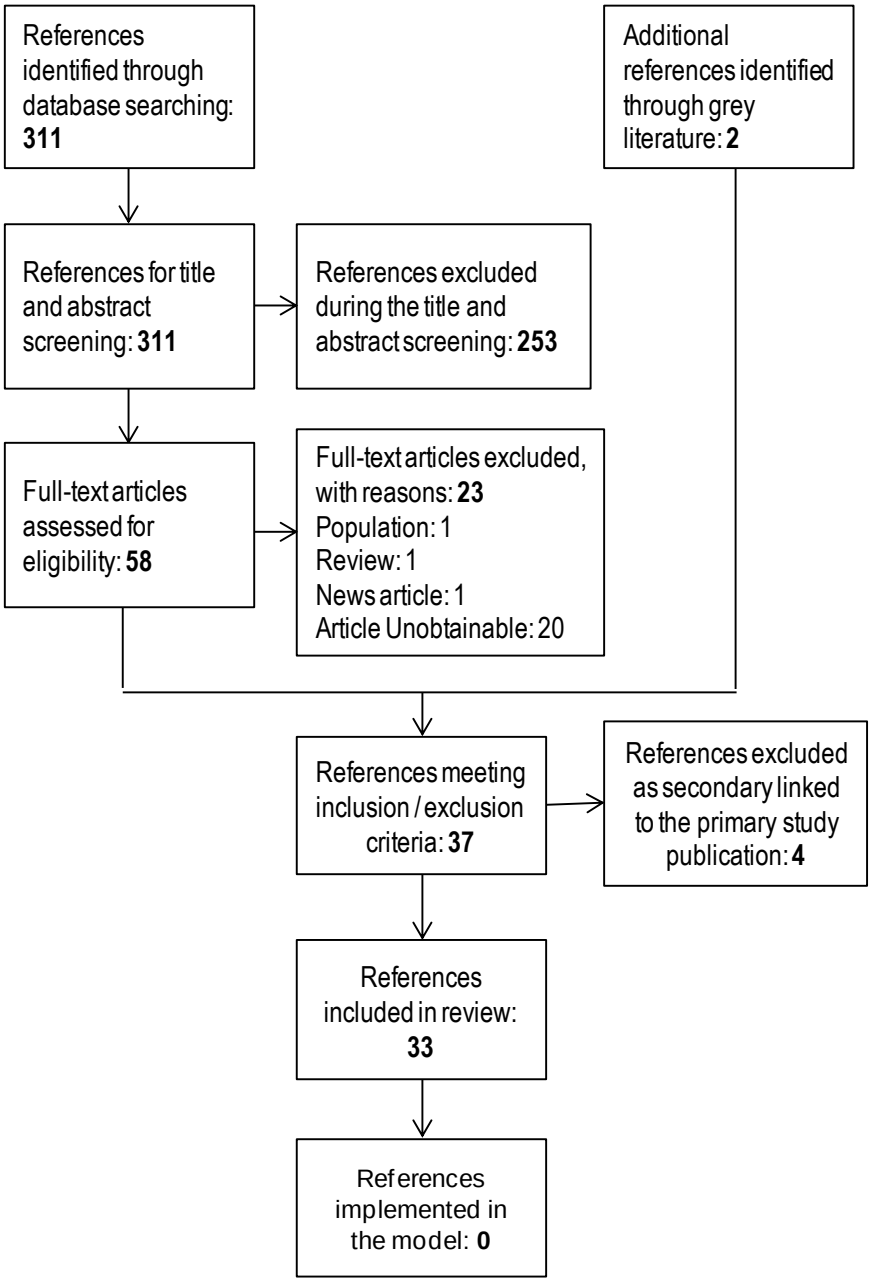
Duplicates were removed for all records obtained in the searches and then a manual review of the titles and abstracts was undertaken using the inclusion/exclusion criteria to identify papers to be included in the review (also known as first passing). This was performed by two independent reviewers and discrepancies were resolved by a third independent reviewer.

Full-text papers identified at first pass were then evaluated and included for review based on the inclusion/exclusion criteria.

Figure B7.1.1 contains a flow diagram which illustrates the numbers of studies included and excluded at each stage of the systematic review. Database searching identified 311 references after removing duplicates. Following title and abstract screening 58 of the 311 references were included. Grey literature identified an additional 2 references, and therefore 60 references were included for full-text evaluation. A total of 37 references met the inclusion/exclusion criteria following full-text evaluation. Of these 37 references, 4 were secondary references to a primary study publication, resulting in 33 studies being identified as evaluating cost-effectiveness in MS.

Of these cost-effectiveness studies, no studies for teriflunomide were identified. However, two cost-effectiveness studies have recently been published for MS DMTs.

Figure B7.1.1 Flow diagram for the cost-effectiveness systematic review



Description of identified studies

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

Although no cost-effectiveness studies for teriflunomide were identified, two cost-effectiveness studies have been analysed and quality assessed since they can be used to inform the cost-effectiveness model for teriflunomide (Table B7.1.2). The two studies are relevant as they were both from the UK perspective, with comparators relevant to teriflunomide and have been assessed by NICE [Chilcott et al. 2003; Gani et al. 2008]. The first identified study by Chilcott et al was developed by the School of Health and Related Research (ScHARR) and was then adapted by Gani et al. to evaluate natalizumab in the treatment of multiple sclerosis.

Key differences identified between the two models were: time horizon, which was 20 years in Chilcott et al. but 30 years in Gani et al; patient population, which was all RRMS in Chilcott et al but restricted to highly active (HA) RRMS in Gani et al; and the method used to model mortality rates. Chilcott et al derived annual relative risk of all cause mortality for the cohort assuming the same as a normal healthy population, minus the death observed in the London Ontario cohort but Gani et all applied an MS mortality multiplier per EDSS to the UK general population mortality rate. Both studies extrapolated the efficacy observed in trials over a much longer time horizon and presumed the treatment effect would persist of the full time horizon of the model. Both studies also followed guidance developed by the Association of British Neurologists (ABN) and switch the cohort to best supportive care, rather than DMT, at EDSS 7.

Table B7.1.2 Table detailing two studies identified as potential informants of the teriflunomide cost-effectiveness model

Study	Year	Country	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Chilcott et al	2003	UK	- The model simulates the clinical course of the disease - Health states were defined according to the Kurtzke expanded disability status scale - The clinical course of the disease, costs, and utilities were assessed with and without treatment over 20 years - The model used an annual cycle length - Patients can remain in their current health state, progress one or more states, die, transit to a secondary progressive health state, or stop treatment	- Patients with relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis - A 20 year time horizon is used, with patients starting treatment at 30 years of age	Not available	Not available	**Base case public model over conventional therapy** - IFNβ-1a 6 MIU/week (Avonex) £42,041 - IFNβ-1a 22 ìg/week (Rebif) £60,963 - IFNβ-1a 44 ìg/week (Rebif) £71,732 - IFNβ-1b 8 MIU/week (Betaferon) £49,664 - Glatiramer acetate 20 mg/week (Copaxone) £97,636 - IFNβ-1b 8 MIU/week (Betaferon) £44,390 **Base case confidential model over conventional therapy** - IFNβ-1b 8 MIU/week (Betaferon) £35,282 - IFNβ-1b 8 MIU/week (Betaferon) £39,872
Gani et al	2008	UK	- The model is based on a previous model for RRMS reported by Chilcott et al. which has been reparameterized for HARRMS patient population - It is a Markov model in which patients are able to progress through a series of disability states, with the states based on the Kurtzke Extended Disability Status Scale (EDSS) - Over time patients may progress to SPMS - Patients are withdrawn from treatment at a given withdrawal rate,	- The baseline characteristics for the patient group were taken from the patient population in the AFFIRM study (mean age 36 years, mean time since diagnosis 5 years and a mean Kurtzke Extended Disability Status Scale [EDSS] score of 2.5)	- Natalizumab 7.4 - INFβ 5.5 - Glatiramer acetate 5.1 - Best supportive care 4.7	- Natalizumab £449,500 - INFβ £445,200 - Glatiramer acetate £444,800 - Best supportive care £427,100	The model suggests that natalizumab is the most cost-effective DMT agent, with an ICER of £2,300 per QALY when compared with IFNβ, £2,000 per QALY compared with GA and £8,200 per QALY compared with BSC) The ICER for natalizumab compared with IFNβ was £2,300 per QALY. Compared with glatiramer acetate, it was £2,000 per QALY, and compared with best supportive care it was £8,200 per QALY. From a health and social care cost perspective, the ICERs were £18,700, £20,400 and £25,500 per QALY, respectively.

			and removed from the cohort at a given mortality rate - The time cycle of the model is 1 year - A 30-year time horizon is taken in the analysis, as this reflects the life-long nature of the disease				

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996) or Philips et al. (2004).

A complete quality assessment of the two identified studies in section B7.1.2 is presented in Appendix 10.11. The results of the quality assessment were almost identical for both studies. However, Gani et al reported resource quantities separately from the unit cost and reported incremental analyses clearly, whilst Chilcott et al did not. Neither study addressed generalisability issues or provided full details of the probabilistic sensitivity analysis undertaken. Nevertheless, the design and structure of the model was clear and appears to be appropriate.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SmPC/IFU and included in the trials.

The patient population considered in the economic evaluation is adults with RRMS. This reflects the licensed indication of treatment of adult patients with relapsing remitting multiple sclerosis, for which teriflunomide was granted a marketing authorisation in March 2013 [EMEA CHMP, 2013]. The MS patient populations treated with teriflunomide 14mg in the phase III pivotal trials (TEMSO, TOWER and TENERE) consisted of 95.8% RRMS, which resulted in the EMA granting marketing authorisation in the RRMS population alone [O'Connor et al. 2011; Kappos et al. 2012; Vermersch et al. 2012].

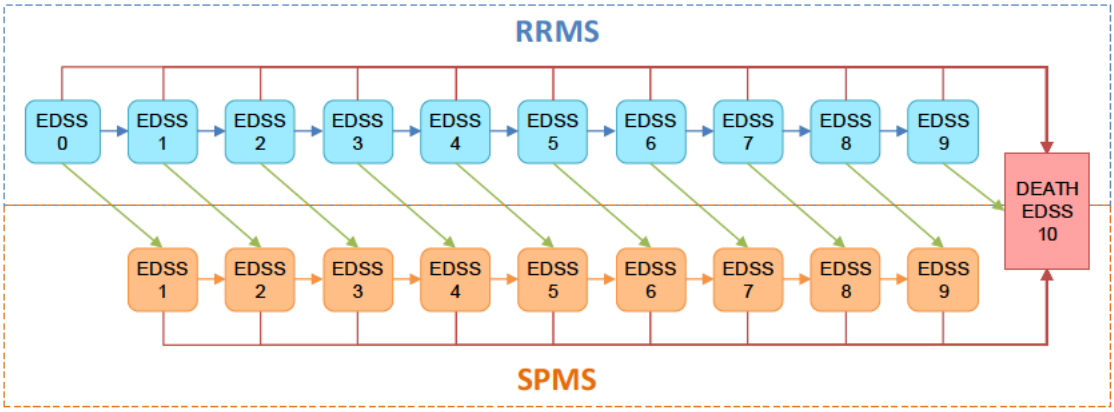
Therefore, the focus of the economic evaluation will be for a population of patients with RRMS, which is in line with the populations specified in the NICE Final Scope. Two additional populations were also specified in the NICE final scope: SPMS with relapses and PRMS. However, teriflunomide has no marketing authorisation for these indications and therefore evidence considering the treatment of teriflunomide in either population is not presented.

Model structure

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

A multi-state Markov model was developed which considered health states based on disease classification and severity, as shown in Figure B7.2.1. RRMS patients enter the model in one of ten health states defined by the Kurtzke Expanded Disability Status Scale (EDSS) [Kurtzke, 1983]. Descriptions of each EDSS state can be found in Section A2.1. In each annual cycle, RRMS patients may remain in the same EDSS state, progress to a greater EDSS state or convert to SPMS. Although the focus of the economic evaluation is on RRMS, it is essential to model conversion to SPMS since approximately 65% of people with RRMS will develop SPMS within 15 years of diagnosis [NICE Final Scope]. Once a patient converts to SPMS, they may remain in the same EDSS state or progress to a greater EDSS state. Patients can also die in any EDSS state 0 to 9. Death is represented by EDSS 10.

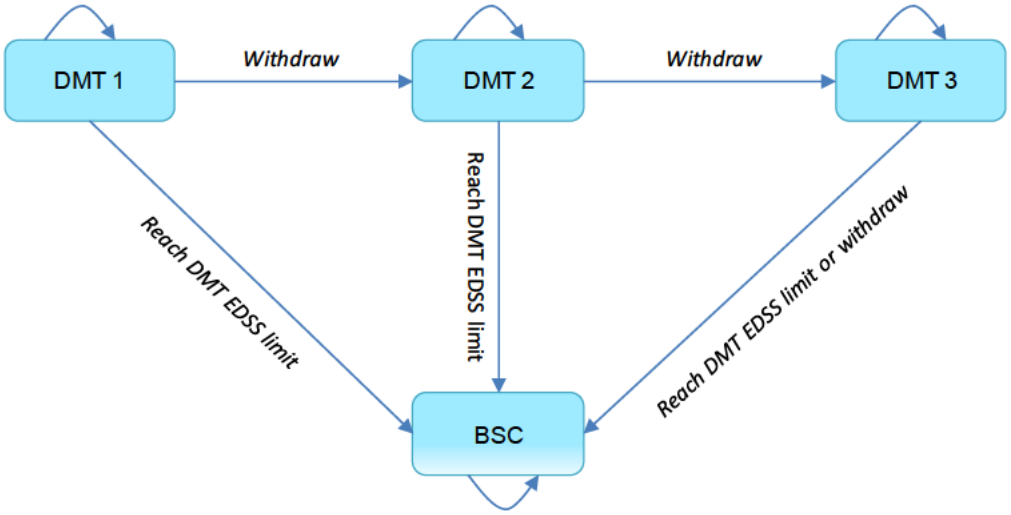
Figure B7.2.1 Schematic of the model



During each annual cycle a patient may: withdraw from treatment; transition between EDSS health states including death; convert to SPMS or reach the EDSS limit for which disease modifying therapy (DMT) is allowed. Please see Section B7.3.2 for further detail.

Additionally, treatment sequencing is considered within the model structure illustrated in Figure B7.2.1. RRMS patients may be treated with up to three lines of DMT during the model time horizon. Therefore, patients who withdraw from treatment may switch to the next DMT treatment line or switch to BSC either when they reach the EDSS DMT limit or following third line DMT (Figure B7.2.2). For comparability with the original ScHARR model and to simplify the decision problem, treatment sequencing is not included as the base case analysis but is explored through sensitivity analyses.

Figure B7.2.2 Treatment sequencing structure of model



Interviews were conducted with neurologists in England and Wales to ascertain possible treatment sequences used in practice that could be tested in scenario analysis (see Section B7.3.5 for details of interviews). There was not a clear typical treatment pathway; the interviewed clinicians had patients which were being treated with a range of beta-interferons and glatiramer acetate at first and second line. The clinicians indicated they would switch to fingolimod or natalizumab after one or two different beta-interferons or glatiramer acetate, assuming they meet the appropriate treatment criteria. Figure B7.2.3 illustrates some of the treatment sequences used by clinicians in current UK practice [Genzyme KOL interview report, 2013].

The clinicians also indicated that patients would be encouraged to remain on treatment for as long as possible rather than switch to best supportive care (BSC). Patients are usually treated with best supportive care only in cases of tolerability issues, adverse event issues or conversion to SPMS. They would also tend to use fingolimod and natalizumab as "stronger" therapies in later stages of the disease but would possibly re-initiate patients on beta-interferons or glatiramer acetate if patients could not tolerate fingolimod or natalizumab. This indicates that are a number of additional possible sequences to those presented in Figure B7.2.3 but the main treatment pathways that occur in England and Wales are captured.

Having reviewed publicly available trial evidence for teriflunomide, the clinicians stated they would, subject to guidance, expect to use teriflunomide at first line as an alternative to beta-interferons or glatiramer acetate. Therefore, the availability of teriflunomide is not expected to increase the number of lines of therapy received by a patient. The clinicians expected that following withdrawal from teriflunomide, a patient would receive a beta-interferon, glatiramer acetate, fingolimod or natalizumab to mirror current clinical practice. Figure B7.2.4 illustrates clinicians' suggested possible treatment sequences if teriflunomide is approved in the UK [Genzyme KOL interview report, 2013]. Fingolimod is recommended specifically for patients with HA RRMS following failure of beta-interferon, which does not extend to glatiramer acetate. This recommendation is therefore also not expected to extend to teriflunomide.

Figure B7.2.3 Current treatment pathway used by interviewed KOLs for patients with RRMS at treatment initiation

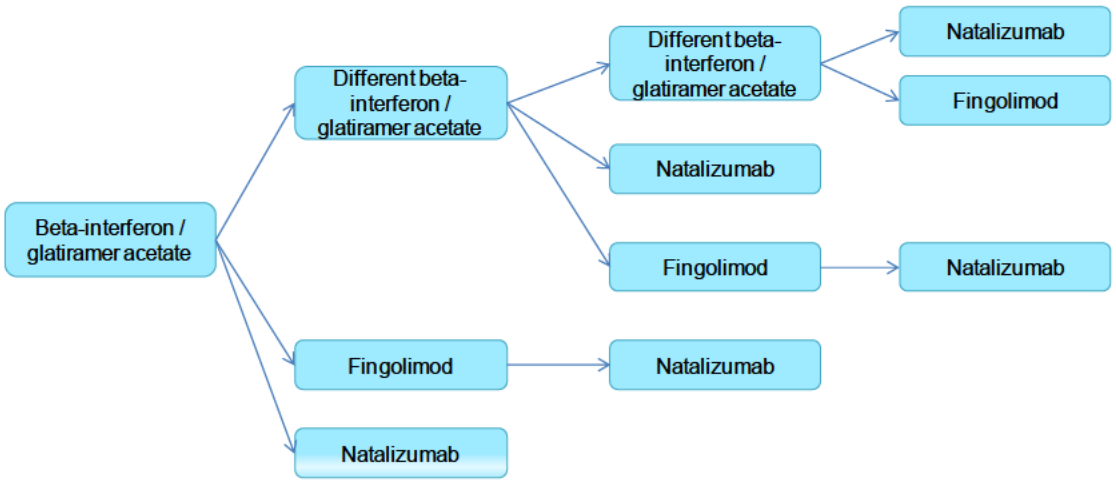
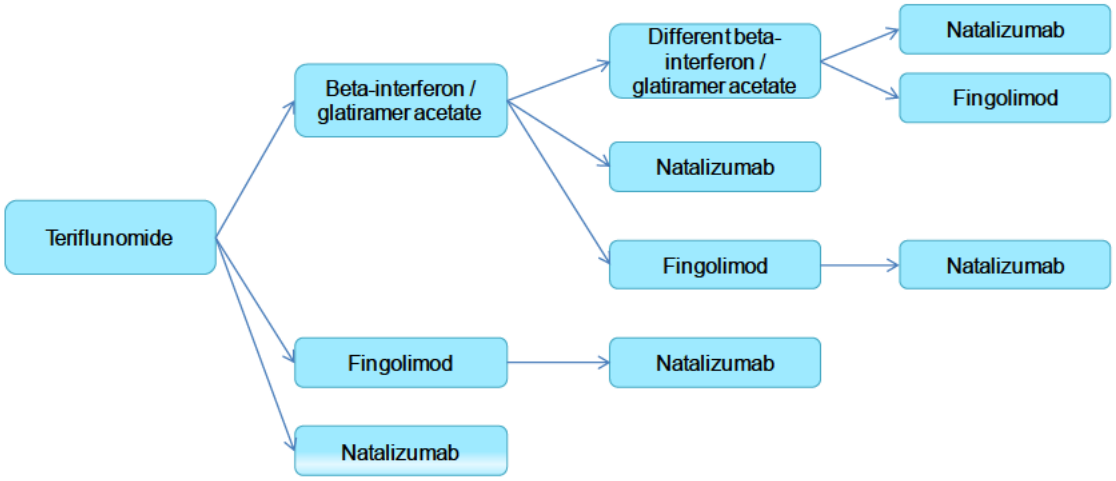


Figure B7.2.4 Possible treatment pathway identified by UK KOLs for patients with RRMS at treatment initiation following teriflunomide approval



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

The structure of the model is based on the previously published ScHARR model, developed for NICE to evaluate the cost-effectiveness of beta-interferon and glatiramer acetate in the treatment of multiple sclerosis [Chilcott et al. 2003]. Adapted versions of the ScHARR model have also been used in previous multiple sclerosis technology appraisals [Biogen, 2006; Novartis, 2011].

The model structure allows estimation of the full impact of the disease across a lifetime, in terms of both costs and quality of life, from pre-diagnosis at EDSS 0 (normal neurological examination), to EDSS 9 (confined to bed) before reaching EDSS 10 (death). The model structure differs from the original ScHARR model by capturing mortality separately from the transitions through EDSS states to allow for an increasing risk of mortality by age and gender.

Capturing disease classification and progression through EDSS health states within RRMS and SPMS meant that the costs and quality of life implications could be identified and captured for: disability progression; relapses; and treatment alternatives. Additionally, results from the systematic review (Section B7.1.1) found that the vast majority of models developed in multiple sclerosis were Markov models. Therefore, it was deemed that a Markov structure was the most appropriative structure to model the cost-effectiveness of teriflunomide.

In line with the ScHARR model and subsequent versions, it was assumed that when a patient progresses from RRMS to SPMS, their EDSS would increase by 1 (see Figure B7.2.1). This assumptions has been validated with UK clinicians [Genzyme KOL interview report, 2013].

Previous economic evaluations in MS have modelled patients to receive BSC following withdrawal from the intervention or comparator. However, in UK clinical practice, a patient is more likely to receive an alternative DMT than BSC, following withdrawal from their first or second-line DMT (see Section B7.2.2). The licensed indication for teriflunomide is in RRMS, and consequently treatment may be considered as an alternative to beta-interferons or glatiramer acetate. Therefore, to accurately reflect UK clinical practice and the positioning of teriflunomide, treatment sequencing has been incorporated into the model structure to allow users the flexibility to consider up to three lines of possible DMT treatment followed by BSC (see

Figure B7.2.2).

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

The objective of the model was to estimate costs and QALYs with teriflunomide compared to alternative DMTs for the treatment of RRMS. The model was developed to capture differences in outcome measures specified in the NICE scope which could affect both costs and QALYs (see Figure B7.2.5):

- There are 21 possible health states in the model: RRMS EDSS 0 to 9, SPMS EDSS 0 to 9 and death. Transition matrices are used to estimate progression of patients through the disease scale (EDSS) as well as the disease classification in terms of RRMS and SPMS. Costs and QALYs are calculated based on both EDSS level and disease classification. Consequently, this would capture disability, symptoms of multiple sclerosis, and freedom of disease activity.

- The number of relapses associated with each health state is estimated along with the corresponding costs and impact on quality of life. Severity of relapses is accounted for both in terms of costs and quality of life (see Section B7.2.5).
- Mortality from disease progression is captured in the model and is adjusted for age and gender.
- Costs and disutility associated with treatment-related adverse events is captured in the model.

Figure B7.2.5 Outcomes in NICE teriflunomide final scope

Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example, expanded disability status scale [EDSS]) • symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • freedom of disease activity • mortality • adverse effects of treatment • health-related quality of life

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

Disease progression

The natural history of the disease was modelled based on real-world longitudinal observational disability progression data obtained from the London Ontario data set and placebo arms of TOWER and TEMSO. Disease progression is captured in terms of both progression of patients through EDSS states, and conversion from RRMS to SPMS. In addition, number of relapses (split by severity) are captured and linked to EDSS states. Further detail of their implementation in the model can be found in Section B7.3.1.

EDSS progression and conversion to SPMS

Previous technology appraisals have used the London Ontario dataset for predicting natural history progression without DMT because this was used in the original ScHARR model [Chilcott et al. 2003]. However, recently there

have been concerns regarding the use of this old data set, which may not accurately reflect current disability progression rates in multiple sclerosis [NICE, 2011 (a)]. Therefore, a systematic review was conducted to identify the most appropriate natural history transition matrix for disability progression for patients receiving no DMT (see Additional Appendix 7). A number of different sources of natural history were identified through the search including the UK Risk Share Scheme [Boggild et al. 2009]. These were assessed and evaluated based on their applicability to the decision problem, availability of use in the model and reliability. As discussed in Additional Appendix 7, from the data available, the London Ontario dataset was found to be most appropriate, robust and clinically plausible. However, a restriction of the London Ontario dataset is that it does not include any patients that regress in EDSS which is known to occur in clinical practice [Jones et al. 2010].

The London Ontario registry analyses provided EDSS transition probabilities for active RRMS patients, all RRMS patients and all SPMS patients as well as conversion probabilities for patients progressing from RRMS to SPMS. Active RRMS was defined as "patients with ≥2 relapse events during the 2-year pre-study period, but <2 relapses in the first pre-study year" in the London Ontario analysis. This definition of active RRMS is in line with the most recent ABN guidelines which states patients with active disease (>2 clinically significant relapses in the previous 2 years) are eligible for beta-interferon or glatiramer acetate [ABN, 2009]. Therefore, active disease is a relevant subset population of RRMS for teriflunomide. In line with the NICE Final Scope and licence for teriflunomide, the base case analysis uses EDSS transition probabilities based on all RRMS patients, whilst a sensitivity analysis considers transitions based on active RRMS.

Since the London Ontario data did not contain any patients with EDSS 0 in RRMS, transition probabilities from EDSS 0 were derived using the placebo arms of the TEMSO and TOWER trials. These TEMSO and TOWER derived transition probabilities from EDSS 0 were combined with probabilities from EDSS 1 to 9 from the London Ontario RRMS dataset to produce the natural history RRMS transition matrix. The London Ontario registry was also used to generate transition probabilities between EDSS states for SPMS patients, as well as probabilities of conversion from RRMS to SPMS.

The progression of patients receiving DMTs is estimated by adjusting the natural history transition matrix by the relative effect of treatment versus placebo derived from the MTC (see Section B6.7). In addition to delaying disability progression, DMTs also reduce relapse rates, which are modelled by applying a relative risk for each treatment to the relapse rate of best supportive care patients (see Section B6.7). Furthermore, DMTs reduce the severity of relapses which impacts costs and utilities so this is also captured in the model.

Relapses

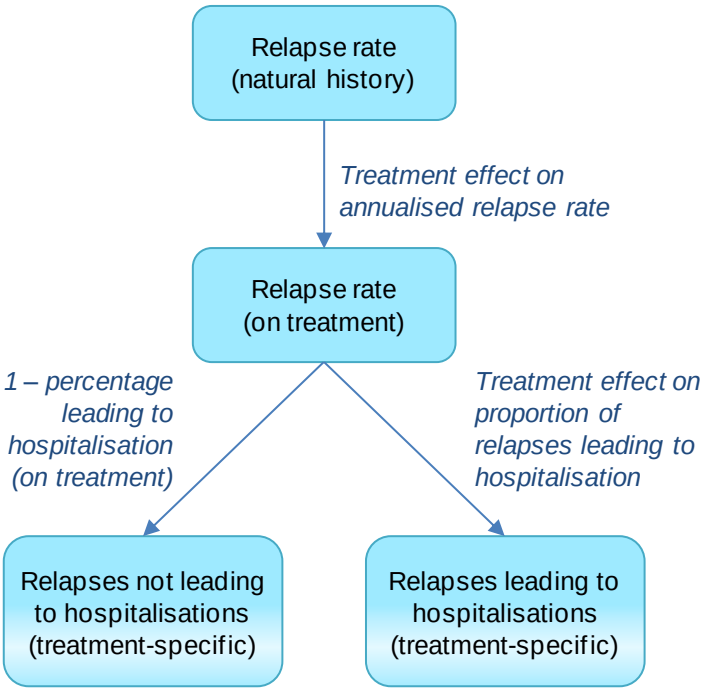
Different severities of relapses are considered in the model because relapses which require hospitalisation incur greater costs and quality of life losses than those which do not lead to hospitalisation. Consequently, relapses are segregated according to:

- Relapses leading to hospitalisation
- Relapses not leading to hospitalisation

The approach used to model these different relapse severities is shown in Figure B7.2.6. Two distinct treatment effects on relapses in the model are considered:

1. Treatment effect leading to reduction of relapses (annualised relapse rate reduction), applied onto a natural history rate of relapse
2. Treatment effect leading to a smaller proportion of relapses leading to hospitalisation (relative rate), applied onto the natural history proportion of relapses that lead to hospitalisation

Figure B7.2.6 Application of treatment effect on relapse segregated by hospitalisation status



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

Table B7.2.11 Key features of analysis

Factor	Chosen values	Justification	Reference
Analytical method	Multi-state Markov model	Long-term chronic condition, clear and reproducible. Considered appropriate by ScHARR in the development of a model to evaluate cost-effectiveness of beta-interferons and glatiramer acetate for NICE.	[Chilcott et al. 2003]
Software	Microsoft Excel	Transparent and widely used software	
Time horizon	Life time (50 years with starting age of 38)	Sufficiently long time to reflect life time differences in costs or outcomes between technologies, as stipulated in reference case	[NICE, 2008]
Cycle length	1 year	Previously considered appropriate by Sheffield University.	[Chilcott et al. 2003]
Half-cycle correction	Mid-year estimate is an average of: the cohort at the start of each cycle following treatment withdrawal; and at the end of each cycle following mortality, disease progression/ conversion and switch to BSC	As stipulated in reference case	[NICE, 2008]
Measure of health effects	Quality adjusted life years (QALYs)	As stipulated in reference case	[NICE, 2008]
Discount for utilities and costs	3.5%	As stipulated in reference case	[NICE, 2008]
Perspective	NHS & PSS	As stipulated in reference case	[NICE, 2008]
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

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

Teriflunomide 14mg is considered as the intervention in line with the marketing authorisation. Comparators considered were based on those outlined in the NICE Final Scope (see Figure B7.2.7).

Figure B7.2.7 Comparators in NICE teriflunomide final scope

Comparators	• beta-interferon • glatiramer acetate • natalizumab (for patients with rapidly-evolving severe relapsing-remitting multiple sclerosis) • fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta interferon)

In the UK, RRMS patients should be offered the following DMTs according to the DoH Risk Sharing Scheme [DoH, 2002] IFNβ-1a (Avonex®), IFNβ-1b (Betaferon®), IFNβ-1a (Rebif®) and glatiramer acetate (Copaxone®). Therefore these four treatments are included as direct comparators to teriflunomide in the model, in line with NICE Final Scope.

There are two doses of IFNβ-1a (Rebif) used in clinical practice: 22µg and 44µg. The lower dose of 22µg is recommended for patients who cannot tolerate the higher dose in view of a treating specialist [Rebif SmPC]. Therefore, a fully incremental analsyiss may not capure clinical practice in how Rebif is administred to patients. Consequently, an aggregated ICER of Rebif 44µg and 22µg, representative of Rebif as a stand-alone intervention is presented. However, for completeness, pairwise comparisons are presented against IFNβ-1a (Avonex), IFNβ-1b, glatiramer acetate, IFNβ-1a 22µg (Rebif) and IFNβ-1a 44µg (Rebif).

As reflected in the NICE scope the primary comparators for teriflunomide are beta-interferons and glatiramer acetate in the licensed population (RRMS). However, DMTs also commonly used in UK practice are natalizumab and fingoliomod which are included also in the scope but limited to specific subgroups. NICE guidance limits natalizumab to RES RRMS and fingolimod to HA RRMS patients that have received prior treatment beta-interferons [NICE, 2012(a); NICE, 2007(a)]. Therefore, comparisons with natalizumab and fingolimod are addressed in two distinct subgroup analyses (see Section B7.9).

In addition to presenting an incremental analysis of teriflunomide compared to each of the beta-interferons and glatiramer acetate in RRMS, a blended comparator consisting of a weighted average of these five comparators has been presented. This analysis has been presented to indicate the cost-effectiveness of teriflunomide compared to the average mix of current relevant treatment comparators in the UK.

A blended comparator has been chosen because there is a lack of clear preferred treatment option in England and Wales (see Figure B7.2.8). Beta-interferons and glatiramer acetate are generally regarded under the same class of DMTs as they have similar efficacy, price and safety profile and are the primary comparators for teriflunomide [Genzyme KOL interview report, 2013]. The blended comparator is composed of weighted

averages of the clinical efficacy, costs and disutilities from the four beta-interferons and glatiramer acetate. The blended comparator includes the full range of commonly used beta-interferons and glatiramer acetate to capture possible treatments for all RRMS patients across early and later stages of the disease.

Note that IFNβ-1b (Extavia®) is not included as a comparator in the model but since it is the same molecule as Betaferon and the list price of Extavia is the same as the RSS price of Betaferon. The weighting of Betaferon within the blended comparator is the sum of Betaferon and Extavia market shares (11%).

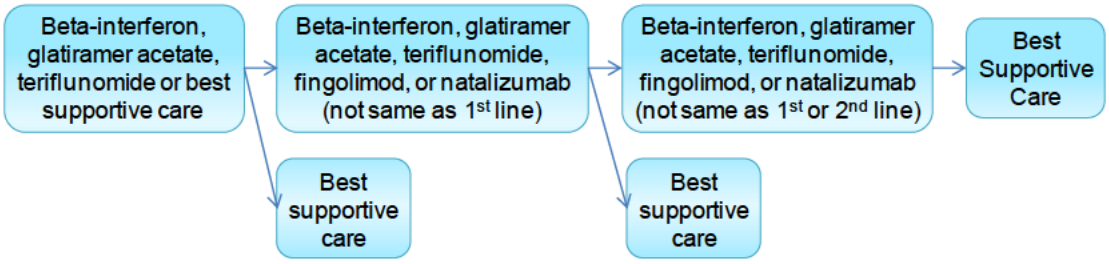
[redacted] Market share of beta-interferons and glatiramer acetate in the UK 2012 [Genzyme Data on file: IMS market shares]

[redacted]

Although we present incremental results and a blended comparator, we would suggest that the blended comparator is considered as a base case. The NICE committee appraising fingolimod acknowledged that there was variation in current practice and consequently fingolimod was compared with a weighted average of the comparators currently used in UK clinical practice to manage HA RRMS [NICE, 2011(a)]. In this technology appraisal, the blended comparator similarly represents the variation in clinical practice which will not be accounted for through incremental analysis.

As outlined in Section B7.2.2, a sensitivity analysis explores the effect of treatment sequences with DMT. Although not included as comparators in the NICE Final Scope, fingolimod, natalizumab and best supportive care are included as treatment options along with beta-interferons and glatiramer acetate for patients who fail first or second-line treatment (see section B7.2.2). In these sensitivity analyses, it is assumed that the RRMS patients that enter the model will have progressed to HA (for treatment with fingolimod) or / then rapidly-evolving-severe (RES) (for treatment with natalizumab).

Figure B7.2.9 Treatment sequencing options available within the model for patients diagnosed with relapsing-remitting multiple sclerosis



7.2.8 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) SmPC/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.

In the RRMS population, guidelines produced in 2001 from the Association of British Neurologists (ABN) do not recommended the use of DMT in patients that have lost the ability to walk [ABN, 2001]. The Department of Health agreed with the ABN criteria to determine eligibility for treatment using beta-interferon and glatiramer acetate for people with MS within the RSS [NICE, 2003]. Therefore, the most recent NICE guidance (2003)

recommends stopping treatment in patients that have the lost the ability to walk, with or without assistance, which corresponds to an EDSS of 6.5 or greater (Figure B7.2.10). The updated 2009 ABN guidelines also recommend treatment in this group of patients [ABN, 2009]. Since states in the model are rounded up to the nearest integer, this stopping rule is implemented as: when a patient progresses to EDSS 7, they switch from a DMT to treatment with BSC only.

Figure B7.2.10 Summary of the criteria suggested by the ABN, and agreed by the Department of Health, to determine eligibility for treatment using beta-interferon and glatiramer acetate for people with MS within the RSS [NICE, 2003]

A People with **relapsing-remitting** MS should be offered **interferon beta** (any type) provided that the following four conditions are met:

- can walk 100 metres or more without assistance
- have had at least two clinically significant relapses in the past two years
- are aged 18 years or older
- do not have contraindications (see specific summary of product characteristics (SPC) for details).

B People with **relapsing-remitting** MS should be offered **glatiramer acetate** provided that the following four conditions are met:

- can walk 100 metres or more without assistance
- have had at least two clinically significant relapses in the past two years
- are aged 18 years or older
- do not have contraindications (see specific SPC for details).

C People with **secondary progressive** MS should be offered **interferon beta** (any type licensed for this use) provided the following five conditions are met:

- can walk 10 metres or more with or without assistance
- have had at least two disabling relapses in the past two years
- have had minimal increase in disability due to gradual progression over the past two years
- are aged over 18 years
- do not have contraindications (see specific SPC for details).

D People with MS offered treatment with **interferon beta** should have the following **stopping criteria** discussed and agreed before starting treatment:

- intolerable side effects
- becoming or trying to become pregnant
- occurrence of two disabling relapses within a 12-month period
- secondary progression with an observable increase in disability over a six-month period
- loss of ability to walk, with or without assistance, that has persisted for longer than six months.

E People with relapsing–remitting MS offered treatment with **glatiramer acetate** should have the following **stopping criteria** discussed and agreed before starting treatment:

- intolerable side effects
- being pregnant or planning pregnancy
- occurrence of two disabling relapses within a 12-month period
- development of secondary progressive MS
- loss of ability to walk, with or without assistance, that has persisted for longer than six months.

In clinical practice, a patient's EDSS level is regularly monitored by a neurologist or MS nurse [Genzyme KOL interview report, 2013]. This is reflected in the model through neurology visits for treatment monitoring, in addition to direct medical and non-medical costs. Therefore, using a stopping rule based on EDSS is accurate, robust, feasible in clinical practice, incurs no additional cost over regular monitoring, and is in line with NICE guidelines.

The RRMS stopping rule of EDSS 7 is applied to all comparators as well as the intervention. Any increase or reduction in costs or QALYs incurred through the application of the stopping rule to the intervention will be equally incurred in the comparators. The sensitivity of the cost-effectiveness results for teriflunomide to the stopping rule at EDSS 7 is explored in a sensitivity analysis (see Section B7.6.1).

Teriflunomide, glatiramer acetate and IFNβ-1a (Avonex) are not indicated for use in SPMS [Teriflunomide SmPC, 2013; Avonex SmPC; Copaxone SmPC; NICE CG8 (Multiple Sclerosis), 2003]. Since teriflunomide will not be used in the SPMS population, a SPMS stopping rule was implemented for all comparators at EDSS 0 such that no patients are treated with a DMT upon conversion to SPMS in the base case model. However, sensitivity analyses were performed to evaluate the impact of modelling IFNβ-1a (Rebif) and IFNβ-1b according to their licence in SPMS up to EDSS 7, in line with NICE guidance [NICE, 2003].

Any withdrawal of treatment prior to stopping at EDSS 7 for RRMS patients is captured by treatment-specific discontinuation rates in the model. These all-cause discontinuation rates are derived from the MTC (see Section B6.7). Therefore, the continuation rule applied through the model is that a patient can remain on a treatment with teriflunomide, IFNβ-1a (Avonex) or glatiramer acetate whilst the following conditions are met:

- Patient does not discontinue treatment due to events specified in the MTC
- Patient has RRMS with an EDSS < 7
- Patient does not have SPMS.

Similarly, a patient can remain on a treatment with IFNβ-1a (Rebif) and IFNβ-1b whilst the following conditions are met:

- Patient does not discontinue treatment due to events specified in the MTC
- Patient has an EDSS < 7.

7.3 *Clinical parameters and variables*

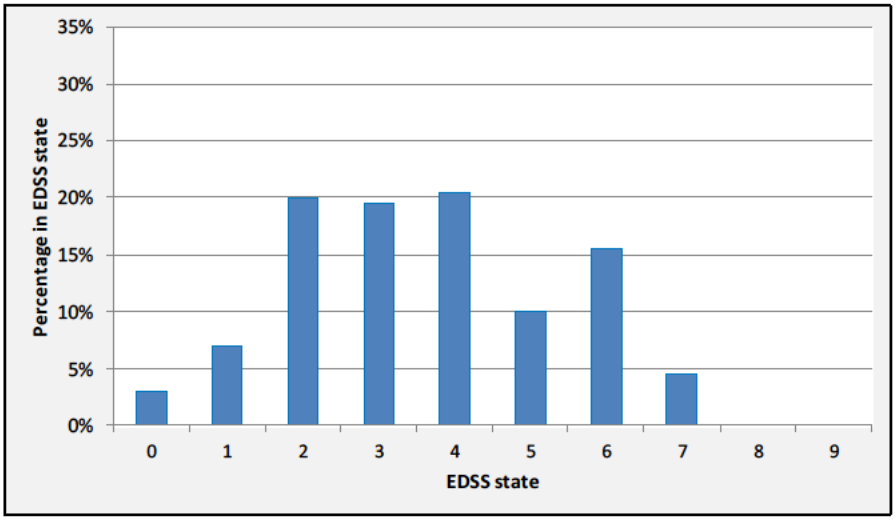
When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section B6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

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

Patient characteristics

The population entering the model was based on the average demographic profile of a RRMS patient in the UK. For the base case, the demographic profile at baseline of RRMS patients was sourced from the UK Risk Sharing Scheme (RSS) [Pickin et al. 2009]. The population of the RSS analysis included 85.8% RRMS patients; for the purposes of using these data to inform baseline characteristics in the model, this was assumed to be a 100% RRMS. The mean age of patients at baseline was 39.3 years. The female to male ratio is 2.98:1. The baseline EDSS distribution is shown in Figure B7.3.1.

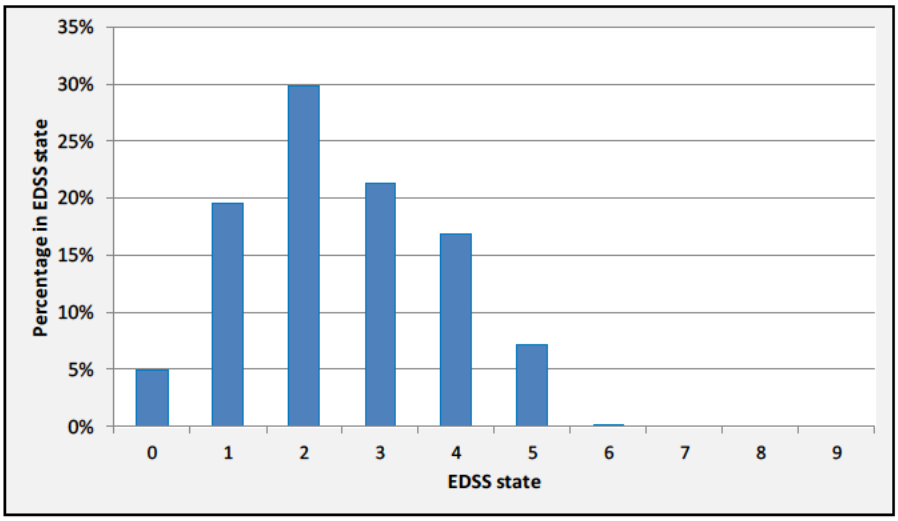
Figure B7.3.1 Baseline EDSS distribution used in base case modelling, sourced from UK Risk Sharing Scheme



As a sensitivity analysis, the age, gender and EDSS distribution at baseline from the pivotal phase III trials (TEMSO and TOWER) for teriflunomide were used. The mean age of patients at baseline was slightly lower in TOWER and TEMSO than the UK RSS at 37.9 years. The female to male ratio was also slightly lower in TOWER

and TEMSO than the UK RSS at 2.52:1. The EDSS distribution indicated slightly milder patients than the UK RSS (Figure B7.3.2). A lower EDSS distribution at treatment initiation is more representative of the UK target population for teriflunomide which is early in the disease as first line treatment [Genzyme KOL interview report, 2013]. Treatment in the earlier stages of the disease is supported, to avoid accumulation of disability [Pugliatti et al. 2013].

Figure B7.3.2 Baseline EDSS distribution used in modelling alternative scenario, sourced from pivotal teriflunomide trials TOWER and TEMSO



Withdrawal

At the start of each cycle, patients may withdraw from treatment. The method used to calculate the probability of treatment withdrawal is based on the 2-year withdrawal probability for teriflunomide combined with results from the MTC (see Section B6.7).

To remain consistent with the teriflunomide trials included in the MTC, the 2 year probability of withdrawal for teriflunomide 14mg was calculated using data from the Phase II, TEMSO, TOWER and TENERE trials (Table B7.3.1).

Given that the majority of MS trials are 2-years in length, a 2 year weighted average withdrawal probability for teriflunomide was calculated. The 36-week probability of withdrawal for the Phase II trial was converted to a 2-year rate and then back to a 2-year probability. Consequently, the 2-year average probability of withdrawal was calculated as 28.71%.

Table B7.3.1 Calculation of all-cause withdrawal rate for teriflunomide 14mg

Trial	Length of trial	Number starting treatment	Number remaining on treatment	% withdraw from trial	2-year probability of withdrawal
TENERE	2 years	111	89	20%	20%
TEMSO	2 years	358	263	27%	27%
TOWER	2 years	370	258	30%	30%
Ph II	36 weeks	57	45	21%	49%
AVERAGE					28.71%

The 2-year average probability of withdrawal for teriflunomide was combined with the MTC to obtain annual probabilities of withdrawal for all treatments using the following method:

1. First, the 2-year odds for teriflunomide was calculated using:

   Odds (treatment) = Probability / (1-Probability)

   2-year Odds (teriflunomide) = 0.2871 / (1-0.2871) = 0.4027

   [redacted]The inverse odds ratios for teriflunomide versus the comparators from the MTC (see Section B6.7 and Table B7.3.2) were applied to the 2-year odds for teriflunomide to give the 2-year odds for each comparator treatment e.g. natalizumab 2-year odds [redacted]

Table B7.3.2 Mean odds ratios of withdrawal for teriflunomide vs. comparators in the model

Treatment	Teriflunomide versus comparator odds ratio	95% Lower confidence interval	95% Upper confidence interval
IFNβ-1a (Avonex)	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]
IFNβ-1a (Rebif 44µg)	[redacted]	[redacted]	[redacted]
IFNβ-1a (Rebif 22µg)	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]

*Calculated based on sensitivity analysis MTC (all-years, 80% RRMS) applied to base case MTC (post-2000, 80% RRMS) (see Additional Appendix 2)

3. The 2-year odds for each comparator treatment were then converted back to 2-year probabilities using:

   Probability = Odds / (1+Odds)

4. The 2-year probabilities were converted to absolute annual withdrawal rates using:

   $r = - [\ln(1-p)] / t$

   where p equals the probability/risk, r is the rate, and time t = 2.

5. Finally, annual rates were converted to annual probabilities using:

   $p = 1 – \exp(-r)$

The resulting annual rates of withdrawal used in the model are reported in Table B7.3.3. The model assumes that the annual probability of withdrawal for each treatment will not persist over the 50-year time horizon. This assumption was made on the basis that a patient suffering adverse events is less likely to withdraw from treatment due to adverse events if they have tolerated them for 2 years. Similar assumptions have been made in other economic evaluations of RRMS treatments [NICE, 2007(b)]. After two years it is assumed that the probability of withdrawal will be 50% of those calculated for all treatments. Sensitivity analyses considered persistence of withdrawal as well as a steeper 75% decline in the probability of withdrawal for all treatments.

Table B7.3.3 Annual all-cause rates of withdrawal rates used in the model

Treatment	2-year odds	Source	2-year risks	All-cause annual withdrawal probability	95% confidence interval of all-cause annual withdrawal probability
Teriflunomide	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
IFNβ-1a (Avonex)	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
IFNβ-1a (Rebif 44µg)	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
IFNβ-1a (Rebif 22µg)	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC with ratio applied from all-years, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]

Fingolimod	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]

Mortality

After determining withdrawals, patient mortality may occur. A relative increase in mortality per EDSS state was sourced and applied to all-cause mortality rates for the general population in the UK. A systematic review of mortality by EDSS revealed no additional literature to inform mortality predictions compared to the methods used in previous submissions (TA 127 and TA 254) (see Additional Appendix 8). Therefore, the same approach considered in the aforementioned submissions was taken for this analysis.

This method uses mortality multipliers by MS disease severity from Pokorski et al [Pokorski, 1997]. It is assumed that there is no excess mortality risk for patients in EDSS 0. Cubic regression analysis was applied to these mortality multipliers to obtain a mortality adjustment for each individual EDSS state [Novartis, 2011]. The final mortality multipliers associated with individual EDSS states are listed in B7.3.4.

Table B7.3.4 Mortality multipliers by EDSS score

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

The assumption was made that mortality per EDSS would not differ for SPMS patients. As per the definition of a progressive MS patient, a SPMS patient is more likely to experience increased disability at a quicker rate than an RRMS patient thus indirectly increasing mortality risk.

All-cause mortality rates were obtained from England & Wales Interim life tables from 2008-2010 [Office for National statistics, 2011]. A weighted average all-cause mortality rate was calculated based upon the female to male ratio of MS patients (2.98:1) [Pickin et al. 2009].

The mortality multipliers reported in Table B7.3.4 are applied to the all-cause weighted average mortality rates to derive the risk of mortality of RRMS and SPMS patients in different EDSS states. Finally, mortality rates were converted in annual probabilities of mortality by EDSS, the results of which are presented in Additional Appendix 9. The probability of mortality per cycle is dependent on the starting age of the cohort such that at cycle 20, the probability of mortality in a cohort with average starting age 38 will correspond to the all-cause mortality probability of a patient aged 58.

Disability progression

As discussed in Section B7.2.5, the London Ontario dataset was found to be the most appropriate natural history data for RRMS and SPMS patients receiving no DMT. Since no data for EDSS 0 were available, these transition probabilities were obtained from the placebo arms of TOWER and TEMSO. The complete natural history data for the RRMS and SPMS populations used in the model, representative of best supportive care, are shown in Tables B7.3.5 and B7.3.6 respectively.

The probabilities of progression at later EDSS states reflect the nature of the disease and the EDSS. The level of neurological damage required to go from walking with a stick (EDSS 6) to being confined to a wheelchair (EDSS 7) is a significant change and thus a person is less likely to transition in EDSS each year once they have passed EDSS 6.

Table B7.3.5 Natural history transition probabilities of RRMS patients. Transition probabilities from EDSS 0 sourced from TOWER and TEMSO placebo arms. Transition probabilities from EDSS 1 to 9 are sourced from London Ontario.

		year i+1									
	EDSS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
year i	**0**										
	1										
	2										
	3										
	4										
	5										
	6										
	7										
	8										
	9										
	10										

Table B7.3.6 Natural history transition probabilities of SPMS patients sourced from London Ontario

		year i+1									
	EDSS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
year i	**0**										
	1										
	2										
	3										
	4										
	5										
	6										
	7										
	8										
	9										
	10										

The probability of converting from RRMS to SPMS is calculated from hazard rates, derived using time to event data and survival analysis. The hazard rate for conversion from EDSS 1 to SPMS is calculated assuming an exponential survival function (i.e. a constant hazard of converting from EDSS 1 to SPMS over time). The exponential survival function has the form of:

$$S(t) = exp(-\lambda t)$$

The hazard rate λ for an exponential distribution can be estimated from the median time of conversion to SPMS, reported to be 15 years from disease onset from London Ontario [Scalfari et al. 2010]. The annual hazard rate of conversion for patients in EDSS 1 is therefore:

$$\lambda = \ln(2)/15 = 0.0462$$

The hazard rate of conversion for the other EDSS states can be calculated from the hazard rate of conversion from EDSS 1 by using a Cox proportional hazards model analysis. The Cox proportional hazards model using EDSS as a continuous variable is reported by analysis of the London Ontario data as:

$$H(t) = H(t)_{EDSS1} \exp(\beta X) = \lambda \exp(\beta X)$$

Where H(t) is the hazard rate of conversion for any EDSS state, $H(t)_{EDDS1}$ the hazard rate of conversion for EDSS 1, and β the coefficient of the relationship between EDSS and the hazard ratio of progression between the base case EDSS 1 and all other EDSS states. The analysis from London Ontario reports [redacted]. This above equation for H(t) is then used to derive the hazard rates of conversion from EDSS 1 to each successive stage to EDSS 8 (Table B7.3.7). Data for EDSS 9 was not available from the London Ontario dataset so a 100% conversion rate for RRMS patients in EDSS 9 was assumed. All estimated hazard rates were subsequently converted into probabilities using the standard formula of $p = 1 – \exp\{-rt\}$.

Table B7.3.7 Annual probability of conversion to SPMS from RRMS by EDSS score

EDSS	Calculation	Hazard rate	Calculation	Probability
0				0
1	ln(2)/15	0.046210	1-exp(-0.046210)	0.045158
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9				[redacted]

The probabilities are reflective of the characteristics of SPMS disease. In practice, very few patients enter SPMS with low EDSS scores. SPMS generally follows RRMS and usually starts around EDSS scores of 4-5. The probabilities used in the model show a low likelihood of converting to SPMS for a patient with an EDSS of less than 4 and are therefore reflective of clinical practice.

The natural history matrix is calculated using the RRMS and SPMS natural history data with the probability of conversion from RRMS to SPMS (Table B7.3.8)

Table B7.3.8 Natural history transition matrix per EDSS health state and classification

		RRMS											SPMS										
	From \ To	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
RRMS	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPMS	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The natural history transition matrix from RRMS to RRMS states is upper triangular, such that a patient does not regress in EDSS, only progresses in EDSS or remain in their existing EDSS. This is also true for the transitions from SPMS to SPMS states. Due to the clinical nature of progressive MS, the probability of transitioning from an SPMS state to an RRMS state is 0.

Relapses rates

EDSS state-dependent relapse rates split by MS classification were included in the model. Due to a lack of relapse data available from the London Ontario dataset or alternative registries, relapse rates were sourced from alternative literature sources, which included two studies: Patzold et al. and Held et al [Patzold et al. 1982; Held et al. 2005].

There are advantages and disadvantages to choosing either Patzold et al. or Held et al. as a source for annualised relapse rate by years since diagnosis (Table B7.3.9). The relapse rates calculated using Held et al. has been used in the base case since these are more recent. The relapse rates calculated from Patzold et al. as per previous submissions (TA 127 and TA 254) is considered in a sensitivity analysis.

Table B7.3.9 Summary of sources for natural relapse rates

Study	Description	Strengths	Limitations
Held, 2005	Retrospective analysis of 821 patients of the placebo arms of the Sylvia Lawry Centre for Multiple Sclerosis database	• Fairly recent data • Large number of patients	• Relapses are not clearly defined and requires adjustment
Patzold, 1982	Long-term prospective analysis of 102 MS patients	• Directly in line with our requirement for relapse rate per years since diagnosis.	• The data analysed dates from 1976 to 1980 • Smaller number of patients

The relapse rates by MS classification and EDSS state and were calculated in a two step process:

Step 1: Mean annual relapse rates by years since diagnosis were derived

Held et al. conducted a multivariable Poisson regression analysis assessing the effect of disease duration and the number of relapses in the previous 24 months on the annual relapse rate. Weighted average relapse rates for 5, 10, 15 and 20 years after diagnosis were estimated using a weighted mean of annual relapse rates for patients who experienced 0, 1, 2, or 3 relapses in the previous 24 months. The regression coefficient of a gain in years since diagnosis was applied to the weighted average relapse rates to give an estimated annual relapse rate per year since diagnosis (Table B7.3.10).

Table B7.3.110 Weighted average of relapse rate per year since diagnosis derived by Held et al [Held et al. 2005]

Years since diagnosis	Weighted average
5	0.932878581
10	0.857517053
15	0.787476126
20	0.725102319

Patzold et al. conducted a regression analysis to investigate the relationship between mean annual relapse rate and the number of years since diagnosis. This regression equation was used to derive the annual relapse rates for each year since diagnosis (Table B7.3.11).

Table B7.3.121 Annual relapse rate per year since diagnosis derived from Patzold et al [Patzold et al. 1982]

Years since diagnosis	Annual relapse rate
1	1.613
2	1.258
3	1.051
4	0.903
5	0.789
6-7	0.656
8-9	0.518
10-11	0.410
12-13	0.320
14-15	0.244
16+	0.136

Step 2: The UK MS survey provides patient level data of the number of patients in each EDSS state by the number of years since diagnosis (Table B7.3.12). The relapses rates per year since diagnosis, derived from Held or Patzold, were applied to the number of patients from the UK MS Survey to give the number of relapses per EDSS per year since diagnosis. For each EDSS, a weighted average was taken of the relapses per year since diagnosis to give the relapse rate per EDSS. Due to the small number of patients in EDSS states 6.5 - 9, numbers were summed together to produce on rate applicable to EDSS states 7, 8 and 9. The final relapse rates by EDSS and MS classification are presented in Table B7.3.13.

Table B7.3.12 UK MS Survey patient numbers per PDDS / EDSS state by year since diagnosis [Orme et al. 2007]

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

Table B7.3.13 Relapse rates by EDSS score and MS classification

EDSS scale	Relapse Rate			
	Base case		Sensitivity analysis	
	RRMS	SPMS	RRMS	SPMS
0	0.905	0.000	0.725	0.000
1	0.905	0.000	0.743	0.000
2	0.895	0.851	0.690	0.448
3	0.899	0.910	0.723	0.788
4	0.900	0.872	0.707	0.567
5	0.881	0.860	0.599	0.517
6	0.859	0.847	0.509	0.445

7	0.856	0.818	0.504	0.312
8	0.856	0.818	0.504	0.312
9	0.856	0.818	0.504	0.312
Source used in derivation	[Held et al. 2005; Orme et al.2007]		[Patzold et al. 1982; Orme et al. 2007]	

Relapses leading to hospitalisation

As discussed in Section B7.2.5, the model distinguishes between relapses which lead to hospitalisation and those that do not. Two sources of natural history data of the proportion of relapses leading to hospitalisation were identified. The first source was Dee et al. 2012 which is a recent study of an Irish population which states 20% of relapses lead to hospitalisation [Dee et al. 2012]. The second source was the placebo arms of TOWER and TEMSO trials which calculated that 30.7% of relapses lead to hospitalisation [Miller (slide 9), 2012]. The base case considers Dee et al. since this is more representative of the UK population. The proportion derived from TOWER and TEMSO trials is used in a sensitivity analysis.

Treatment effect on disability progression

See Section B7.3.2 for details on how the hazard ratio of 3 month confirmed disability progression was used to generate treatment transition matrices.

Treatment effect on Relapse rate

To evaluate the effect of treatment with DMT on relapse rate, the ARR derived from the MTC (see Section B6.7 and Table B7.3.14) was applied to the natural relapse rate (Table B7.3.13). As discussed in Section B6.7, ARR data were not available from the PRISMS trial for Rebif 22µg so it has been assumed equal to Rebif 44µg. This is a conservative assumption since the higher dose of Rebif reduces relapses more than the lower dose so in fact the ARR for Rebif 22µg would be higher [PRISMS, 1998].

Table B7.3.14 Relative risk of relapse compared to placebo sourced from mixed-treatment comparisons

Treatment	Relative ARR	95% CI Lower	95% CI Higher
Teriflunomide	0.67	0.57	0.77
IFNβ-1a (Avonex)	0.78	0.67	0.91
IFNβ-1b	0.68	0.52	0.88
IFNβ-1a (Rebif 44µg)	0.62	0.51	0.76
IFNβ-1a (Rebif 22µg)	[redacted]	[redacted]	[redacted]
Glatiramer acetate	0.64	0.53	0.76
Fingolimod	0.46	0.40	0.54

Natalizumab	0.31	0.25	0.39

*No results available from base case MTC or sensitivity analysis MTC so assumed ARR equal to Rebif 44µg

Treatment effect on Relapse severity

There is limited published literature regarding the treatment effect of reducing the proportion of relapses which lead to hospitalisation, and consequently this was not included as an outcome for the MTC. Table B7.3.15 summarises the assumptions used in the cost-effectiveness model. Relative risks of relapses leading to hospitalisation are applied to the proportion of patients who would be hospitalised receiving placebo [Dee et al. 2012].

Table B7.3.15 Relative effects of treatments on relapses leading to hospitalisation

Treatment	Relative effects on proportion leading to hospitalisation	Risk of hospitalisation per relapse / Source	Assumptions
Teriflunomide	0.570	TEMSO placebo (335 relapses, 103 hospitalised) 30.7%; teriflunomide 14mg (227 relapses, 40 hospitalised) 17.6%. Risk vs. placebo -43%, p<0.0005 [Miller et al. 2012]	
IFNβ-1a (Avonex)	0.495	TRANSFORMS IFNβ-1a (179 relapses, 36 hospitalised) 20.1%; FREEDOMS placebo (359 relapses, 146 hospitalised) 40.7%. Risk vs. placebo -50.5% [Haas et al. 2011]	FREEDOMS (fingolimod vs. placebo) and TRANSFORMS (fingolimod vs. IFNβ-1a) used to derive risk of IFNβ-1a vs. placebo
IFNβ-1b	0.495	-	Assumed same as Avonex
IFNβ-1a (Rebif 44µg)	0.495	-	Assumed same as Avonex
IFNβ-1a (Rebif 22µg)	0.495	-	Assumed same as Avonex
Glatiramer acetate	0.495	-	Assumed same as Avonex
Fingolimod	0.600	TRANSFORMS fingolimod 0.5mg (89 relapses, 11 hospitalised) 12.4%; FREEDOMS fingolimod 0.5mg (172 relapses, 63 hospitalised) 36.6%; FREEDOMS placebo (359 relapses, 146 hospitalised) 40.7%	Weighted average of Fingolimod risk of hospitalisation from FREEDOMS and TRANSFORMS relative to placebo arm of FREEDOMS only

		Risk vs. placebo -40% [Haas et al. 2011]	
Natalizumab	0.600	-	Assumed same as fingolimod

Adverse events

To ensure differences in adverse events between treatment and placebo were adequately captured a criterion for the inclusion of a treatment adverse event within the model was established as a difference of ≥4% in the probability of occurrence, compared to placebo. This conservative arbitrary threshold will identify the most common adverse events that occur with DMTs.

Some multiple sclerosis treatments have more severe adverse events such as cardiac issues associated with fingolimod and progressive multifocal leukoencephalopathy (PML) associated with natalizumab. In an attempt to ensure all serious adverse events were included, trial publications and SmPCs were assessed for Grade III/IV adverse events. Unfortunately, the severity of events was inconsistently reported [Polman et al. 2006; Comi et al. 2001; Rebif SmPC; Jacob et al. 1996]. Applying a threshold for inclusion by severity would create bias amongst the treatments with the most detailed publications / SmPCs. No events of PML occurred in the AFFIRM study [Polman et al. 2006]. By only including common adverse events, rather than severe adverse events, the costs of DMTs may be slightly underestimated in the model. However, since the probability of serious adverse events is so low, this has a negligible impact on cost and utility.

The sources of data for each DMT were placebo controlled studies that had been included in the sensitivity analysis MTC (All-years, 80% RRMS – see Additional Appendix 2). The frequencies of adverse events were adjusted for length of trial to give annual probability of occurrence. Unless the publications used detailed otherwise, adverse events were assumed to occur equally in year 1 and subsequent years.

Five adverse events were identified as ≥4% different between teriflunomide and placebo from the clinical trials (see Section B6.10.1). There is no cost or disutility associated directly with elevated alanine transaminase so this has not been included in the model. Similarly, a systemically well patient with neutropenia will not incur any costs or disutility; the subsequent infections of a systemically unwell patient were captured separately in the trials and have not been identified as ≥4% different between teriflunomide and placebo. Therefore, the adverse events included in the model for teriflunomide were headache, diarrhoea and hair thinning. The cumulative event probability of hair thinning reached a plateau at 10 months in the TEMSO study [Freedman, 2012(b)]. However, 10% of patients recovered with sequelae so 10% of the cohort was modelled to receive the associated costs and disutility of hair thinning in the subsequent years of the event. The adverse event probabilities included in the model are given in Table B7.3.16.

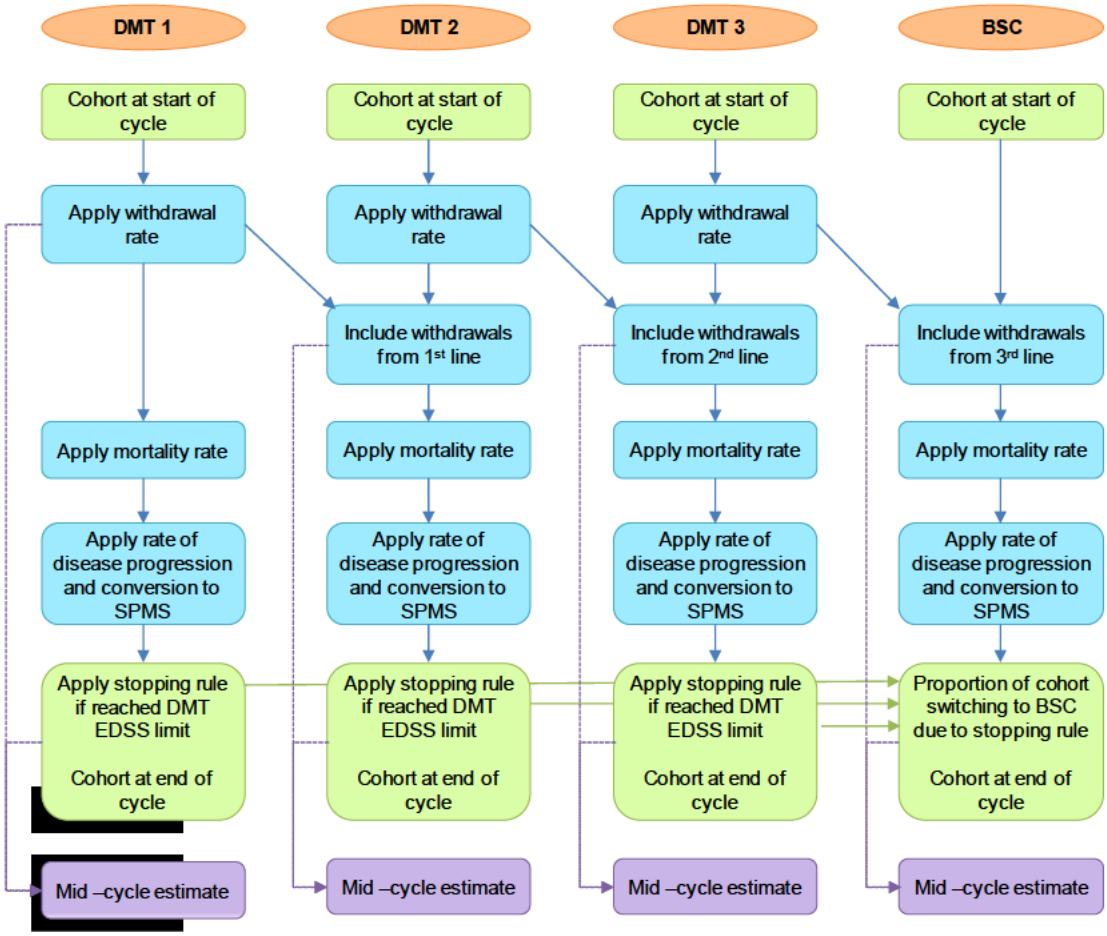
Table B7.3.16 Adverse events probabilities used in the model

	Probability (first year)	Probability (subsequent years)	Source
Teriflunomide			Phase II, TOWER and TEMSO CSRs
Nausea	7.37%	7.37%	
Diarrhoea	7.97%	7.97%	
Hair thinning	16.38%	1.64%	
IFNβ-1a (Avonex)			[Jacobs et al. 1996]
Headache	33.54%	33.54%	
Influenza-like symptoms	30.38%	30.38%	
IFNβ-1b			[IFNβ MS study group, 1995]
Influenza-like symptoms	18.00%	7.00%	
Injection site reaction	80.00%	47.00%	
IFNβ-1a (Rebif 44µg)			[PRISMS, 1998], [Ebers, 1999], [SPECTRIMS, 2001]
Headache	54.17%	54.17%	
Injection site reaction	43.93%	43.93%	
Influenza-like symptoms	65.00%	65.00%	
IFNβ-1a (Rebif 22µg)			
Headache	52.00%	52.00%	
Injection site reaction	44.71%	44.71%	
Influenza-like symptoms	44.42%	44.42%	
Glatiramer acetate			[Johnson et al. 1995]
Injection site reaction	45.00%	45.00%	
Immediate postinjection systemic reactions	7.60%	7.60%	
Fingolimod			[Kappos et al. 2010]
Lower respiratory tract infection	4.82%	4.82%	
Diarrhoea	5.88%	5.88%	
Back pain	5.88%	5.88%	
Natalizumab			[Polman et al. 2006]
Headache	19.00%	19.00%	
Fatigue	13.50%	13.50%	
Arthralgia	9.50%	9.50%	

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

Figure B7.3.3 illustrates how patients transition through the model accounting for withdrawal (Section B7.3.1), mortality (Section B7.3.1), disease progression and conversion (see below), DMT stopping rule (Section B7.2.8).

Figure B7.3.3 Markov transition matrices for cohort



Section B7.3.1 details how the natural history transition matrix (Table B7.3.8) was calculated. Transition matrices for the treatments were calculated from the clinical data are described below.

Firstly, the relative effects of treatment on disease progression compared to placebo (r) were obtained from the MTC (see Section B6.7 and Table B7.3.17).

Table B7.3.17 Relative effects of treatments on 3-month disability progression

Treatment	Hazard ratio versus placebo	95% Lower Confidence Interval	95% Upper Confidence Interval
Teriflunomide	0.71	0.53	0.92
IFNβ-1a (Avonex)	0.91	0.61	1.33
IFNβ-1b	1.21	0.68	2.16
IFNβ-1a (Rebif 44µg)	0.79	0.51	1.24
IFNβ-1a (Rebif 22µg)	[redacted]	[redacted]	[redacted]
Glatiramer acetate	0.93	0.59	1.45
Fingolimod	0.75	0.58	0.96
Natalizumab	0.58	0.40	0.84

*Calculated based on sensitivity analysis MTC applied to base case MTC (see Additional Appendix 2)

Treatment transition probabilities, p_t, for patients receiving each DMT were calculated by applying the relative effect of treatment, r, to the underlying natural history transition probabilities, p_n, where progression had occurred (e.g. EDSS 1 -> EDSS 2).

$$p_t = 1 – exp(-(-(ln(1 - p_n))r)).$$

In line with the original ScHARR model, it was assumed that the treatment effect on conversion from RRMS to SPMS is reduced such that the treatment transition probabilities are calculated as:

$$p_t = 1 – exp(-(-(ln(1 - pn))*0.5*(1+r))).$$

The probability of a patient staying in the same EDSS state was calculated as 1- the probability of transitioning to a greater EDSS or converting to SPMS. The resulting transition matrix for patients receiving teriflunomide is given in Table B7.3.19. The transition matrices for the comparators (fingolimod, natalizumab, beta-interferons, glatiramer acetate and blended comparator) are in Additional Appendix 10.

Using this method, applying very high hazard ratios of treatment effect may result in negative transition probabilities of staying in the same EDSS. This is important when considering the probabilistic sensitivity analysis results, where 95% confidence intervals are very wide. Applying a 3-month SAD treatment effect hazard ratio greater than 1.39 to the natural history transition matrix (London Ontario, TOWER and TEMSO) results in a negative transition probability for EDSS 0 to EDSS 0 i.e. a negative probability of remaining in the same EDSS state. The issue to negative transition probabilities was identified by the ERG Group during the NICE appraisal of fingolimod [NICE, 2011(b)].

The solution applied in the teriflunomide model was if the probability of staying the same EDSS was negative, this was set to zero. This method assumes that if the hazard ratio is very high, i.e. worse than placebo, then the probability of remaining in the same EDSS is 0. Retaining the distribution of progressing from that state, the negative transition probability was redistributed over the probabilities of increasing in EDSS. An example of the application of this solution is given in Table B7.3.18.

Table B 7.3.18 Example of adjustment of transition probabilities to account for negative probabilities of staying in EDSS states for high hazard ratios where negative probability is N

EDSS state	0	1	2	3	4	5	6	7+	Check total
Unadjusted transition probabilities from EDSS 0	-0.209 *(N)*	0.623	0.375	0.144	0.054	0.008	0.005	0.000	1
Distribution of probabilities for progressing	-	51%	31%	12%	4%	1%	0%	0%	100%

Adjustment	+N	N*51%	N*31%	N*12%	N*4%	N*1%	N*0%	N*0%	
Adjusted probabilities used in model	0	0.515	0.310	0.119	0.045	0.007	0.004	0.000	1

Table B7.3.19 Teriflunomide transition matrix for EDSS health states and MS classification

		RRMS											SPMS										
	From \ To	0	0	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
RRMS	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPMS	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

There is no evidence to suggest that the transition probabilities should vary over time for the disease for a patient receiving best supportive care. However, a full treatment effect in reduction on disability progression and relapse rate may not persist throughout the 50 year model. A constant treatment effect in patients on DMT over a 50 year time horizon was deemed optimistic by the ERG in their assessment of fingolimod [NICE, 2011(b)].

The beneficial effects of teriflunomide on clinical and MRI endpoints reported in TEMSO were maintained in the extension study, 5 years after initial randomisation [O'Connor, 2011]. The beneficial effects of teriflunomide on clinical and MRI endpoints were also maintained over the long-term, for up to 8.5 years in the Phase II extension study [Confavreux et al. 2012]. Therefore the effectiveness of teriflunomide appears to maintain for at least 5 years (see Section B6.10.1).

The base case assumes that the treatment effect of teriflunomide and associated comparators persist over a lifetime horizon, in line with the fingolimod STA [Novartis, 2011]. Therefore, a scenario analysis was performed, assuming that the effectiveness of all treatments in the model will be reduced by 25% or 50% from year 6 and onwards. The waning of efficacy occurs equally across all treatments in order to be conservative.

This waning of treatment effect has been implemented in the model by reducing the treatment effect on disability progression and relapse rate by the % decline, used to create the treatment transition matrices and relapse rate per EDSS, respectively. The treatment effect in years 1 and 2 is fixed to 100% as the TEMSO and TOWER trials were conducted over a 2 year time interval.

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

The secondary efficacy outcome from the TOWER and TEMSO Phase III trials was time to sustained disability progression, measured by the EDSS. As higher EDSS states have an increased mortality risk, slowing disease progression will result in a reduced mortality risk. See Section B7.2.5 for details of mortality sources and calculations.

7.3.5 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 specialist 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).

No clinical values in the model were estimated based on expert opinion. However, experts did assess the appropriateness of clinical assumptions within the model and appropriate treatment pathways. Three experts were approached from a range of locations across England and Wales. Three experts, from Leeds, Salford and

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

Manchester participated in telephone interviews. These experts had a combined MS patient population of approximately 7,500. Prior to interviews, the experts were provided with the mapped treatment pathway (Figure A2.5) and publicly available literature for teriflunomide (Confavreax, 2012; O'Connor, 2006; O'Connor, 201; Vermersch, 2012).

The experts were asked to describe the typical treatment pathway of an RRMS patient. The experts provided appropriate treatment sequences to be tested in scenario analyses (see Section B7.2.2) and confirmed the treatment guidelines adhered to, including stopping rules (see Section B7.2.8) [Genzyme KOL interview report, 2013]. Experts were also asked to describe the baseline characteristics of an average patient at treatment initiation to validate the baseline characteristics of the cohort entering the model. The experts believed the patients were younger and generally had milder disease than the modelled cohort. The experts believed the use of a blended comparator was a reasonable comparator for teriflunomide.

Summary of selected values

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

Table B7.3.20 Summary of variables applied in the economic model

Variable / [treatment if applicable]	**Value**	**CI (distribution)**	**Reference to section in submission**
Age at baseline	UK RSS: 37.9 years TOWER + TEMSO: 39.3 years	Deterministic only	Patient characteristics 7.3.1
Female to male ratio	UK RSS: 2.52 : 1 TOWER + TEMSO: 2.98 : 1	Deterministic only	Patient characteristics 7.3.1
Baseline EDSS distribution	UK RSS 0: 3% 1: 7% 2: 20% 3: 19.5% 4: 20.5% 5: 10% 6: 15.5% 7: 4.5% TOWER+TEMSO 0: 4.9%	Deterministic only	Patient characteristics 7.3.1

		1: 19.5% 2: 29.9% 3: 21:4% 4: 16.9% 5: 7.2% 6: 0.1% 7: 0%		
3-month sustained disability progression hazard ratio versus placebo	Teriflunomide	0.71	0.53 to 0.92 (gamma)	7.3.2
	IFNβ-1a (Avonex)	0.91	0.61 to 1.33 (gamma)	
	IFNβ-1b	1.21	0.68 to 2.16 (gamma)	
	IFNβ-1a (Rebif 44µg)	0.79	0.51 to 1.24 (gamma)	
	IFNβ-1a (Rebif 22µg)	[redacted]	[redacted]	
	Glatiramer acetate	0.93	0.59 to 1.45 (gamma)	
	Fingolimod	0.75	0.58 to 0.96 (gamma)	
	Natalizumab	0.58	0.40 to 0.84 (gamma)	
Relative risk of relapse	Teriflunomide	0.67	0.57 to 0.77 (gamma)	Relapse rates 7.3.1
	IFNβ-1a (Avonex)	0.78	0.67 to 0.91 (gamma)	
	IFNβ-1b	0.68	0.52 to 0.88 (gamma)	
	IFNβ-1a (Rebif 44µg)	0.62	0.51 to 0.76 (gamma)	
	IFNβ-1a (Rebif 22µg)	[redacted]	[redacted]	
	Glatiramer acetate	0.64	0.53 to 0.76 (gamma)	
	Fingolimod	0.46	0.40 to 0.54 (gamma)	
	Natalizumab	0.31	0.25 to 0.39 (gamma)	
All-case withdrawal probability	Teriflunomide	[redacted]	0.14 to 0.17 (beta)	Discontinuations 7.3.1
	IFNβ-1a (Avonex)	[redacted]	0.10 to 0.20 (gamma)	
	IFNβ-1b	[redacted]	0.05 to 0.13 (gamma)	
	IFNβ-1a (Rebif 44µg)	[redacted]	0.13 to 0.24 (gamma)	
	IFNβ-1a (Rebif 22µg)	[redacted]	0.05 to 0.20 (gamma)	
	Glatiramer acetate	[redacted]	0.08 to 0.15 (gamma)	
	Fingolimod	[redacted]	0.08 to 0.16 (gamma)	
	Natalizumab	[redacted]	0.08 to 0.19 (gamma)	
Relative risk of relapse leading to	Teriflunomide	[redacted]	Gamma assuming standard error is 10% of mean	Treatment effect on Relapse severity 7.3.1
	Natalizumab, fingolimod	[redacted]		

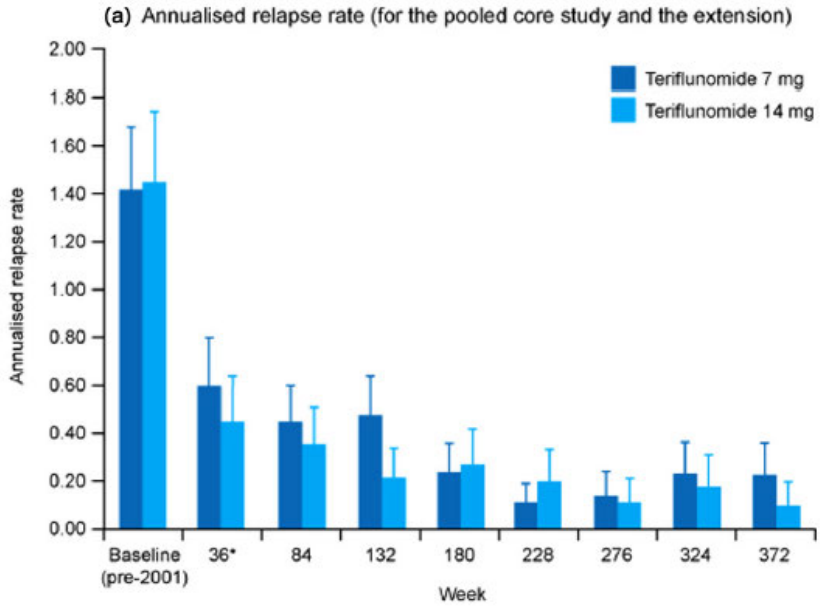
hospitalisation	IFNβ, glatiramer acetate	[redacted]		
Probability of progression in RRMS (natural history transitions)		EDSS 0: TOWER + TEMSO EDSS 1-9: London Ontario	Deterministic only	Disability progression 7.3.1
Probability of progression in SPMS (natural history transitions)		London Ontario	Deterministic only	Disability progression 7.3.1
Probability of conversion from RRMS to SPMS (natural history transitions)		London Ontario	Deterministic only	Disease progression 7.2.5
Natural history relapse rate		Held 2005 Patzold 1982	Normal assuming standard error is 10% of mean	Relapse rates 7.3.1
Natural history proportion of relapses leading to hospitalisation		TEMSO: 30.7% Dee 2012: 20%	0.5 to 0.875 (beta, TEMSO sample size of 335)	Relapses leading to hospitalisation 7.3.1

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

The clinical outcomes used in the model are derived from MTCs which include RCTs that reported outcomes at time points ranging from 6-36 months following treatment. SAD hazard ratios, ARR and withdrawal ORs have been extrapolated from 6-36 months to the 50 year time horizon. The base case assumption is that treatment effects on disability progression and relapse rate are not expected to decline over time. As discussed in Section B7.3.3, there is evidence of continued treatment effect with teriflunomide 14mg. The Phase II study provides the longest evidence of the treatment effect, with an extension up to 492 weeks (Figure B7.3.4). Therefore, the SAD HRs and relative ARRs stay fixed throughout the duration of the model in the base case.

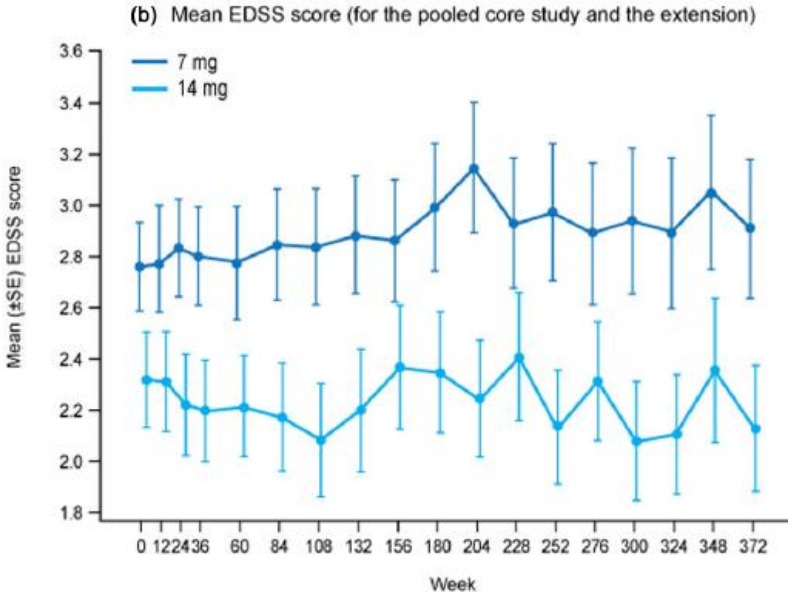
On the other hand, the probability of withdrawal for all treatments is expected to decline, and this has consequently been reduced by 50% after 2 years [Genzyme KOL interview report, 2013]. However, sensitivity analyses have been performed where the effectiveness of the treatments are modelled to reduce by 25% or 50% after 5 years. Similarly, the probability of withdrawal for all treatments is modelled to persist or reduce by 75% after 2 years. See Sections 7.3.1 and 7.3.3.

Figure B7.3.4 Mean EDSS score in Phase II study and extension (2001 + LTSLTS6048) with numbers at risk shows evidence of continued treatment effect [Confavreux et al. 2012]



No. of subjects									
7 mg	81	81	81	72	68	64	62	54	52
14 mg	66	66	66	56	51	48	42	41	38

*At Week 36, placebo patients were re-allocated to teriflunomide, 7 mg or 14 mg



No. of subjects															
7 mg	81	78	72	71	70	69	66	64	64	57	54	50	51	49	49
14 mg	66	65	58	55	53	49	49	47	44	41	40	38	38	38	35

EDSS, Expanded Disability Status Scale

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

Table B7.3.21 Assumptions with justifications, used in the cost-effectiveness model

Assumption	Justification
Model structure	
The treatment sequencing feature of the model (used in scenario analyses) simulates switching between three different DMTs before ending on BSC.	In clinical practice, MS patients are unlikely to receive only one treatment following their diagnosis [Genzyme KOL interview port, 2013]. MS patients are likely to receive other DMTs after discontinuation of their current therapy. Although the exact treatment sequence for MS is not well defined and is inconsistent across the UK, KOL opinion states that following diagnosis, an RRMS patient will generally be treated with one or two different beta-interferons / glatiramer acetate / teriflunomide, before progressing to HA or RES and therefore receiving fingolimod and natalizumab respectively. The benefit in modelling second and third-line treatments is to highlight the impact that differences in treatment effect on slowing disease progression and reduced withdrawal rates in first or second-line treatments have on delaying treatment with more costly drugs (fingolimod and natalizumab).
A patient switches directly between treatments, with no time delay between withdrawal and starting a new drug.	No waiting period is required when initiating teriflunomide after beta-interferon or glatiramer acetate or when starting beta-interferon or glatiramer acetate, after teriflunomide [Aubagio SmPC]. Therefore it appears reasonable to assume that a patient will switch directly from a treatment at first or second line to another, without contradicting the SmPCs of beta-interferons or glatiramer acetate.
The model does not include transitions or progression to EDSS state 10 (i.e. MS related death) directly into the transition matrices. Rather, it uses the mortality multiplier by MS state to account for the increased mortality in higher EDSS states.	Pokorski et al. provided evidence that the risk of mortality increases as MS progresses [Pokorski, 1997]. To account for the increased mortality risk with disease state as well as the increased mortality risk with age, mortality is captured separately from the transition matrices.
Progression from RRMS to SPMS results in an increase in EDSS by 1.	This is in line with the original ScHARR model. A conversion from relapsing-remitting to progressive disease is an indication of an increase in disability that will likely result in an increase on the EDSS scale of 1, in the one year period of conversion. This assumption has been validated by KOLs [Genzyme KOL interview report, 2013].
Half cycle correction	
A cohorts disease status and relapse events at each cycle are from mid-year estimates	Avoids over- or under-estimation of disease status and severity in the model
Costs and utilities are applied to a mid-year	Avoids over- or under-estimation of cost and QALYs

estimate of the cohort distribution	from the model
At any point of time all patients must exist in one of the health states which are a combination of disease state and EDSS score.	Mid-year estimates provide a snapshot of the cohort in terms of disease state and EDSS for one cycle. A patient cannot be 'transitioning' between states; they switch directly from being in one state to another.
No patient is exposed to treatment effects, withdrawals, mortality, and progression risks more than once in any individual annual cycle.	Mid-year estimates are taken from the cohort at the start of the cycle, once withdrawals have been included from the previous line, and the end of the cycle once any withdrawals to BSC have taken place (see Figure B7.3.3). Mortality and treatment effect on disability progression takes place between this start and end of the cycle.
Treatment effect	
The results of the mixed treatment comparison that was limited to inclusion of studies with ≥80% RRMS populations are representative of treatment effects in an RRMS population	An MTC with 100% RRMS inclusion criteria would have excluded the teriflunomide Phase III trials TEMSO and TOWER as well as five additional studies that were included in the base case MTC. See Additional Appendix 2 for full details regarding the criteria chosen for the MTC.
Disability progression and relapses are modelled independently, with independent treatment effects being applied to each	Some treatments may be more effective in reducing relapses than slowing disease progression, or vice versa. Modelling the two outcomes separately shows the impact that the different costs and QALYs associated with a reduction is disability to a number of relapses have on the cost-effectiveness of treatments.
In the base case, the treatment effect is assumed to be constant and not degrade over time	There is no evidence beyond 8.5 years to indicate that the effect of teriflunomide wanes over time thus the base case is 100% efficacy over the time horizon of the model (see Section B7.3.3 and 7.3.7). However, it is optimistic to assume the treatment effect will persist over the full 50 years of the model. Therefore, to test the sensitivity of the model to waning treatment effect, scenario analyses have been performed with a 50% and 75% reduction in efficacy after 5 years.
A patient may only be receiving BSC or one active treatment at a time (either active treatment or active comparator).	In clinical practice, it is possible that a patient would receive more than one treatment within a year, as no waiting period is required when switching between treatment with teriflunomide, beta-interferon or glatiramer acetate [Teriflunomide SmPC]. However, mid-year estimates are used to avoid over- or under-estimation of the disease and as such a patient can only be on one treatment of BSC within one cycle, which represents one year.
Treatment effect is reduced by 50% whilst patients convert from RRMS to SPMS	This assumption is implemented in the calculation of natural history transition matrices. It was an assumption made within the original ScHARR model [Chilcott et al. 2003].
Withdrawal	
Patient withdrawals are assumed to happen at the start of the year; therefore treatment	To avoid double-counting, patient withdrawals occur at the start of the year, before mortality and disease

costs and effects are taken for the treatment the patient is switched to (as opposed to the treatment withdrawn from).	progression. As seen in Figure B7.3.3, mid-year estimates are taken following withdrawal. This ensures that a patient may only be receiving BSC or one active treatment at a time (see assumption above).
Patients can withdraw from treatment in any year; in the base case the probability of withdrawal is reduced by 50% after year 2.	All-cause annual withdrawal rates have been derived from 2 year odds ratio for teriflunomide thus a full withdrawal rate has been used for years 1 and 2. As discussed in Section B7.3.7, it is anticipated that following two years on treatment, a patient is likely to be more tolerant to adverse events and thus the all-cause discontinuation would decrease. The sensitivity of the model to this scenario has been tested in one-way sensitivity analysis.
Relapse classification	
Relapses can be classified into relapse with and without hospitalisation, with associated rates, costs and disutility weights.	The costs associated with relapses leading to hospitalisation are significantly higher than the costs of relapses not leading to hospitalisation. To assess the impact of a treatment on reduction of relapse costs and utilities, it is essential to measure these two relapse types separately.
The proportion of relapses leading to hospitalisation is the same for: all beta-interferons and glatiramer acetate; and fingolimod and natalizumab.	The proportion of relapses which lead to hospitalisation is not well measured in MS trial data. Therefore, they are few sources of evidence. One source reports the proportion for IFNβ-1a (Avonex), which is then assumed to represent the proportion for IFNβ-1a (Rebif), IFNβ-1b and glatiramer acetate. The proportion for fingolimod is used to represent natalizumab also.
Cycle length and time horizon	
The model adopts one-year cycles, over a maximum 50-year time horizon	Following the NICE reference case, a 50-year lifetime horizon is used to measure the full impact of treatments on costs and QALYs [NICE, 2008]. Although shorter time horizons have been used in previous MS submissions, the 50-year time horizon was used in the appraisal of fingolimod and was deemed to better represent the lifetime perspective for the patients in the model [NICE, 2011(b); Biogen, 2006]. A patients EDSS is measured at least once every 6 months, but a one year time horizon is used as this is believed to accurately capture disease progression.

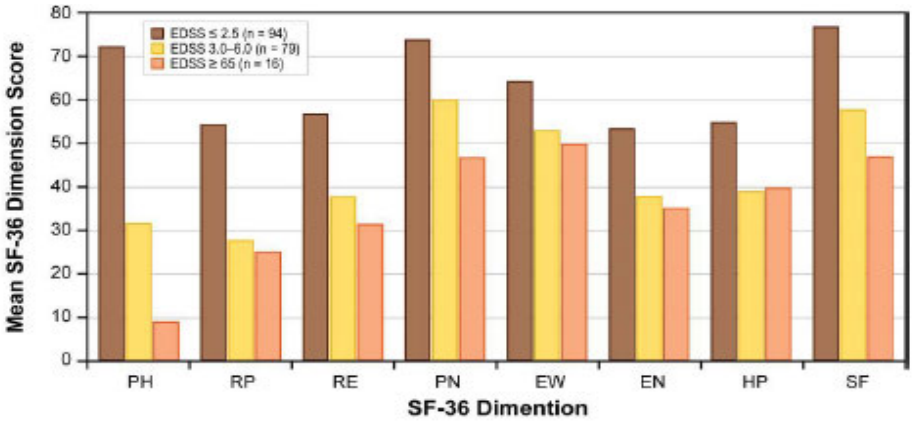
7.4 *Measurement and valuation of health effects*

Patient experience

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

MS has a significant negative impact on the quality of life (QOL) of patients [Aronson, 1997]. It has been shown that disability progression (as measured by EDSS) significantly impacts QOL [Gray, 2009; Kobelt 2006]. As detailed in Section B7.4.6, in later stages of the disease, a patient's quality of life is worse than death [Orme et al. 2007]. These studies have shown a strong negative correlation between increases in EDSS and decreases in QOL as measured by the EQ-5D or condition specific instruments (Figure B7.4.1). Consequently, this has been captured as the primary driver of quality of life differences in the cost-effectiveness model (see Section B7.4.6).

Figure B7.4.1 Health-related quality of life and disability levels [Novartis, 2011]



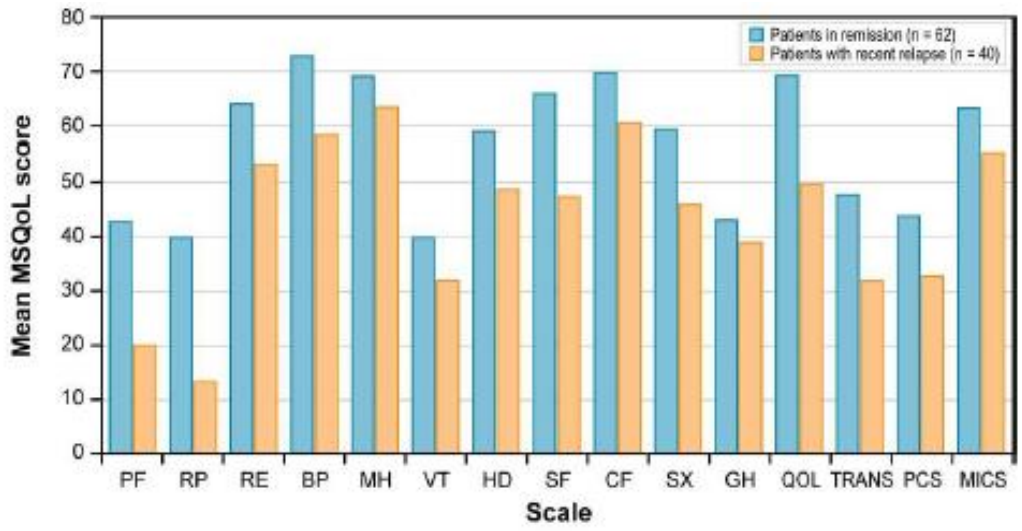
EDSS, Expanded Disability Status Scale; HP, Health Perceptions; HRQL, health-related quality of life; EN, Energy; EW, Emotional Well-Being; PH, Physical Health; PN, Pain; RE, Emotional Role Limitations; RP, Physical Role Limitations; SF, Social Function.

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

Source: Miller et al., 2006.

In addition, relapses also have an impact on QOL (Figure B7.4.2) and have also therefore been captured within the cost-effectiveness model (see Section B7.4.6). Relapses may result in hospitalisation and be associated with a level of disability that disrupts work, social and family life [Stolp-Smith et al. 1998; Yorkston et al. 2003; McCabew et al. 2005; De Judicibus et al. 2007].

Figure B7.4.2 Health-related quality of life and relapses [Novartis, 2011]

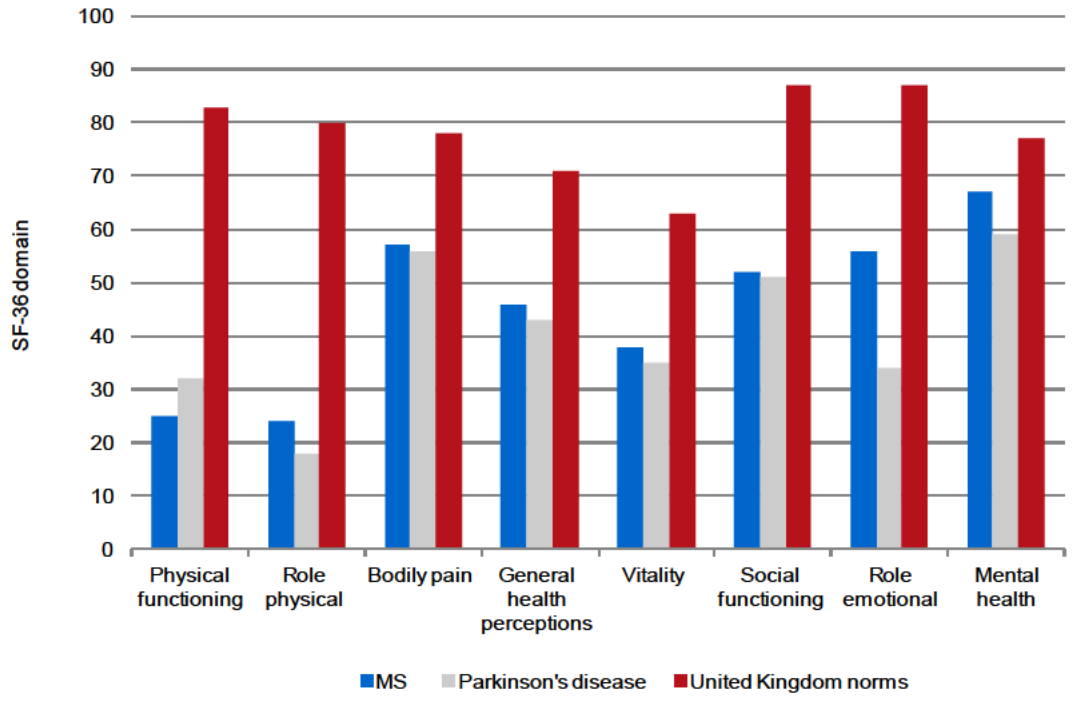


BP, Bodily pain; CF, Cognitive function; GH, General health; HD, Health distress; MH, Mental Health; MICS, Mental health composite score; PCS, Physical health composite score; PF, Physical function; QOL, Overall quality of life; RE, Role emotional; RP, Role physical; VT, Energy/vitality; SF, Social function;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

As well as impacting on day to day life roles, MS can diminish QOL by interfering with the ability to work which in turn causes economic burdens. Symptoms that affect QOL may include impaired mobility, fatigue, weakness, depression, pain, spasticity, cognitive impairment, sexual dysfunction, bowel and bladder dysfunction, vision and hearing problems, seizures, and swallowing and breathing difficulties [Zwibel et al. 2011]. Even in its early stages, these symptoms can undermine patients' confidence and restrict professional and personal activities. Symptoms can result in depression and isolation, further magnifying the consequences of reduced economic activity [Ford et al. 2001]. The symptoms of MS increase as a patient progresses though the EDSS thus incurring lower quality of life. Treatments which slow disability progression will therefore prolong the mobility of patients, improving quality of life.

Studies evaluating the impact of MS on QOL using generic scales consistently show substantial negative effects from the disease, particularly in physical functioning. There are also significant effects on social and mental functioning. In the UK, MS patients were found to have worse health than the UK general population for all eight domains measured by the Short Form-36 (SF-36) (Figure B7.4.1) [Riazi et al. 2003]. As seen in Figure B7.4.3 when compared with patients with Parkinson's disease, MS patients had significantly lower mean scores for physical function (difference 11 points; $P<0.001$) but higher scores for the mental health dimension (difference 6 points; $P<0.05$) than Parkinson's disease patients [Riazi et al. 2003].

Figure B7.4.3 Short Form-36 (SF-36) scores in MS patients compared with patients with Parkinson's disease and UK norms [Riazi et al. 2003]



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

As a progressive disease, disability from MS increases substantially over time. Ultimately, significant changes in QOL are observed as EDSS increases due to disease progression (Section B7.4.1). Relapses contribute to QOL deterioration but are usually only observed over the course of the relapse [Orme et al. 2007; Novartis, 2011]. Conversion to SPMS also results in a QOL loss [Orme et al. 2007]. Other factors such as time since diagnosis may impact QOL [Orme et al. 2007] but these are less pronounced.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section B6 (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.

The following quality of life data was collected in the pivotal trials:

- **TEMSO**: The SF-36 was to be completed during screening, Weeks 20, 42, 66, 90, and at the close-out visit (Week 108). EQ-5D scores were obtained at baseline, every 12 weeks throughout the study, and at unscheduled relapses.

- **TOWER**: Measurement of the SF-36 at: Weeks 12 and 24, and then every 24 weeks while on treatment; the end of treatment visit; the early permanent treatment discontinuation visit; and at unscheduled relapses.

- **Phase II**: The study subjects were to complete the MSQOL–54 at visits 1 and 3 before administration of study medication for training purposes. The test was further administered at visits 6, 8, and 10.

A utility value is required for the 20 health states in the model (RRMS EDSS 0-9; SPMS EDSS 0-9). EQ-5D is consistent with the reference case so the EQ-5D data collected in the TEMSO trial was considered for inclusion in the cost-effectiveness model. However, the TEMSO trial only included patients up to EDSS 7 and the majority of patients were RRMS. Therefore, utilities for SPMS and RRMS EDSS>7 would have to be sourced from literature. Consequently, to ensure consistency in data used in the model, the TEMSO trial EQ-5D data were considered in a sensitivity analysis and not the base case analysis (see Section B7.4.6).

Although, the SF-36 is the most widely used measure of health-related quality of life in RRMS, it is not consistent with the reference case. EQ-5D sourced directly from literature is preferable to mapping SF-36 data from the trial onto the EQ-5D. Consequently, SF-36 trial data has not been considered for inclusion in the cost-effectiveness model.

Mapping

7.4.4 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.

EQ-5D data were sourced from the literature and the TEMSO trial and thus mapping was not required.

HRQL studies

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

A systematic review was conducted to obtain all relevant quality of life studies in MS. The PICOS (population, interventions, comparators, outcomes and study type) principal was applied to define the following review questions:

- *"What is the utility of patients and carers with MS?"*
- *"What is the disutility of patients who experience a relapse after treatment for multiple sclerosis?"*
- *"What is the disutility of patients who experience an adverse event after treatment for multiple sclerosis?"*

Studies of interest were identified by searching a number of electronic databases which included Embase, Medline, Medline (R) In-Process, EconLIT and NHS EED. A search strategy was developed to identify studies indexed in Embase (this platform covers Embase, MEDLINE and MEDLINE (R) In-Process) and then modified for searches in OVIDSP (this platform covers EconLIT) and The Cochrane Library (this platform covers NHS EED) to account for differences in syntax and thesaurus headings. Searches were ran from 2007 to 2012 and included terms for free text and keywords (e.g. Medical Subject Heading (MESH) terms) with no restrictions on language of publication. The reason for not considering references prior to 2007 was because QOL measures considered for UK cost-effectiveness studies reference Orme et al [Orme 2007], which has been the mainstay of defining utilities in MS economic evaluations. Hence it was assumed that studies prior to the date of this publication would have already been found by previous HTA bodies. To find additional references to those identified during database searching a grey literature search was performed. Section 10.12, Appendix 10 details the search strategies, databases searched and subsequent results from the database sites searched.

Searches were conducted during the period mid-October to November 2012 with the final searches carried out on the 5th November 2012. References included for the review had to meet the pre-specified inclusion/exclusion criteria shown in Table B7.4.1.

Table B7.4.1 Eligibility criteria used in the quality of life systematic review

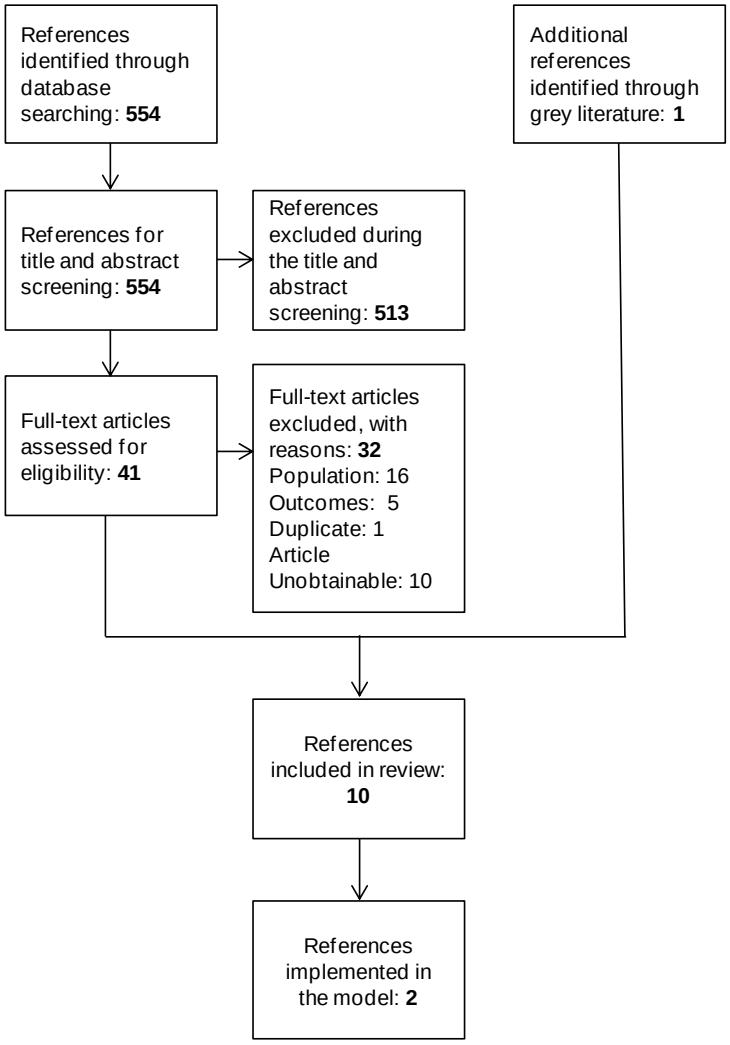
Selection criteria	Inclusion	Exclusion
Population	• Adults with either RRMS or progressive MS (including SPMS or PRMS) • UK	• Primary progressive multiple sclerosis (PPMS)
Outcomes (QOL)	• Utility in MS (e.g. EQ5D) • Disutility of relapse • Disutility of adverse events • Disutility to carers	

Duplicates were removed for all records obtained in the searches and then a manual review of the titles and abstracts was undertaken using the inclusion/exclusion criteria to identify papers to be included in the review (also known as first passing). This was performed by two independent reviewers and discrepancies were resolved by a third independent reviewer. Full-text papers identified at first pass were then evaluated and included for review based on the inclusion/exclusion criteria.

The following databases were searched: Embase, Medline, Medline (R) In-Process, EconLIT and NHS EED and a total of 554 references were found after duplicates were removed. These 554 references were then reviewed by hand, by screening the title and abstract of which 41 were included. The full-text articles of these 41 references with 1 references from grey literature were then obtained to assess eligibility resulting in 10 studies that met inclusion/exclusion criteria and as such were identified as evaluating quality of life in MS.

Figure B7.4.4 contains a flow diagram which illustrates the numbers of studies included and excluded at each stage of the systematic review.

Figure B7.4.4 Flow diagram for the quality of life systematic review



7.4.6 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.

Identified quality of life studies

Of the 10 studies included in the full review, 2 were implemented in the model and are summarised in Table B7.4.2 below.

Table B7.4.2 Summary of identified quality of life studies implemented in the model

	Orme et al. 2007
Population in which health effects were measured	Subjects were people with MS in the UK identified by a database managed by a UK charity (the MS Trust).
Information on recruitment	A postal questionnaire was sent to 12,968 people in a database managed by the MS Trust as an insert to the February 2005 edition of the UK MS Trust quarterly newsletter "Open Door".
Interventions and comparators	Respondents were asked whether they were currently taking MS treatment and if so whether it was glatiramer acetate, or beta-interferon. Results were not presented.
Sample size	2,048 patients
Response rates	The number of questionnaires returned was 2,708 (20.9%) and 2,048 (15.8%) were suitable for analysis.
Description of health states	A cross-sectional study of people with MS.
Adverse events	Not collected.
Appropriateness of health states given condition and treatment pathway	Appropriate.
Method of elicitation	EQ-5D.
Method of valuation	Questionnaires were completed by the patient or a carer on behalf of the patient.
Mapping	N/A
Uncertainty around values	See confidence intervals below

Consistency with reference case	Consistent with reference case.
Results with confidence intervals	Three quarters of respondents are female and the mean age of the sample is 51.4 years. First symptoms are reported at 32 years. The type of MS reported is slightly biased toward SPMS and RRMS disease, although all three types are well represented. More than three quarters of the population report moderate or severe disease (EDSS 4 or greater) and 29% of the sample reported a relapse in the preceding 3 months. Coefficients from regression analysis for utility derived from EQ-5D:

Parameter	Coefficient	95% CI
Reference case	0.870	(0.782, 0.958)
EDSS 1–1.5	−0.071	(−0.165, 0.023)
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	(−0.3[illegible]4, −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[illegible] −0.477)
EDSS 8–8.5	−0.919	(−1.017, −0.820)
EDSS 9–9.5	−1.065	(−1.210, −0.919)

People with MS who have suffered a recent relapse also have a significant utility decrement (−0.071); 95% CI (−0.096, −0.046).

Appropriateness of the study for cost-effectiveness analysis	Appropriate.
	Gani et al. 2008
Population in which health effects were measured	The model was parameterised with data from a UK Multiple Sclerosis (MS) Survey 2005 and data from the AFFIRM study, a 2-year multicentre, randomized, double-blind, placebo-controlled trial of natalizumab in RRMS patients. Additional data were sourced from literature.
Information on recruitment	The AFFIRM study involved 942 patients who were randomly assigned to receive either natalizumab (at a dose of 300 mg; n = 627) or placebo (n = 315), both by intravenous infusion every 4 weeks, and was the largest published placebo-controlled RRMS trial to date. Data from the UK MS Medical Resource Utilisation Survey was conducted in 2005 and involved data collected from 2,048 MS patients across the UK.
Interventions and comparators	Natalizumab compared with IFNβ, glatiramer acetate and best supportive care.
Sample size	942 patients from the AFFIRM study, 2,048 patients from the UK MS survey

	plus additional data sourced from literature.
Response rates	The number of questionnaires returned was 2,708 (20.9%) and 2,048 (15.8%) were suitable for analysis.
Description of health states	Patients with RRMS and SPMS.
Adverse events	Applied the disutility rates of 0.156 for interferon-treated patients and 0.066 for GA-treated patients for each year included in the model.
Appropriateness of health states given condition and treatment pathway	Appropriate.
Method of elicitation	EQ-5D.
Method of valuation	Results from the UK MS survey and literature.
Mapping	N/A
Uncertainty around values	Not given.
Consistency with reference case	Consistent with reference case.
Results with confidence intervals	The average length of a relapse is estimated to be 46 days. Carer disutility was extracted: **Table II.** Utilities of caregivers by Kurtzke Extended Disability Status Scale (EDSS) score[20] EDSS score — Average caregivers disutility per patient 0.0 — 0.00 1.0 — 0.00 1.5–2.0 — 0.00 2.5–3.0 — 0.01 3.5–4.0 — 0.01 4.5–5.0 — 0.02 5.5–6.0 — 0.03 6.5–7.0 — 0.05 7.5–8.0 — 0.11 8.5–9.5 — 0.14
Appropriateness of the study for cost-effectiveness analysis	Appropriate.

Utility by health state

In the base case, utility weights were based on a published regression of quality of life responses from a survey of patients and carers of patients with MS (Table B7.4.3). EQ-5D utility scoring system was applied, with respondent domain scores converted to a single utility weight using the UK value set [Orme et al. 2007].

Table B7.4.3 EDSS utilities [Orme et al. 2007]

EDSS state	0	1	2	3	4	5	6	7	8	9
RRMS	0.870	0.799	0.705	0.574	0.610	0.518	0.460	0.297	-0.049	-0.195
RRMS LCI	0.782	0.617	0.523	0.384	0.428	0.338	0.279	0.112	-0.289	-0.428
RRMS UCI	0.958	0.981	0.886	0.763	0.791	0.698	0.642	0.481	0.138	0.039
SPMS	0.825	0.754	0.660	0.529	0.565	0.473	0.415	0.252	-0.094	-0.240
SPMS LCI	0.706	0.541	0.447	0.308	0.352	0.262	0.203	0.036	-0.365	-0.504
SPMS UCI	0.944	0.967	0.872	0.749	0.777	0.684	0.628	0.467	0.124	0.025

Relapse disutility

The utility loss for relapse in the UK was sourced from Orme et al [Orme, 2007]. Currently no UK studies have been identified which report utility values by relapse type. However, a US study has reported considerably higher disutilities for relapses leading to hospitalisation and relapses that do not, -0.302 versus -0.091 respectively [Prosser, 2004]. The disutility associated with relapses not leading to hospitalisation in the US source (-0.091) corresponds well with the value reported for the disutility of a relapse in the UK (-0.071) [Orme, 2007; Prosser, 2004]. Therefore, to derive a disutility of relapses leading to hospitalisation in the UK, we applied the increase observed for severe relapses in the US study ((0.302-0.091)/0.091)=2.32% to the average UK disutility of relapse, equating to -0.2356.The average duration of a relapse, sourced from Gani et al. (1.51 months) is combined with the disutility during a relapse to give the disutility per relapse.

Caregiver disutility

Health-related disutility for carers has been included in the model using the method developed by Gani et al [Gani, 2008]. As actual measurements were not available, Gani et al assumed that disutility had a maximum value of 0.14, based on the value accepted by NICE in an assessment of treatments for Alzheimer's Disease. The disutility for MS carers by patient EDSS score was calculated as the product of the percentage of time spent caring and the maximum disutility of 0.14. This was then divided by the maximum percentage of time spent caring, which occurred at EDSS 8.5–9.5. This provided an index of disutilities from 0.00 at EDSS 0.0 to 0.14 at EDSS 8.5–9.5. The percentage of time spent by friends and family caring for a person with MS was available from the UK MS Survey by EDSS score. The carer disutilities by EDSS are given in Table B7.4.4.

Table B7.4.4 Carer disutility used in the model [Gani, 2008]

EDSS state	0	1	2	3	4	5	6	7	8	9
Disutility	0.000	-0.001	-0.003	-0.009	-0.009	-0.020	-0.027	-0.053	-0.107	-0.140

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

EQ-5D values used in the model were derived from the literature [Orme, 2007]. In comparison to the EQ-5D values collected in the TEMSO trial, the literature results appear to have a lower utility overall (see Figure B7.4.5). The utilities reported by Orme compared closely to other studies in the majority of EDSS states [Orme, 2007] and are expected to be more robust that the TEMSO results for this reason. Furthermore, the Orme study is specific analysis of UK patients' quality of life, whereas TEMSO is an international study. As discussed in Section B7.4.3, a sensitivity analysis explores using the TEMSO utilities; utilities for RRMS EDSS > 6 are sourced from Orme et al. and the coefficient derived by Orme et al between RRMS and SPMS is applied to the TEMSO utilities for SPMS since the SPMS patient numbers in TEMSO were too low for robust analysis.

Comparison of utility between Orme and TEMSO

Table B7.4.5 Health state utilities from TEMSO

EDSS state	0	1	2	3	4	5	6	7	8	9
RRMS										
RRMS LCI										

**Derived from Orme et al; **Sourced directly from Orme et al*

Adverse events

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

As described in section B7.3.1, the criteria for inclusion of adverse events within the model of ≥4% difference from placebo captures only the common events associated with DMTs. There are significant disutilities

associated with nausea, diarrhoea, immediate post-injection systemic reactions, arthralgia and back pain. Since the probability of severe adverse events (such as PML associated with natalizumab) is very low the potential impact on the modelled cohort in terms of costs and utilities is negligible. Therefore, the model does not fully capture all disutilities that could be associated with the DMT but does capture all adverse events that will impact the ICER.

The disutility of influenza like symptoms was derived from a UK population-base study [van Hoek et al. 2011]. The final QALY loss due to the whole period of disease was 0.0075 for the influenza like symptoms group which lasted 8.7 days. The annual disutility is therefore:

$$QALY = 0.0075 / 8.7 \times 365 = 0.315$$

It is conservatively assumed that DMY associated flu like symptoms are only a quarter of this QALY less, equating to -0.08 annual disutility.

The total disutility of an event occurring is calculated using instantaneous disutility, multiplied by the duration that the event is likely to occur. Since there is so much variation in how long an event is likely to occur, and limited literature, several assumptions have been made regarding duration. Occurrences of injection-associated adverse events are assumed to last once a day following each administration. Table B7.4.6 shows the disutilities and durations of adverse events in the model.

Table B 7.4.6 Utilities of adverse events, when combined with expected duration of event

	Utility of event	Source of utility of event	Utility assumptions	Duration of event	Source for duration of event	Annual disutility
Teriflunomide						
Nausea	-0.048	[Nafees et al. 2008]	Sourced from small cell lung cancer study	1 day	Assumption	-0.0001
Diarrhoea	-0.047	[Nafees et al. 2008]	Sourced from small cell lung cancer study	3 days	Assumption	-0.0004
Hair thinning	-0.114	[Nafees et al. 2008]	Sourced from small cell lung cancer study	1 year	[Freedman, 2012(b)]	-0.1140
Natalizumab						
Fatigue	-0.073	[Nafees et al. 2008]	Sourced from small cell lung cancer study	1 week	Assumption	-0.0014
Arthralgia	-0.040	[Sullivan et al. 2006]	Based on ICD-9 719 Joint Disorder	1 month	Assumption	-0.0034
Headache	-0.030	[Sullivan et al.	Based on ICD-9	2 days	Assumption	-0.0002

		2006]	346 Migraine			
Glatiramer acetate						
Injection site reaction	-0.011	[Boye et al. 2011]	Sourced from study evaluating diabetes population	1 day every dose (every day [Copaxone SmPC])	Assumption	-0.0110
Immediate postinjection systemic reactions	-0.041	[Sullivan et al. 2006]	Based on ICD-9 413 Angina Pectoris	0.5 days	Assumption	-0.0001
Fingolimod						
Lower respiratory tract infection	-0.020	[van Hoek, 2011]	Assumed same as disutility value for influenza-like symptoms	2 weeks	[NHS choices, 2013]	-0.0008
Back pain	-0.046	[van Hoek, 2011]	Based on ICD-9 724 Back Disorder	2 weeks	Assumption	-0.0018
Diarrhoea	-0.047	[Nafees et al. 2008]	Sourced from small cell lung cancer study	3 days	Assumption	-0.0004
IFNβ-1a (Avonex)						
Headache	-0.030	[Sullivan et al. 2006]	Based on ICD-9 346 Migraine	2 days	Assumption	-0.0002
Influenza-like symptoms	-0.08	[van Hoek, 2011]		1 day every dose (once weekly [Avonex SmPC])	[van Hoek, 2011]	-0.0114
IFNβ-1a (Rebif 44µg)						
Headache	-0.030	[Sullivan et al. 2006]	Based on ICD-9 346 Migraine	2 days	Assumption	-0.0002
Influenza-like symptoms	-0.08	[van Hoek, 2011]		1 day every dose (thrice weekly [Rebif SmPC])	[van Hoek, 2011]	-0.0343
Injection site reaction	-0.011	[Boye et al. 2011]	Sourced from study evaluating diabetes population	1 day every dose (thrice weekly [Rebif SmPC])	Assumption	-0.0047
IFNβ-1a (Rebif 22µg)						
Headache	-0.0297	[Sullivan et al. 2006]	Based on ICD-9 346 Migraine	2 days	Assumption	-0.0002
Influenza-like symptoms	-0.08	[van Hoek, 2011]		1 day every dose (thrice weekly [Rebif SmPC])	[van Hoek, 2011]	-0.0343
Injection site reaction	-0.011	[Boye et al. 2011]	Sourced from study evaluating diabetes population	1 day every dose (thrice weekly [Rebif SmPC])	Assumption	-0.0047
IFNβ-1b						

Influenza-like symptoms	-0.08	[van Hoek, 2011]		1 day every dose (every other day [Betaferon SmPC])	[van Hoek, 2011]	-0.040
Injection site reaction	-0.011	[Boye et al. 2011]	Sourced from study evaluating diabetes population	1 day every dose (every other day [Betaferon SmPC])	Assumption	-0.0055

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

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

Table B7.4.7 Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
RRMS	Orme, 2007 EDSS 0: 0.870 EDSS 1: 0.799 EDSS 2: 0.705 EDSS 3: 0.574 EDSS 4: 0.610 EDSS 5: 0.518 EDSS 6: 0.460 EDSS 7: 0.297 EDSS 8: -0.049 EDSS 9: -0.195 [redacted]	 (0.782, 0.958) (0.617, 0.523) (0.523, 0.886) (0.384, 0.763) (0.428, 0.791) (0.338, 0.698) (0.279, 0.642) (0.112, 0.481) (-0.289, 0.138) (-0.428, 0.039) Probabilistic variation using 10% standard error (gamma)	7.4.6 7.4.3	Orme data is used in the base case, with TEMSO in sensitivity analysis as data is only from EDSS 0-6. As discussed in Section B7.4.7, Orme is a more comprehensive source of utility since it is specifically for UK patients, provides values across all EDSS states and has been used in previous HTA UK assessments [Novartis, 2011].
SPMS	Orme: 0.045 less than RRMS	(-0.076, -0.014) less than RRMS	7.4.6	No specific SPMS data values area available; SPMS utilities are calculated from RRMS with a

				weighted coefficient to reflect the progressive disease.
Utility loss of relapse leading to hospitalisation	Using Orme duration: -0.0589 Using Gani duration: -0.0297	Using Orme duration: (-0.0734, -0.0444) Using Gani duration: (−0.0370, -0.0224)	7.4.6	Orme utility with Gani duration used in the base case. As discussed in 7.4.6, the percentage difference between relapses leading and not leading to hospitalisation from US study were applied to Orme disutility for relapse not leading to hospitalisation. This method was used as there is no reported UK literature for relapses leading to hospitalisation. Duration is applied to this disutility to calculate the disutility per relapse event.
Utility loss of relapse not leading to hospitalisation	Using Orme duration: -0.0178 Using Gani duration: -0.0089	Using Orme duration: (-0.0240, -0.0155) Using Gani duration: (−0.0121, -0.0058)	7.4.6	Orme utility with Gani duration used in the base case. Assumption that the recent relapse disutility coefficient reported by Orme was for a relapse not leading to hospitalisation. Duration is applied to this disutility to calculate the disutility per relapse event.
Caregiver disutility	EDSS 0: 0.000 EDSS 1: -0.001 EDSS 2: -0.003 EDSS 3: -0.009 EDSS 4: -0.009 EDSS 5: -0.020 EDSS 6: -0.027 EDSS 7: -0.053 EDSS 8: -0.107 EDSS 9: -0.140	Probabilistic variation using 10% standard error (gamma)	7.4.6	From the NHS & PSS perspective, as defined by the reference case [NICE, 2008], disutility from caregivers should be included within the cost-effectiveness analysis. Gani et al was the only source identified that detailed caregiver disutility. It is a relevant source for the economic evaluation since it includes UK perspective.
Nausea	-0.0001	Probabilistic variation using 10% standard error (gamma)	7.4.8	Annual disutility derived from utility loss per event, multiplied by the duration in months.
Diarrhoea	-0.0004			
Hair thinning	-0.0070			
Fatigue	-0.0004			
Arthralgia	-0.0034			
Headache	-0.0002			
Injection site reaction	0.0000			
Influenza-like symptoms	-0.0005			

Immediate postinjection systemic reactions	-0.0001			
Lower respiratory tract infection	-0.0008			
Back pain	-0.0018			

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[2]:

- 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 specialist 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).

No clinical values in the model were estimated based on expert opinion.

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

Firstly, patients transition through health states based on EDSS level and classification type (RRMS vs. SPMS). As discussed in Section B7.4.1, a patient will also experience increasing physical disability as their disease

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

status progresses, in EDSS or conversion to SPMS. This increased physical disability will consequently increase psychosocial impact of the disease [Aronson, 1997]. The QOL of a multiple sclerosis patient will continue to decrease as their condition worsens in terms of EDSS and towards the final stages of the disease, a patient's utility will decrease below zero, i.e. worse than death [Orme, 2007]. Consequently, in the cost-effectiveness model, the patient experiences reduced utility as they progress through health states from EDSS 0 to EDSS 9.

Whilst in an EDSS state, a patient will experience relapses which will negatively impact QOL. The disutility associated with a relapse is dependent on severity, which is associated with hospitalisation requirements (see Section B7.4.6). Finally disutility due to adverse events from treatment also affects the final utility for each patient by EDSS state.

Once a patient enters an EDSS health state, and relapses/treatment related adverse events are accounted for, the utility associated with the health state is constant for that annual cycle.

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

Although injection site reactions are included as a disutilities in the model for patients that experience this adverse event whilst receiving beta-interferon or glatiramer acetate, disutility associated with route of administration has not been included in the analysis [Prosser, 2004]. Including the utility associated with a preference of an oral alternative could improve the results for teriflunomide within the cost-effectiveness model. This has been highlighted in Section A.

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

QOL in terms of utility (Table B7.4.5) was based on EDSS level, for which the distribution is presented in Figure B7.3.1.

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

The HRQL associated with each health state does not change over time although progression to different health states does change over time. Please see Section B7.4.11.

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

None of the utility values derived in sections 7.4.3 to 7.4.8 have been amended.

7.5 Resource identification, measurement and valuation

NHS costs

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

The costs of managing the condition using DMTs are captured by reference costs and the PbR tariff, in terms of administration, monitoring and adverse events. Management of multiple sclerosis patients treated with best supportive care has not been costed directly from reference costs and the payment by results (PbR) tariff.

The guide to method of technology appraisal recommends the use of reduced resource prices that are transparent and can be consistently available across the NHS. Since the UK RSS applies to England and Wales, acquisition costs of beta-interferons and glatiramer acetate have been sourced from UK RSS [DoH Health Service Circular, 2002]. The annual cost of natalizumab has been derived from the British National Formulary (BNF) [BNF Tysabri, 2013]. There is a patient access scheme for fingolimod in existence but at time of submission, the annual cost had not been provided in confidence from the manufacturer so the list price was used (Table B7.5.1).

Table B7.5.1 Acquisition costs of DMTs

Treatment	Dosage	Treatment regimen	Total annual cost
Teriflunomide	14 mg	Teriflunomide 14mg once daily in oral form	£13,529
IFNβ-1a 44µg (Rebif)	44 µg	44µg 3 times per week, self-injected subcutaneously	£8,942
IFNβ-1a 22µg (Rebif)	22 µg	22µg 3 times per week, self-injected subcutaneously	£7,513
IFNβ-1a (Avonex)	30 µg	30 µg once a week, self-injected subcutaneously	£8,502
IFNβ-1b	250 µg	250 µg every other day, self-injected subcutaneously	£7,259
Glatiramer acetate	1 mL vial 20mg/mL	20 mg per day, self-injected subcutaneously	£5,823
Fingolimod	28-tab pack 0.5 mg capsule	0.5 mg once daily in oral form	£19,110
Natalizumab	15 mL vial	300 mg intravenous injection by a health	£14,690

	20 mg/mL	professional every 4 weeks	

There are no administration costs for teriflunomide since it is an oral treatment. Although fingolimod is also an oral treatment, the SmPC recommends continuous ECG and blood pressure monitoring for 6 hours after the first dose of fingolimod, which has been costed as a day case for a multiple sclerosis patient. Beta-interferons and glatiramer acetate are self-injected by patients but there is an initial one-off cost of training by a clinical nurse specialist (Table B7.5.2). Natalizumab is administered as an IV infusion 13 times per year, incurring costs for time at medical facility and IV methylprednisolone.

Table B7.5.2 Administration costs associated with DMTs

Treatment	Year 1 cost	Year 2 cost	Source	Justification
Teriflunomide	£0	£0	-	Oral so no administration costs
IFNβ-1a (Avonex)	£174	£0	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)	3 hours required for nurse to teach self-administration; no administration following initial training
IFNβ-1b	£174	£0	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)	3 hours required for nurse to teach self-administration; no administration following initial training
IFNβ-1a (Rebif 44µg)	£174	£0	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)	3 hours required for nurse to teach self-administration; no administration following initial training
IFNβ-1a (Rebif 22µg)	£174	£0	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)	3 hours required for nurse to teach self-administration; no administration following initial training
Glatiramer acetate	£174	£0	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)	3 hours required for nurse to teach self-administration; no administration following initial training
Fingolimod	£474	£0	NHS Reference Costs AA30C Medical Care of Patients with Multiple Sclerosis without CC Day Case @ £474 per visit.	Continuous ECG and blood presume monitoring for 6 hours following first dose
Natalizumab	£6162	£6162	NHS Reference Costs	13 infusions per year

			AA30C Medical Care of Patients with Multiple Sclerosis without CC Day Case @ £474 per visit.	

The monitoring resource associated with each DMT is shown in Table B7.5.3. The references for these values are obtained from SmPCs of each product where possible, and using the NICE fingolimod costing template [NICE, 2012(b)]. The costs associated with the monitoring resource in Table B7.5.3 are given in Table B7.5.4.

Table B7.5.3 Monitoring resource use associated with DMTs

Treatment	Monitoring requirement	Resource use year 1	Resource use subsequent years	Reference
Teriflunomide	Liver function test	[redacted]	[redacted]	[Teriflunoide SmPC]
	Full blood count	[redacted]	[redacted]	[Teriflunoide SmPC]
	Neurology visit	2	2	Assumption
IFNβ-1a (Rebif)	Liver function test	4	2	[Rebif SmPC]
	Full blood count	4	2	[Rebif SmPC]
	Neurology visit	2	2	[NICE, 2012(b)]
IFNβ-1a (Avonex)	Liver function test	4	2	[Avonex SmPC]
	Full blood count	4	2	[Avonex SmPC]
	Neurology visit	2	2	[NICE, 2012(b)]
IFNβ-1b	Liver function test	4	2	[Betaferon SmPC]
	Full blood count	4	2	[Betaferon SmPC]
	Neurology visit	2	2	[NICE, 2012(b)]
Glatiramer acetate	Neurology visit	2	2	[NICE, 2012(b)]
Fingolimod	Liver function test	6	2	[Gilenya SmPC]
	Full blood count	4	2	[Gilenya SmPC]
	Neurology visit	3	2	[NICE, 2012(b)]
	Ophthamology visit	1	0	[NICE, 2012(b)]
Natalizumab	Liver function test	2	2	[Tysabri SmPC]
	MRI scan	1	1	[Tysabri SmPC]
	Neurology visit	2	2	Assumption

Table B7.5.4 Monitoring costs associated with DMTs

Monitoring requirement	Reference costs / payment by results tariff	Cost
Liver function test	NHS Reference costs 2011-12, Pathology services, Biochemistry DAP841	£1.23
Full blood count	NHS Reference costs 2011-12, Pathology services, Haematology [Excluding Anti-Coagulant Services] DAP823	£3.09
MRI scan (to detect PML)	Payment by Results other-mandatory tariff 2012-13, RA01A: Magnetic Resonance Imaging Scan, one area, no contrast, 19 years and over	£153.00
ECG	NHS Reference costs 2011-12, EA47Z: Electrocardiogram Monitoring and Stress Testing	£111.72
Neurology visit	NHS Reference costs 2011-12, Outpatient Attendances, Neurology 400	£169
Opthamology visit (treatment initiation)	Payment by Results mandatory tariff 2012-13, Oupatient attendance: 130 Opthamology, Single professional, first attendance	£115.00

The costs associated with adverse events are given in Table B7.5.5. For many adverse events the associated cost is assumed to be only a telephone call between the patient and their MS nurse. The cost of a telephone call with an MS nurse was taken from the PSSRU Unit Costs of Health & Social Care 2012 [PSSRU, 2012].

Table B7.5.5 Costs of treatment of DMT adverse events

Adverse events	Associated cost	Source	Source cost	Unit Cost
Headache	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Diarrhoea	GP consultation + loperamide	PSSRU 2012 GP with qualifications surgery consultation cost per patient contact lasting 11.7 minutes BNF April 2013 loperamide hydrochloride 2 mg capsules, 30-cap pack [BNF loperamide, 2013]	£43 £0.98	£43.98
Hair thinning	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Nausea	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Lower respiratory tract infection	2 GP consultations + 5-day regimen of amoxicillin	PSSRU 2012 GP with qualifications cost per patient contact lasting 11.7 minutes	£43	£86.95

		BNF April 2013 amoxicillin (as trihydrate) capsules 250 mg, net price 21 [BNF amoxicillin, 2013]	£0.95	
Back pain	GP consultation	PSSRU 2012 GP with qualifications cost per patient contact lasting 11.7 minutes	£43	£43.00
Injection-site reaction	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Influenza-like symptoms	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Immediate post injection systemic reaction	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Fatigue	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Arthralgia	GP consultation and 3 days treatment with methylprednisolone	BNF April 2013 methylprednisolone 1 mg injection [BNF methylprednisolone, 2013] National Reference costs 2011-12 Consultant lead Pain management (service code 191)	£17.30 £114.63	£166.53

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

NHS reference costs 2011-12 have been used wherever possible in the cost-effectiveness analysis. When compared to PbR Tariff values, the NHS reference costs also allow for a greater level of granularity to be assessed.

NHS reference costs and PbR tariffs have been used to differentiate the intervention costs from comparators in terms of administration, monitoring and adverse event costs.

Where NHS reference costs have not been available or are irrelevant, alternative figures from literature have been used. In particular, defining an annual cost of the disease by disease classification and severity is difficult because there are so many factors to the management of multiple sclerosis. Disease costs are likely to increase with severity, in particular: inpatient care, outpatient care, consultations with specialists, consultations with other medical professionals, investigations/tests, prescribed medication, over-the-counter medication, professional non-medical care and informal non-medical care. The total cost of a relapse is also expected to include a wide range of medical and non-medical costs and thus has not been taken from reference costs or PbR tariffs.

Resource identification, measurement and valuation studies

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

The PICOS (population, interventions, comparators, outcomes and study type) principal was applied to define the following review questions:

- *"What are the direct and indirect costs associated with treating patients with multiple sclerosis?"*
- *"What are the direct costs per relapse that lead to hospitalisation/do not lead to hospitalisation?"*
- *"What is the acquisition costs associated with treatment for multiple sclerosis?"*
- *"What are the costs of administration and monitoring of patients treated for multiple sclerosis?"*
- *"What are the costs of adverse events associated with treating patients with multiple sclerosis?"*

Studies of interest were identified by searching a number of electronic databases which included Embase, Medline, Medline (R) In-Process, EconLIT and NHS EED. A search strategy was developed to identify studies indexed in Embase (this platform covers Embase, MEDLINE and MEDLINE (R) In-Process) and then modified for searches in OVIDSP (this platform covers EconLIT) and The Cochrane Library (this platform covers NHS EED) to account for differences in syntax and thesaurus headings. Searches were ran from 2007 to 2012 and included terms for free text and keywords (e.g. Medical Subject Heading (MESH) terms) with no restrictions on language of publication. To find additional references to those identified during database searching a grey

literature search was performed. Section 10.13, Appendix 10 details the search strategies, databases searched and subsequent results from the database sites searched.

Searches were conducted on the 10th and 11th October 2012. References included for the review had to meet the pre-specified inclusion/exclusion criteria shown in Table B7.5.6.

Table B7.5.6 Eligibility criteria used in cost and resource use systematic review

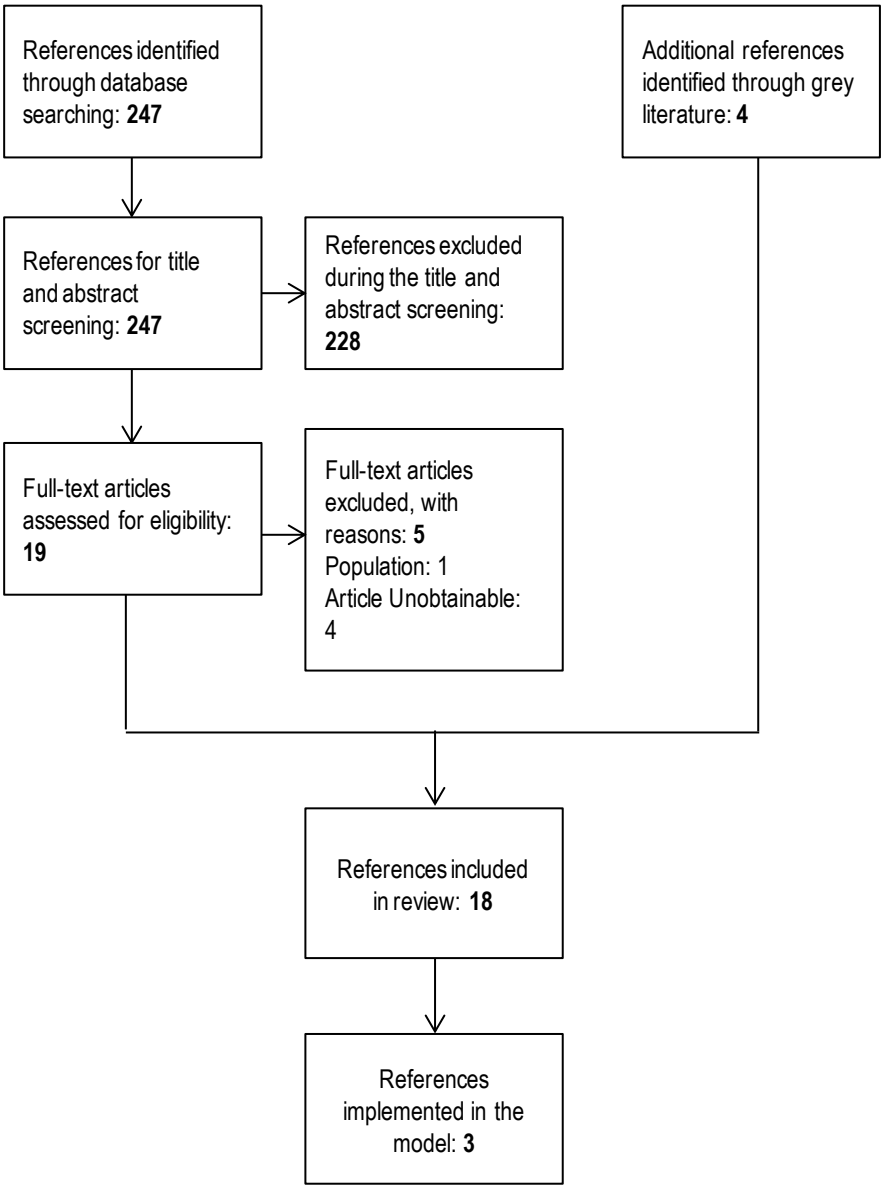
Selection criteria	Inclusion	Exclusion
Population	• Adults with either RRMS or progressive MS (including SPMS or PRMS) • UK	• Primary progressive multiple sclerosis (PPMS)
Cost	• Direct medical costs (e.g. ambulatory costs, inpatient costs, tests, non-DMT costs) • Other direct costs (e.g. services, investments, other OTC treatments) • Informal care costs • Direct costs per relapse (not leading to hospitalisation) • Direct costs per relapse (leading to hospitalisation) • Drug acquisition costs • Drug administration costs • Drug monitoring costs	• Indirect costs (e.g. short-term absence, reduced hours, early retirement)

Duplicates were removed for all records obtained in the searches and then a manual review of the titles and abstracts was undertaken using the inclusion/exclusion criteria to identify papers to be included in the review (also known as first passing). This was performed by two independent reviewers and discrepancies were resolved by a third independent reviewer. Full-text papers identified at first pass were then evaluated and included for review based on the inclusion/exclusion criteria.

The following databases were searched: Embase, Medline, Medline (R) In-Process, EconLIT and NHS EED and a total of 247 records were found after duplicates were removed. These 247 records were then reviewed by hand, by screening the title and abstract of which 19 were included. The full-text articles of these 19 records with 4 records from grey literature were then obtained to assess eligibility resulting in 18 studies that met inclusion/exclusion criteria and as such identified as evaluating cost and resource use in MS.

Figure B7.5.1 contains a flow diagram which illustrates the numbers of studies included and excluded at each stage of the systematic review.

Figure B7.5.1 Flow diagram for the cost and resource use systematic review



Identified cost and resource use studies

Of the 18 studies included in the full review, 3 were implemented in the model and are summarised in Table B7.5.7 below.

Table B7.5.7 Summary of identified cost and resource use studies implemented in the model

	[Dee et al. 2012]
Country of study	Ireland
Date of study	24 November 2010
Applicability to UK clinical practice	Appropriate.
Cost valuations	N/A

used in study	
Costs for use in economic analysis	Using data from the six large neurology centres the average length of stay for a neurology bed. MS admission in 2007 was calculated as 10.71 days. Only about 20% of MS relapses are treated as in-patients, the remaining 80% attend as day cases for 5 days steroid treatment.
Technology costs	N/A
	[Karampampa et al. 2012]
Country of study	UK
Date of study	2009
Applicability to UK clinical practice	Appropriate
Cost valuations used in study	Patients self-completed a questionnaire in English using a web-based electronic data capturing system.
Costs for use in economic analysis	See Figure B7.5.2
Technology costs	N/A
	[Tyas et al. 2007]
Country of study	UK
Date of study	2005
Applicability to UK clinical practice	Appropriate
Cost valuations used in study	Questionnaires were completed by the patient.
Costs for use in economic analysis	See Figure B7.5.3
Technology costs	N/A

Figure B7.5.2 Data extracted from Karampampa et al. 2012

Table 2. Cost per patient per year by disease severity (in £ 2009), 95% CI.

	EDSS 0 – 3 (n = 77)			EDSS 4 – 6.5 (n = 110)			EDSS 7 – 9 (n = 7)		
	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI
Inpatient care	70	367	(25 – 229)	54	319	(17 – 146)	1838[b,c]	3205	(758 – 5191)
Outpatient care	346	973	(200 – 754)	698	1770	(435 – 1103)	435	636	(106 – 986)
Consultations	578	972	(404 – 838)	923[a]	1135	(745 – 1192)	826	910	(334 – 1609)
Investigations	82	148	(56 – 123)	74	164	(49 – 109)	29	78	(0 – 147)
MS treatments	5369	4054	(4494 – 6270)	5499	4443	(4682 – 6351)	2098[†b,c]	5552	(0 – 10,491)
Prescribed & OTC medication	269	363	(205 – 378)	851[a]	1488	(685 – 1398)	832[b]	420	(535 – 1101)
Total direct medical costs	**6714**	**4484**	**(5760 – 7717)**	**8101[a]**	**5271**	**(7153 – 9072)**	**6059**	**5716**	**(2907 – 10,735)**
Investments/modifications	48	315	(16 – 226)	1457[a]	1704	(1127 – 1761)	2989[b]	2325	(1168 – 4433)
Professional care	0	0	n.a.	950[a]	3911	(6885 – 11,462)	16,430[b,c]	18,995	(16,763 – 54,939)
Informal care	1865	7349	(789 – 5321)	7893[a]	10,522	(6115 – 10,237)	21,824[b,c]	18,263	(9957 – 34,697)
Total direct non-medical costs	**1913**	**7396**	**(811 – 5038)**	**10,299[a]**	**12,178**	**(8170 – 12,772)**	**41,242[b,c]**	**30,086**	**(17,653 – 59,378)**
Sick leave	1202	3784	(571 – 2441)	1686	4752	(963 – 2941)	654	1730	(0 – 3269)
Retirement due to MS	2011	5946	(1006 – 4023)	5808[a]	8912	(4224 – 7568)	11,063	10,348	(5531 – 19,360)
Total indirect costs	**3214**	**6691**	**(1920 – 5111)**	**7494**	**9069[a]**	**(5789 – 9200)**	**11,717[b]**	**9654**	**(6185 – 19,360)**
Total costs	**11,841**	**13,288**	**(9673 – 16,182)**	**25,894[a]**	**17,411**	**(22,861 – 29,391)**	**59,018[b,c]**	**34,435**	**(30,659 – 79,668)**

EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; OTC: over-the-counter; n.a.: not applicable.
[a]Difference is statistically significant compared to the mild sub-group of patients (p-value<0.05).
[b]Difference is statistically significant compared to the mild sub-group of patients (p-value<0.05).
[c]Difference is statistically significant compared to the moderate sub-group of patients (p-value<0.05).

Figure B7.5.3 Data extracted from Tyas et al. 2007

Table 1 Direct government-funded costs

Coefficient	Estimate (£)	SE (£)	95% CI (£)	*P*-value
a. Direct annual medical cost coefficients funded by UK government (DMG)				
EDSS 0†	250	1,975	(−3,623, 4,123)	0.90
EDSS 1	85	899	(−1,678, 1,849)	0.92
EDSS 2	213	868	(−1,489, 1,915)	0.81
EDSS 3	850	1,237	(−1,575, 3,275)	0.49
EDSS 4	806	884	(−927, 2,539)	0.36
EDSS 5	1,419	823	(−195, 3,032)	0.09
EDSS 6	2,162	851	(492, 3,832)	0.01
EDSS 6.5	3,429	909	(1,645, 5,212)	*
EDSS 7	6,583	995	(4,632, 8,534)	*
EDSS 8	10,761	1,069	(8,665, 12,857)	*
EDSS 9	15,121	2,656	(9,912, 20,330)	*
RRMS†				
SPMS	280	705	(−1,103, 1,663)	0.69
PPMS	−1,517	815	(−3,114, 81)	0.06
Relapse	1,623	545	(554, 2,692)	*
DMD + EDSS 0–2	9,174	1,161	(6,896, 11,452)	*
DMD + EDSS 3–6.5	467	1,349	(−2,179, 3,113)	0.73
DMD + EDSS 7–9	−689	3,735	(−8,015, 6,636)	0.85
b. Direct annual nonmedical cost coefficients funded by UK government (DNMG)				
EDSS 0†	2,536	2,183	(−1,745, 6,817)	0.25
EDSS 1	3,462	1,314	(886, 6,039)	0.01
EDSS 2	4,414	1,314	(1,836, 6,991)	*
EDSS 3	6,212	1,585	(3,103, 9,321)	*
EDSS 4	4,028	1,320	(1,439, 6,617)	*
EDSS 5	6,333	1,338	(3,709, 8,958)	*
EDSS 6	6,580	1,338	(3,956, 9,204)	*
EDSS 6.5	8,212	1,398	(5,471, 10,953)	*
EDSS 7	10,808	1,485	(7,895, 13,721)	*
EDSS 8	15,339	1,514	(12,369, 18,309)	*
EDSS 9	10,161	2,837	(4,598, 15,725)	*
Age	−66	25	(−116, −16)	0.01
Years since diagnosis	54	29	(−2, 110)	0.06

*$P < 0.01$. †Reference case.
CI, confidence interval.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- 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 specialist 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

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

- 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).

As discussed in Section B7.3.5, interviews were conducted with three neurologists from England and Wales. Monitoring resource use derived from SmPCs and NICE costing templates were assessed by the three experts to ensure it accurately reflects the monitoring that occurs with DMTs in clinical practice [Genzyme KOL interview report, 2013]. The experts were also asked if they believed the cost of the resource was an accurate reflection of what they would expect.

The experts' monitoring of fingolimod varied in terms of the number of liver function tests, full blood counts and neurology visits. Since the difference may be local variation or clinician preference, the conservative approach has been taken of sourcing these values from the NICE fingolimod costing template [NICE, 2012(b)]. Similarly there was local variation in the number of neurology visits for all other DMTs; the NICE fingolimod costing template states two per year but one expert believed there would be four in the first year and two in subsequent years. Again the conservative approach has been taken to use the more robust source: the NICE fingolimod costing template. However, even if the NICE fingolimod costing template does underestimate the number of neurology visits, an increase would apply to all DMTs so the ICER would not change significantly.

Furthermore, the experts believed that the high number of LFTs and FBCs would not happen in clinical practice (Table B7.5.3). They believed they would only be conducted if a patient was showing symptoms. One expert stated that the tests were done in the trial to assess abnormalities but in clinical practice such a high number of tests would not be conducted. Despite clinical opinion, the number of tests has been aligned with the SmPC [Teriflunomide SmPC].

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section B7.2.2.

A summary of the acquisition costs, administration and monitoring costs for each DMT, which were individually detailed in section B7.5.1, is summarised in Table B7.5.8. All costs in Table B7.5.8 are assumed to stay constant for all health states; they do not vary by EDSS or classification of RRMS or SPMS.

Table B7.5.8 Annual costs associated with the technologies in the economic model

	Technology cost	Administration cost (year 1)	Administration cost (year 2+)	Monitoring cost (year 1)	Monitoring cost (year 2+)	Total (year 1)	Total (year 2+)
Teriflunomide	13,529.00	0	0	407.12	368.24	13,936.12	13,897.24
IFNβ-1a 44µg (Rebif)	8,942.00	174.00	0	355.28	346.64	9,471.28	9,288.64
IFNβ-1a 22µg (Rebif)	7,513.00	174.00	0	355.28	346.64	8,042.28	7,859.64
IFNβ-1a (Avonex)	8,502.00	174.00	0	355.28	346.64	9,031.28	8,848.64
IFNβ-1b	7,259.00	174.00	0	355.28	346.64	7,788.28	7,605.64
Glatiramer acetate	5,823.00	174.00	0	338.00	338.00	6,335.00	6,161.00
Fingolimod	19,110.00	474.00	0	641.74	346.64	20,225.74	19,456.64
Natalizumab	14,690.00	6162.00	6162.00	493.46	493.46	21,345.46	21,795.26
Blended comparator	7,721.08	174.00	0	351.22	344.61	8,246.30	8,065.69

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section B7.2.4.

There are significant changes in costs per health state. As seen in Figure B7.5.2 and Figure B7.5.3, the natural history costs rapidly increase by disease severity. From the literature search detailed in Section B7.5.3, two sources of natural history costs were obtained. In the base case scenario, costs are from Tyas et al as this source is well cited and consistent with two previous NICE submissions [Tyas et al. 2007; Biogen, 2006; Novartis, 2011]. Only direct medical costs and other direct costs have been applied to the analysis; indirect costs are not consistent with the NHS & PSS perspective.

An alternative source obtained through the literature search is a study by Karampampa et al which although it is a more recent study, only provides aggregated natural history costs for EDSS 0-3, 4-6 and 7-9, rather than costs per individual EDSS state. Karampampa et al has more difference between direct medical and non-medical costs, as well as a much greater % increase in costs as EDSS increases (see Figure B7.5.4). Since Karampampa et al does not provide the costs in sufficient detail i.e. not be each EDSS state, it has not been used in the base case analysis. However, it is the most recent source and thus important to consider and has therefore been tested in sensitivity analysis.

Both natural history cost sources have been inflated to Q3, 2012 and the final values used in the model shown in Table B7.5.9 [ONS CPI indices].

Figure B7.5.4 Illustration of the difference in natural history costs from available sources

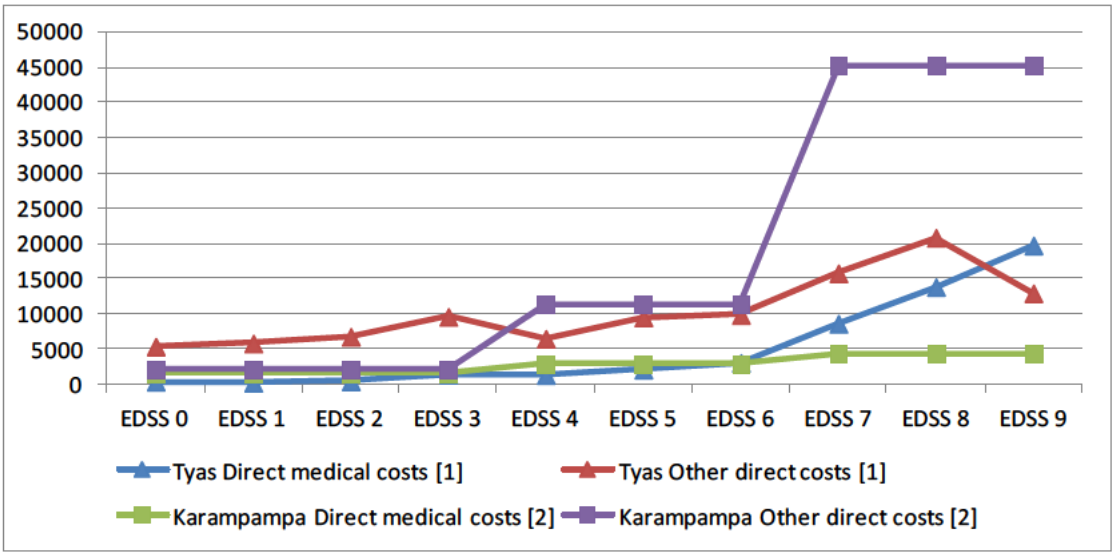


Table B7.5.92 List of health states and associated costs in the economic model

Health states (applies to RRMS and SPMS)	Items	Base case value [Tyas et al. 2007]	Sensitivity analysis value [Karampampa, 2012]
EDSS 0	Direct medical costs	336.19	1477.707
	Other direct costs	5334.58	2101.749
	Total	5670.77	3579.456
EDSS 1	Direct medical costs	200.23	1477.707
	Other direct costs	5779.54	2101.749
	Total	5979.77	3579.456
EDSS 2	Direct medical costs	399.23	1477.707
	Other direct costs	6734.96	2101.749
	Total	7134.19	3579.456

EDSS 3	Direct medical costs	1315.10	1477.707
	Other direct costs	9565.40	2101.749
	Total	10880.51	3579.456
EDSS 4	Direct medical costs	1294.09	2856.533
	Other direct costs	6461.81	11315.17
	Total	7755.90	14171.7
EDSS 5	Direct medical costs	2056.70	2856.533
	Other direct costs	9488.77	11315.17
	Total	11545.48	14171.7
EDSS 6	Direct medical costs	3025.73	2856.533
	Other direct costs	9811.37	11315.17
	Total	12837.10	14171.7
EDSS 7	Direct medical costs	8595.14	4350.72
	Other direct costs	15761.47	45311.21
	Total	24356.62	49661.93
EDSS 8	Direct medical costs	13806.12	4350.72
	Other direct costs	20810.53	45311.21
	Total	34616.65	49661.93
EDSS 9	Direct medical costs	19704.31	4350.72
	Other direct costs	12914.96	45311.21
	Total	32619.28	49661.93
EDSS 10	Direct medical costs	0	0
	Other direct costs	0	0
	Total	0	0

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section B6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. 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 B7.2.2.

Details of the adverse events that have been included in the model and justification for inclusion/exclusion are detailed in section B7.3.1. The costs associated with each adverse event are detailed in Table B7.5.10.

Table B7.5.10 List of adverse events and summary of costs included in the economic model

Adverse event	Items	Cost details	Unit Cost
Headache	Staff costs	MS nurse phone call	£5.80
Diarrhoea	Staff costs	GP consultation	
	Technology costs	Loperamide hydrochloride	£43.98
Hair thinning	Staff costs	MS nurse phone call	£5.80
Nausea	Staff costs	MS nurse phone call	£5.80
Lower respiratory tract infection	Staff costs	2 GP consultations	£86.00
	Technology costs	5-day regimen of amoxicillin	£0.95
	Total		
Back pain	Staff costs	GP consultation	£43.00
Injection-site reaction	Staff costs	MS nurse phone call	£5.80
Influenza-like symptoms	Staff costs	MS nurse phone call	£5.80
Immediate post injection systemic reaction	Staff costs	MS nurse phone call	£5.80
Fatigue	Staff costs	MS nurse phone call	£5.80
Arthralgia	Staff costs	GP consultation and	£114.63
	Technology costs	3 days treatment with methylprednisolone	£51.90
	Total		£166.53

Miscellaneous costs

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

In addition to costs associated with DMTs and natural history costs, there are also costs associated with hospitalisations. As detailed in section B7.2.5, relapses in the model are captured by those that lead to hospitalisation and those that do not. Two sources were identified in the literature review for relapses costs (see Section B7.5.3). As discussed in section B7.5.6, Tyas et al is a robust study of costs associated with MS. However, Tyas does not differentiate between costs of relapses leading to hospitalisation and those that do not. Therefore, although natural history costs are sourced from Tyas in the base case, costs of relapse are sourced from Dee et al. which used data collected from Irish neurology centres to obtain a length of hospital stay of 10.7 days from relapse. Relapses not leading to hospitalisation require 5 days steroid treatment as day cases. UK NHS reference costs have been substituted for the HIPE Irish costs used in the publication to gain a UK equivalent cost. Table B7.5.11 provides details of the calculation of relapse costs. The relapse costs used in the base case and sensitivity analysis are detailed in Table B7.5.12.

Table B7.5.11 Cost calculations for costs associated with relapses [Dee et al. 2012]

Parameter	Resource use	Number of days	Source of cost	Cost per day
Cost calculation for relapses leading to hospitalisation	Length of stay of relapse leading to hospitalisation	10.71	National Reference Costs 2011-12 Regular Day / Night Admissions. Service code AA30B: Medical Care of Patients with Multiple Sclerosis without CC	£575.58
Cost calculation for relapses not leading to hospitalisation	Days of steroid treatment	5	National Reference Costs 2011-12- Outpatient Attendances Data. Service code 400: Neurology	£168.93

Table B7.5.12 Costs associated with relapses included in the economic model

Category	Base case cost [Dee, 2012]	Sensitivity analysis cost [Tyas, 2007]
Relapse not leading to hospitalisation	£ 844.65	£ 2,006.03
Relapse leading to hospitalisation	£ 6,164.46	£ 2,006.03

7.6 Sensitivity analysis

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

To test structural uncertainty within the cost-effectiveness model, a number of scenario analyses were performed. Firstly, incremental results were presented including all potential comparators in the model. Secondly, treatment sequencing was introduced to reflect current clinical practice more accurately (see Table B7.6.1). Finally, structural scenario analyses of assumptions regarding active RRMS patient population, discount rates and long-term treatment effect and discontinuations were explored (see Table B7.6.2).

The treatment sequences explored were reflective of those used by interviewed KOLs. As discussed in Section B7.2.2, there is so much diversity in the disease progression of the every patient that it is unfeasible to elicit a 'typical' treatment pathway for a patient diagnosed with RRMS. The tested scenarios were designed to capture the range in cost-effectiveness over treatment pathways that a patient in England and Wales may experience. In two scenarios, it is assumed that when a patient receives fingolimod, the patient has developed HA disease (scenarios 1 and 3 in Table B7.6.1). Similarly, in an additional two scenarios it is assumed that when a patient receives natalizumab, the patient has developed RES (scenarios 2 and 2 in Table B7.6.1). Since the PAS price of fingolimod is unknown, a range of possible prices have been tested within the treatment sequencing scenario analysis, in line with NICE guidance [NICE, 2008].

Table B7.6.1 Treatment sequences tested in scenario analyses due to uncertainty in fixed patent treatment pathway in MS

Scenario	Intervention sequence			Comparator sequence		
	1st	2nd	3rd	1st	2nd	3rd
Base case	Teriflunomide	BSC	BSC	Blended comparator	BSC	BSC
1	Teriflunomide	Fingolimod	BSC	Blended comparator	Fingolimod	BSC
2	Teriflunomide	Natalizumab	BSC	Blended comparator	Natalizumab	BSC
3	Teriflunomide	Blended comparator	Fingolimod	Blended comparator	Blended comparator	Fingolimod
4	Teriflunomide	Blended comparator	Natalizumab	Blended comparator	Blended comparator	Natalizumab

Table B7.6.2 Structural uncertainty analyses performed in the economic model

Area of uncertainty	Base case	Alternative scenarios	Justification
Extrapolation of clinical parameters over duration of model	No waning of treatment effect	Treatment effect reduction by 50% after 5 years	See Section B7.3.2
		Treatment effect reduction by 25% after 5 years	See Section B7.3.2
	Rate of discontinuation wanes to 50% after year 2	No waning of discontinuation	See Section B7.3.1
		Rate of discontinuation reduction by 75% after year 2	See Section B7.3.1
RRMS population	London Ontario (all RRMS) combined with TOWER and TEMSO transitions probabilities from EDSS 0	London Ontario (active RRMS) combined with TOWER and TEMSO transitions probabilities from EDSS 0	See Section B7.2.5
Rebif comparator	In the incremental analsyis, separate ICERs are presented for Rebif 22µg and 44µg	Aggregated ICER of deterministic Rebif 22µg and 44µg ICERs using weighting of market share	See Section B7.2.7
Discount rates for costs and outcomes	3.5%	0%	Recommended by NICE [NICE, 2008]
		6%	Recommended by NICE [NICE, 2008]
Treatment within SPMS	No patients treated in SPMS (SPMS stopping rule EDSS 0 for all treatments)	Stopping rule for SPMS at EDSS 7 for IFNβ-1a (Rebif) and IFNβ-1b only; all other treatments EDSS 0 SPMS stopping rule	IFNβ-1a (Rebif) and IFNβ-1b licences include SPMS. See Section B7.2.8
No treatment effect on relapses or proportion of relapses leading to hospitalisation	ARR from MTC and proportions or relapses leading to hospitalisation from published literature	Only treatment effect on 3-month SAD	Treatment effect on disability progression indirectly impacts relapses so there may be some double-counting when modelling treatment effect on both relapses and disability progression [NICE, 2011(b)]

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section B7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

One-way deterministic sensitivity analyses (DSA) were performed for teriflunomide versus blended comparator to test variation of parameters through upper and lower confidence intervals where possible, 10% variation in the absence of standard errors (Table B7.6.3 and B7.6.4). Drug costs were omitted as these are assumed to have no variation. Additionally, three-way parameter sensitivity analysis was performed for the clinical parameters sourced from the MTC (3-month SAD, ARR, withdrawal) on both teriflunomide versus blended comparator as well as teriflunomide versus incremental results (beta-interferons and glatiramer acetate).

Table B7.6.3 Deterministic one-way parameter uncertainty analyses performed in the economic model presented through tornado diagram for teriflunomide versus blended comparator

Area of uncertainty	Parameter	Variation	Reference to submission
Clinical data	Hazard ratio of sustained disability progression	95% confidence intervals	Section B7.3.2
	ARR	95% confidence intervals	Section B7.3.1
	Withdrawal	95% confidence intervals	Section B7.3.1
	Proportion hospitalised RR	10%	Section B7.3.1
Quality of life	EQ-5D utilities by EDSS score and MS classification	95% confidence intervals	Section B7.4.6
	Adverse event disutility	10%	Section B7.4.8
	Carer disutility	10%	Section B7.4.6
	Disutility of relapse leading to hospitalisation	10%	Section B7.4.6
	Disutility of relapse not leading to hospitalisation	10%	Section B7.4.6
Cost and resource use parameters	Administration costs	10%	Section B7.4.1
	Monitoring costs	10%	Section B7.4.1
	Total adverse events	10%	Section B7.4.7
	Cost of relapse leading to hospitalisation	10%	Section B7.4.8
	Cost of relapse not leading to hospitalisation	10%	Section B7.4.8
	Disease costs (direct medical, indirect medical, other direct)	10%	Section B7.5.6

Table B7.6.4 Deterministic parameter uncertainty analyses performed in the economic model to test sources of data used

Area of uncertainty	Base case	Alternative scenarios	Reference to submission
Clinical data	Sourced from base case MTC (Post-2000, ≥80% RRMS)	Sourced from sensitivity analysis MTC (All-years, ≥80% RRMS)	See Additional Appendix 2 and Section B7.3.1

	Different probabilities of adverse events in year 1 to subsequent years	Adverse event probability in all years equal to derived probability for year 1	See Section B7.3.1
Cost sources	Natural history costs from Tyas, 2007	Natural history costs from Karampampa, 2012	See Section B7.5.6
	Relapse costs from Dee, 2012	Relapse costs from Tyas, 2007	See Section B7.5.8
Utility sources	Baseline EDSS utility score from Orme, 2007	Baseline EDSS utility score from TEMSO study	See Section B7.4.7
	Disutility of relapse from Orme, 2007	Disutility of relapse from Gani, 2008	See Section B7.4.6
	Initial EDSS distribution from UK risk-sharing scheme	Initial EDSS distribution from TOWER and TEMSO studies	See Section B7.3.1
	Starting age and male: female ratio from UK risk-sharing scheme	Starting age and male: female ratio from TOWER and TEMSO studies	See Section B7.3.1
	Natural history relapse rate from Held, 2005	Natural history relapse rate from Patzold, 1982	See Section B7.3.1
	Proportion of relapses leading to hospitalisation from Dee, 2012	Proportion of relapses leading to hospitalisation from placebo arms of TEMSO study	See Section B7.3.1
	Fingolimod annual price set as list price of £19,110	Possible PAS prices of £11,000, £13,000 and £15,000	At the time of analysis, the manufacturer had not provided the PAS acquisition price of fingolimod so a range of plausible prices are tested

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section B7.3.6, 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).

Table B7.6.5 details which parameters were included in the PSA along with the distribution used to generate stochastic values. Natural history transition probabilities from London Ontario and placebo arms of TEMSO/TOWER were omitted from the probabilistic sensitivity analysis because there are small sample sizes in

high RRMS EDSS states and low SPMS EDSS states resulting in unrealistic stochastic transition probabilities that would not be feasible in clinical practice. The probabilities of conversion from RRMS to SPMS estimated from London Ontario were also excluded for the same reason. Transition probability variation was captured by varying the hazard ratio of disability probabilistically which is applied to the natural history transitions to create the treatment transitions matrices (see Section B7.3.2). Furthermore, parameter sensitivity analysis was performed using active RRMS patients rather than the base case of all RRMS patients.

Table B7.6.5 Parameters included in probabilistic sensitivity analysis (PSA)

Parameter	Included in PSA	Distribution	Derivation of priors or assumptions
Discount rates on costs and outcomes	No	-	-
Time horizon	No	-	-
Initial EDSS distribution		-	-
Baseline characteristics of cohort (male to female ratio and age)	No	-	-
Natural history transition matrices	No	-	-
Natural history RRMS to SPMS conversion probabilities	No	-	-
Natural history relapse rate	Yes	Normal	Assumption of 10% standard error
Natural history proportion of relapses leading to hospitalisation	Yes	Beta	-
3-month SAD HRs	Yes	Gamma	Standard error derived from 95% confidence intervals sourced from MTC
ARRs	Yes	Gamma	Standard error derived from 95% confidence intervals sourced from MTC
Proportion hospitalised	Yes	Gamma	Assumption of 10% standard error
Withdrawal rates	Yes	Beta	Standard error derived from 95% confidence intervals sourced from MTC
Disease costs (direct medical, indirect medical, other direct)	Yes	Gamma	Assumption of 10% standard error
Cost of relapse	Yes	Gamma	Assumption of 10% standard error
Drug acquisition costs	No	-	-
Administration costs	Yes	Gamma	Assumption of 10% standard error
Monitoring costs	Yes	Gamma	Assumption of 10% standard error
Adverse event costs	Yes	Gamma	Assumption of 10% standard error
Utility values per EDSS and MS classification	Yes	Gamma	Assumption of 10% standard error. 95% confidence intervals were not used as these were only available for the base case data source, not the

			sensitivity analysis
Disutility per relapse	Yes	Gamma	Assumption of 10% standard error
Disutility of adverse events	Yes	Gamma	Assumption of 10% standard error

7.7 Results

Clinical outcomes from the model

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

The outcomes described in the decision problem (see Table A5.1 in Section A5) are assessed comparing appropriate trial outcomes to the outcomes in the Teriflunomide 14mg arm from the cost-effectiveness base case model (see Table B7.7.1). The model estimated higher disability progression and relapses than occurred in the trial. Consequently, the model prediction of quality of life was lower than observed in the clinical trials of teriflunomide and mortality was higher in the model. The change in disability progression is the driver of the model since each clinical parameter is dependent on the health state and disability progression is the transition between health states.

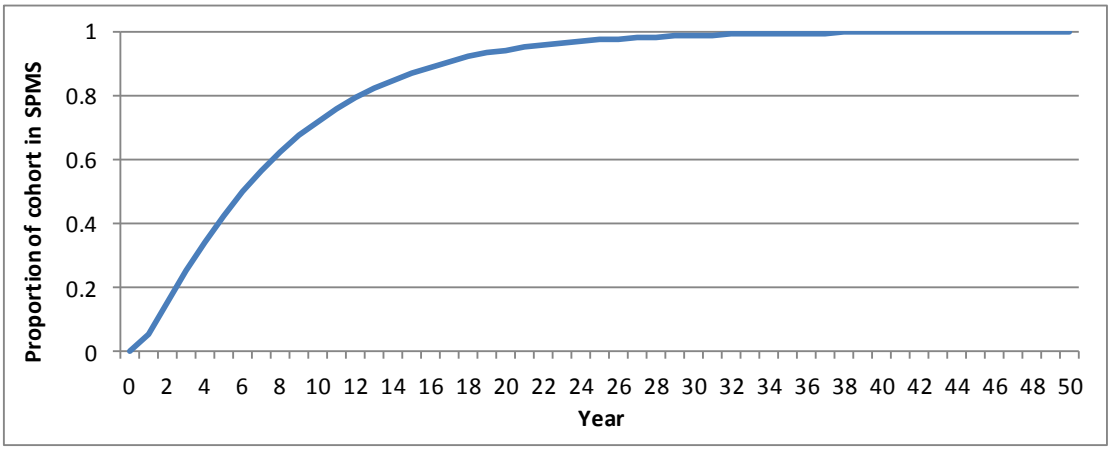
Table B7.7.1 Summary of teriflunomide model results compared with clinical data

Outcome tested	Specific parameter	Clinical trial result	Model result
Disability / Symptoms of multiple sclerosis / Freedom of disease activity	Change in mean EDSS from baseline	TOWER 0.038 (1.4%) (at week 108) TEMSO 0.339 (4.9%) (at week 96)	0.53 (14.5%) (at year 2)
Relapse rate / Severity of relapse / Resource utilisation: hospitalisation	Average number of relapses leading to hospitalisation per patient in 2 years	TEMSO 0.111 (n=40 relapses)	0.207
	Average number of relapses not leading to hospitalisation per patient in 2 years	TEMSO 0.522 (n=187 relapses)	1.167
Health related quality of life	Change in EQ-5D from baseline	TEMSO -0.006 (-0.82%) (at week 96)	-0.103 (-17.2%) (at week 104)
Mortality	2-year mortality	0.0028% (No deaths occurred in TEMSO, 2 deaths in TOWER)	0.0039%

The population in the clinical trials was milder than one might expect to see in clinical practice, evidenced by the difference in EDSS distribution of the cohort that started TOWER and TEMSO compared to the risk--sharing scheme (see Table B7.3.10). Therefore, one would expect that the model output using baseline characteristics of the risk-sharing scheme would show, as it has done, more change in disability progression and relapses than the clinical trials [Boggild, 2009]. The increased disability progression modelled impacts quality of life and mortality so these are also estimated to be greater than the observations from clinical trials. An estimation of the impact of severe disease is a conservative approach; the costs are higher than one would expect to incur in practice.

The clinical trial cohort being at an earlier stage of the disease also impacted the time to conversion to SPMS. 65% of RRMS patients not treated with a DMT will develop SPMS within 15 years of diagnosis [NICE Final Scope]. The economic model estimated that at year 15, 90% of patients will have converted to SPMS. However, this is 15 years since modelled treatment initiation rather than 15 years since diagnoses. Since teriflunomide slows disability progression and probability of conversion is increased with EDSS (see Table B7.3.9), the proportion of patients converted to SPMS should be less than placebo. The model accurately reflected this assumption, with 87% of the cohort modelled as converting to SPMS by year 15 following treatment intiation (see Figure B7.7.1). This assumption is also comparable to an estimate by Trojano et al that approximately 90% of untreated RRMS patients will transition to SPMS after 20–25 years [Trojano et al. 2003].

Figure B7.7.1 Conversion of teriflunomide cohort to SPMS



Wynia et al found that the probabilities of mortality of a cohort with starting age 51 years over a five-year period for EDSS intervals were 1.4% for 0<EDSS<4.5, 5.8% for 4.5≤EDSS<7 and 23.7% for 7≤EDSS<10 [Wynia et al. 2012]. However, it was estimated that cohort observed had a higher progress of disease than other studies indicating that these mortality rates could be an overestimation. The model BSC results for years 13 to 18, corresponding to age 51 to 55, are 1.56% for 0<EDSS≤5, 3.20% for 6≤EDSS≤7 and 9.71% for 8≤EDSS<10. Thus the model outputs are lower than the published mortality rates as expected the modelled cohort is milder than the cohort observed in Wynia et al.

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

The mid-year estimate Markov traces for teriflunomide and the blended comparator are presented in Additional Appendix 11. The Markov traces show that after one year of treatment, 24% of the cohort are no longer receiving teriflunomide. This is a consequence of disease progression, withdrawal and stopping rule at EDSS 7 (4.5% of the initial cohort had EDSS of 7). In comparison, a slightly greater proportion of the cohort remains on treatment with the blended comparator after one year.

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

The total QALYs from a cohort are composed of: health state utility, adverse event disutility, caregiver disutility and relapse disutility. Utility scores for each health state are added to caregiver disutility per health state and

applied to the Markov trace for each treatment to give the EDSS utility for the cohort. Relapse rates and adverse event disutilities are also applied to Markov traces separately. The three sets of the utility per health state over time are combined and accrued QALYs calculated. Discounted cumulative QALYs over time for teriflunomide and the blended comparator are presented in Table B7.7.2.

Table B7.7.2 Teriflunomide and Blended comparator accrued deterministic QALYs over time

	Teriflunomide					Blended comparator				
Year	EDSS utility	Non-hospital relapse disutility	Hospital relapse disutility	Adverse event disutility	Cumulative QALYs	EDSS utility	Non-hospital relapse disutility	Hospital relapse disutility	Adverse event disutility	Cumulative QALYs
1	0.56	-0.01	0.00	-0.01	0.54	0.56	-0.01	0.00	-0.01	0.55
2	1.07	-0.01	-0.01	-0.02	1.03	1.06	-0.01	-0.01	-0.01	1.03
3	1.51	-0.02	-0.01	-0.02	1.47	1.49	-0.02	-0.01	-0.01	1.45
4	1.90	-0.02	-0.01	-0.02	1.85	1.87	-0.02	-0.01	-0.01	1.82
5	2.24	-0.03	-0.02	-0.02	2.18	2.19	-0.03	-0.02	-0.02	2.13
6	2.53	-0.03	-0.02	-0.02	2.46	2.46	-0.03	-0.02	-0.02	2.40
7	2.78	-0.03	-0.02	-0.02	2.70	2.69	-0.03	-0.02	-0.02	2.62
8	2.99	-0.04	-0.03	-0.02	2.90	2.88	-0.04	-0.03	-0.02	2.80
9	3.16	-0.04	-0.03	-0.02	3.07	3.03	-0.04	-0.03	-0.02	2.94
10	3.30	-0.05	-0.03	-0.02	3.20	3.16	-0.05	-0.03	-0.02	3.06
11	3.41	-0.05	-0.04	-0.02	3.31	3.26	-0.05	-0.04	-0.02	3.15
12	3.50	-0.06	-0.04	-0.02	3.39	3.33	-0.06	-0.04	-0.02	3.22
13	3.57	-0.06	-0.04	-0.02	3.45	3.38	-0.06	-0.04	-0.02	3.26
14	3.62	-0.06	-0.05	-0.02	3.50	3.42	-0.06	-0.05	-0.02	3.30
15	3.66	-0.07	-0.05	-0.02	3.53	3.45	-0.07	-0.05	-0.02	3.31
16	3.68	-0.07	-0.05	-0.02	3.55	3.46	-0.07	-0.05	-0.02	3.32
17	3.70	-0.07	-0.05	-0.02	3.55	3.47	-0.07	-0.05	-0.02	3.32
18	3.70	-0.08	-0.06	-0.02	3.55	3.46	-0.08	-0.06	-0.02	3.31
19	3.70	-0.08	-0.06	-0.02	3.55	3.45	-0.08	-0.06	-0.02	3.30
20	3.69	-0.08	-0.06	-0.02	3.53	3.44	-0.08	-0.06	-0.02	3.28
21	3.68	-0.08	-0.06	-0.02	3.52	3.42	-0.08	-0.06	-0.02	3.26
22	3.67	-0.09	-0.06	-0.02	3.50	3.40	-0.09	-0.06	-0.02	3.23
23	3.65	-0.09	-0.07	-0.02	3.48	3.38	-0.09	-0.07	-0.02	3.21
24	3.63	-0.09	-0.07	-0.02	3.45	3.36	-0.09	-0.07	-0.02	3.18
25	3.61	-0.09	-0.07	-0.02	3.43	3.33	-0.09	-0.07	-0.02	3.15
26	3.59	-0.09	-0.07	-0.02	3.40	3.31	-0.09	-0.07	-0.02	3.13
27	3.56	-0.09	-0.07	-0.02	3.38	3.29	-0.09	-0.07	-0.02	3.10

28	3.54	-0.10	-0.07	-0.02	3.36	3.26	-0.10	-0.07	-0.02	3.08
29	3.52	-0.10	-0.07	-0.02	3.33	3.24	-0.10	-0.07	-0.02	3.05
30	3.50	-0.10	-0.08	-0.02	3.31	3.22	-0.10	-0.07	-0.02	3.03
31	3.49	-0.10	-0.08	-0.02	3.29	3.20	-0.10	-0.08	-0.02	3.01
32	3.47	-0.10	-0.08	-0.02	3.27	3.18	-0.10	-0.08	-0.02	2.99
33	3.45	-0.10	-0.08	-0.02	3.26	3.17	-0.10	-0.08	-0.02	2.97
34	3.44	-0.10	-0.08	-0.02	3.24	3.15	-0.10	-0.08	-0.02	2.95
35	3.43	-0.10	-0.08	-0.02	3.23	3.14	-0.10	-0.08	-0.02	2.94
36	3.42	-0.10	-0.08	-0.02	3.21	3.13	-0.10	-0.08	-0.02	2.93
37	3.41	-0.10	-0.08	-0.02	3.20	3.12	-0.10	-0.08	-0.02	2.92
38	3.40	-0.10	-0.08	-0.02	3.20	3.11	-0.10	-0.08	-0.02	2.91
39	3.39	-0.10	-0.08	-0.02	3.19	3.11	-0.10	-0.08	-0.02	2.90
40	3.39	-0.11	-0.08	-0.02	3.18	3.10	-0.11	-0.08	-0.02	2.89
41	3.38	-0.11	-0.08	-0.02	3.18	3.10	-0.11	-0.08	-0.02	2.89
42	3.38	-0.11	-0.08	-0.02	3.17	3.09	-0.11	-0.08	-0.02	2.89
43	3.38	-0.11	-0.08	-0.02	3.17	3.09	-0.11	-0.08	-0.02	2.88
44	3.37	-0.11	-0.08	-0.02	3.17	3.09	-0.11	-0.08	-0.02	2.88
45	3.37	-0.11	-0.08	-0.02	3.17	3.09	-0.11	-0.08	-0.02	2.88
46	3.37	-0.11	-0.08	-0.02	3.17	3.09	-0.11	-0.08	-0.02	2.88
47	3.37	-0.11	-0.08	-0.02	3.17	3.08	-0.11	-0.08	-0.02	2.88
48	3.37	-0.11	-0.08	-0.02	3.16	3.08	-0.11	-0.08	-0.02	2.88
49	3.37	-0.11	-0.08	-0.02	3.16	3.08	-0.11	-0.08	-0.02	2.88
50	3.37	-0.11	-0.08	-0.02	3.16	3.08	-0.11	-0.08	-0.02	2.88

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

Life years are derived directly from the Markov trace; there is no probability of death from adverse events or relapse. QALYs accrued for the clinical outcomes of disability progression and relapse are presented in Table B7.7.2.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table B7.7.3 Summary of deterministic QALY gain by health state over 50 year time horizon of model

Health state	QALY Teriflunomide	QALY Blended comparator	Increment	Absolute increment	% absolute increment
RRMS EDSS 0	0.029	0.023	0.006	0.006	2%
RRMS EDSS 1	0.295	0.264	0.031	0.031	10%
RRMS EDSS 2	0.715	0.65	0.065	0.065	22%
RRMS EDSS 3	0.731	0.683	0.048	0.048	16%
RRMS EDSS 4	0.422	0.381	0.041	0.041	14%
RRMS EDSS 5	0.206	0.19	0.016	0.016	5%
RRMS EDSS 6	0.639	0.623	0.016	0.016	5%
RRMS EDSS 7	0.063	0.067	-0.004	0.004	1%
RRMS EDSS 8	-0.053	-0.057	0.004	0.004	1%
RRMS EDSS 9	-0.001	-0.001	0	0	0%
SPMS EDSS 0	0	0	0	0	0%
SPMS EDSS 1	0	0	0	0	0%
SPMS EDSS 2	0.019	0.018	0.001	0.001	0%
SPMS EDSS 3	0.096	0.094	0.002	0.002	1%
SPMS EDSS 4	0.177	0.175	0.002	0.002	1%
SPMS EDSS 5	0.131	0.128	0.003	0.003	1%
SPMS EDSS 6	0.742	0.732	0.01	0.01	3%
SPMS EDSS 7	0.275	0.279	-0.004	0.004	1%
SPMS EDSS 8	-0.648	-0.662	0.014	0.014	5%
SPMS EDSS 9	-0.468	-0.501	0.033	0.033	11%
Adverse event utilities	-0.019	-0.02	0.001	0.001	0%
Relapse leading to hospitalisation utility	-0.082	-0.081	-0.001	0.001	0%
Relapse not leading to hospitalisation utility	-0.106	-0.106	0	0	0%
Total	**3.16**	**2.88**	**0.28**	**0.30**	**100%**

Table B7.7.4 Summary of deterministic costs by health state

Cost parameter	Health state	Cost Teri	Cost Blended com	Inc	Absolute inc	% absolute inc
Disease costs (direct medical, direct non-medical)	RRMS EDSS 0	190	149	41	41	0%
	RRMS EDSS 1	2214	1977	237	237	1%
	RRMS EDSS 2	7271	6610	661	661	2%
	RRMS EDSS 3	14088	13152	936	936	3%
	RRMS EDSS 4	5452	4913	539	539	2%
	RRMS EDSS 5	4768	4403	365	365	1%
	RRMS EDSS 6	18950	18471	479	479	1%
	RRMS EDSS 7	6341	6704	-363	363	1%
	RRMS EDSS 8	11764	12671	-907	907	3%
	RRMS EDSS 9	98	105	-7	7	0%
	SPMS EDSS 0	0	0	0	0	0%
	SPMS EDSS 1	0	0	0	0	0%
	SPMS EDSS 2	204	197	7	7	0%
	SPMS EDSS 3	1976	1927	49	49	0%
	SPMS EDSS 4	2430	2400	30	30	0%
	SPMS EDSS 5	3187	3128	59	59	0%
	SPMS EDSS 6	22955	22649	306	306	1%
	SPMS EDSS 7	26605	26930	-325	325	1%
	SPMS EDSS 8	238513	243964	-5451	5451	16%
	SPMS EDSS 9	63630	68089	-4459	4459	13%
Treatment costs (Acquisition, administration, monitoring, adverse events)	RRMS EDSS 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RRMS EDSS 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RRMS EDSS 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RRMS EDSS 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RRMS EDSS 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RRMS EDSS 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RRMS EDSS 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RRMS EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RRMS EDSS 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RRMS EDSS 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS EDSS 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS EDSS 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS EDSS 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	SPMS EDSS 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS EDSS 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS EDSS 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS EDSS 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS EDSS 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPMS EDSS 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of relapse leading to hospitalisation	All health states – not captured separately	17017	16797	220	220	1%
Cost of relapse not leading to hospitalisation	All health states – not captured separately	10021	10021	0	0	0%
Total Cost		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inc, incremental, Teri, teriflunomide, Comp, comparator						

Table B7.7.5 Summary of predicted resource use by category of cost (£)

Item	Cost Teriflunomide	Cost Blended comparator	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	0	135	-135	135	[redacted]
Monitoring cost	1215	1100	115	115	[redacted]
Adverse event cost	14	18	-4	4	[redacted]
Relapse cost	27038	26818	220	220	[redacted]
Disease cost	430636	438439	-7803	7803	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

As discussed in Section B7.2.7, the most appropriate comparator for teriflunomide is a blended comparator of the treatments used in UK clinical practice. Base case cost-effectiveness results of teriflunomide versus a blended comparator of beta-interferons and glatiramer acetate are provided in Table B7.7.6. The weighting used in the blended comparator is illustrated in Figure B7.2.5. In addition, incremental results for each separate comparator using the base case model are shown in Table B7.7.7.

The base case results presented are probabilistic since the model is a complex non-linear model. The use of probabilistic base case results were recommended by the ERG reviewing the fingolimod STA submission [Novartis, 2011]. The corresponding deterministic results are presented in Table B7.7.7.

Due to the nature of calculating Rebif 22µg effectiveness via both the MTC base case and MTC sensitivity analysis, the associated standard error with Rebif 22µg is large and consequently both deterministic and probabilistic results for Rebif 22µg should be interpreted with caution. Furthermore, the recommended posology of Rebif is 44µg; 22µg is recommended for patients that cannot tolerate the higher dose in view of the treating specialist [Rebif SmPC]. Therefore, the results of Rebif 44µg are more relevant to the decision problem than the results of Rebif 22µg. An aggregated ICER weighted by the ratio of Rebif 44µg and Rebif 22µg is presented in Table B7.7.8 evaluating the cost-effectiveness of teriflunomide versus a weighted Rebif comparator (based on the weighted usage of Rebif 22 µg and 44 µg as shown in Figure B7.2.8).

Table B7.7.6 Probabilistic base-case results of teriflunomide versus blended comparator

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Blended comparator	[redacted]	[redacted]			
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year					

Table B7.7.7 Incremental probabilistic base-case results of teriflunomide versus all comparators

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Glatiramer acetate	[redacted]	[redacted]				
IFNβ-1a 22µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

Table B7.7.8 Probabilistic base-case results of teriflunomide versus aggregated Rebif comparator

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Rebif	[redacted]	[redacted]			
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year					

Table B7.7.9 Deterministic base-case results of teriflunomide versus blended comparator

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£) incremental (QALYs)
Blended comparator	[redacted]	[redacted]	[redacted]				
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year, LY,life year							

Table B7.7.10 Incremental deterministic base-case results of teriflunomide versus all comparators

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc costs (£)	Inc LYs	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) inc (QALYs)
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 22µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year, LY,life year								

Table B7.7.11 Deterministic base-case results of teriflunomide versus aggregated Rebif comparator

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Rebif	[redacted]	[redacted]			
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year					

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

As described in Section B7.6.2, deterministic one-way sensitivity analyses were run for the base case of teriflunomide versus a blended comparator. The results of the one-way analysis are presented in a tornado diagram in Figure B7.7.2 and Table B7.7.12.

[redacted] **Tornado diagram illustrating one-way sensitivity analysis results**

[redacted]

Table B7.7.12 One way sensitivity analysis results

		Minimum						Maximum					
	Variation	Teri cost	Teri QALY	Inc Cost	Inc QALY	ICER	INMB	Teri cost	Teri QALY	Inc Cost	Inc QALY	ICER	INMB
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]						
Blended comparator hazard ratio on disability progression	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide hazard ratio on disability progression	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blended comparator withdrawal rate	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide withdrawal rate	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease costs	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blended comparator ARR	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide ARR	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D utility	95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide proportion relapses leading to hospitalisation	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide monitoring costs	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blended comparator proportion relapses leading to hospitalisation	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator monitoring costs	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blended comparator adverse event disutility	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide adverse event disutility	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse leading to hospitalisation cost	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blended comparator administration costs	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse leading to hospitalisation disutility	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blended comparator adverse event costs	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide adverse event costs	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Caregiver disutility	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse not leading to hospitalisation cost	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse not leading to hospitalisation disutility	+/- 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INC, Incremental, ICER, Incremental cost-effectiveness ratio, Teri, teriflunomide, INMB, incremental net monetary benefit													

In addition, deterministic parameter sensitivity analysis was also performed using alternative sources of data; results are presented in Table B7.7.13.

Table B7.7.13 Deterministic parameter sensitivity analysis

Scenario	Teri total costs (£)	Teri total QALYs	Blended comp total costs (£)	Blended comp total QALYs (£)	Inc costs (£)	Inc QALYs	ICER (£) Inc (QALYs)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical data sourced from all-years, ≥80% RRMS MTC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical data sourced from all-years, ≥80% RRMS MTC excluding Bornstein et al.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural history costs from Karampampa, 2012	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse costs from Tyas, 2007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EDSS utility score from TEMSO study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of relapse from Orme, 2007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initial EDSS distribution from TOWER and TEMSO studies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Starting age and male: female ratio from TOWER and TEMSO studies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural history relapse rate from Patzold, 1982	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of relapses leading to hospitalisation from placebo arms of TEMSO study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probability of adverse events in subsequent years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

equal to adverse events in year 1							
INC, Incremental, ICER, Incremental cost-effectiveness ratio, Teri, teriflunomide, Comp, comparator							

The sensitivity of the incremental results to the clinical parameters sourced from the MTC was tested for the SA MTC of studies from all-years, rather than the base case of post-2000 with corresponding results presented in Tables B7.7.14 and B7.7.15. As discussed in Section B6.7.8, there is suggestion of substantial clinical and outcome measurement heterogeneity in one of the glatiramer acetate versus placebo studies in the all-years MTC so the impact of excluding this study from the clinical data estimates used in the model was also tested; the results are presented in Tables B7.7.15 and B7.7.16 [Bornstein et al. 1987].

Table B7.7.14 Incremental deterministic results of teriflunomide versus all comparators using sensitivity analysis MTC (all-years) for 3-month SAD, ARR and withdrawal

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc costs (£)	Inc LYs	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) Inc (QALYs)
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 22µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inc, incremental, QALY, quality adjusted life-year, LY, life year								

Table B7.7.15 Incremental deterministic results of teriflunomide versus aggregated Rebif comparator using sensitivity analysis MTC (all-years) for 3-month SAD, ARR and withdrawal

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc costs (£)	Inc LYs	Inc QALYs	ICER (£) versus baseline (QALYs)
Rebif	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inc, incremental, QALY, quality adjusted life-year, LY, life year							

Table B7.7.16 Incremental deterministic results of teriflunomide versus all comparators using sensitivity analysis MTC (all-years), excluding Bornstein et al. for 3-month SAD and sensitivity analysis MTC (all-years), including Bornstein et al. for ARR and withdrawal

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc costs (£)	Inc LYs	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) Inc (QALYs)
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 44µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a 22µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Inc, incremental, QALY, quality adjusted life-year, LY, life year

Table B7.7.17 Incremental deterministic results of teriflunomide versus aggregated Rebif using sensitivity analysis MTC (all-years) , excluding Bornstein et al. for 3-month SAD and sensitivity analysis MTC (all-years), including Bornstein et al. for ARR and withdrawal

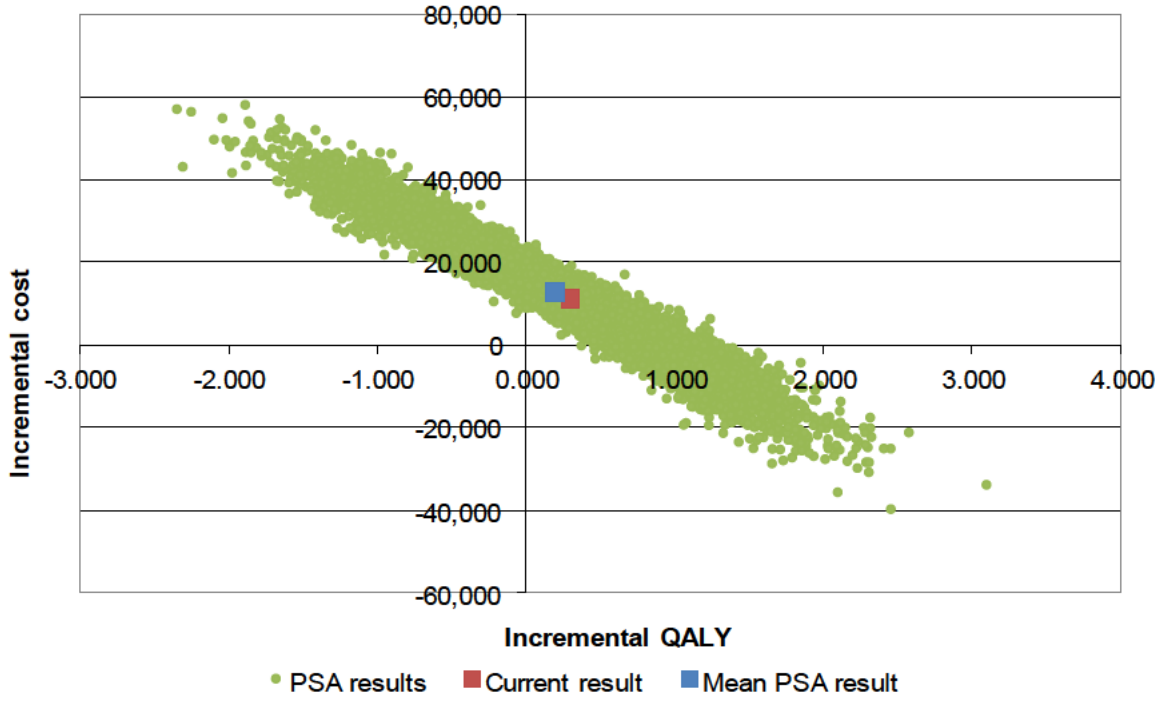
Technologies	Total costs (£)	Total LYs	Total QALYs	Inc costs (£)	Inc LYs	Inc QALYs	ICER (£) versus baseline (QALYs)
Rebif	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Inc, incremental, QALY, quality adjusted life-year, LY, life year

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

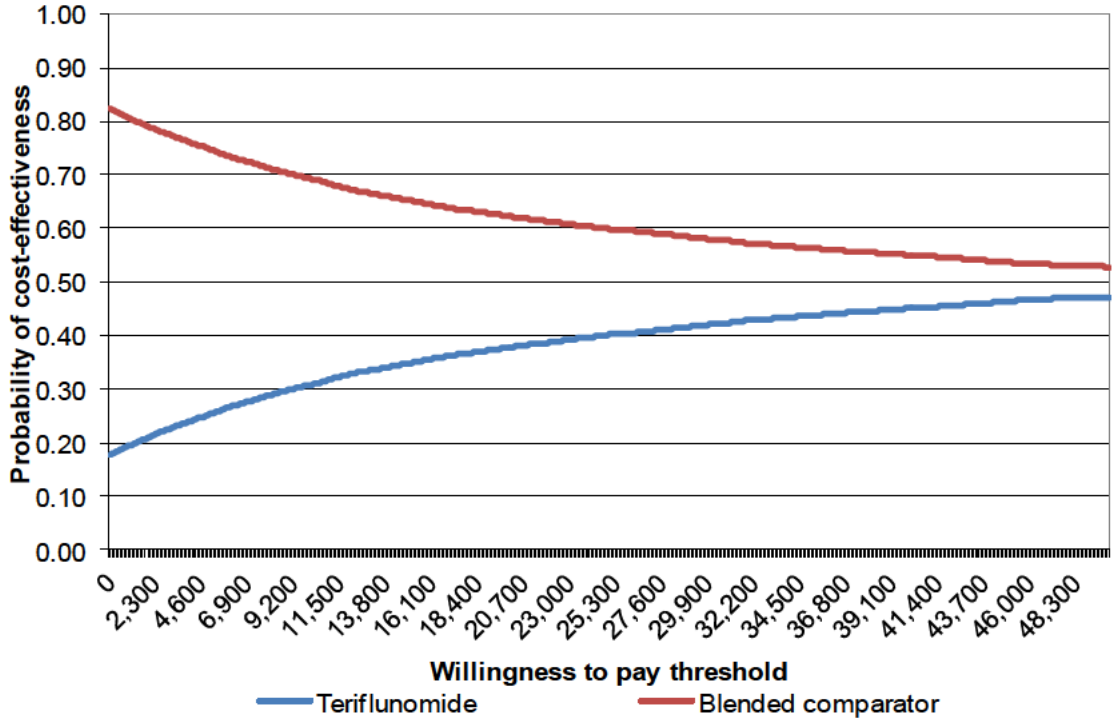
Mean results of the probabilistic sensitivity analysis with 10,000 simulations are given in Table B7.7.6 as the base case. Figure B7.7.3 shows the scatter plot of the base case PSA of teriflunomide versus the blended comparator.

Figure B7.7.3 PSA scatter plot of teriflunomide versus blended comparator



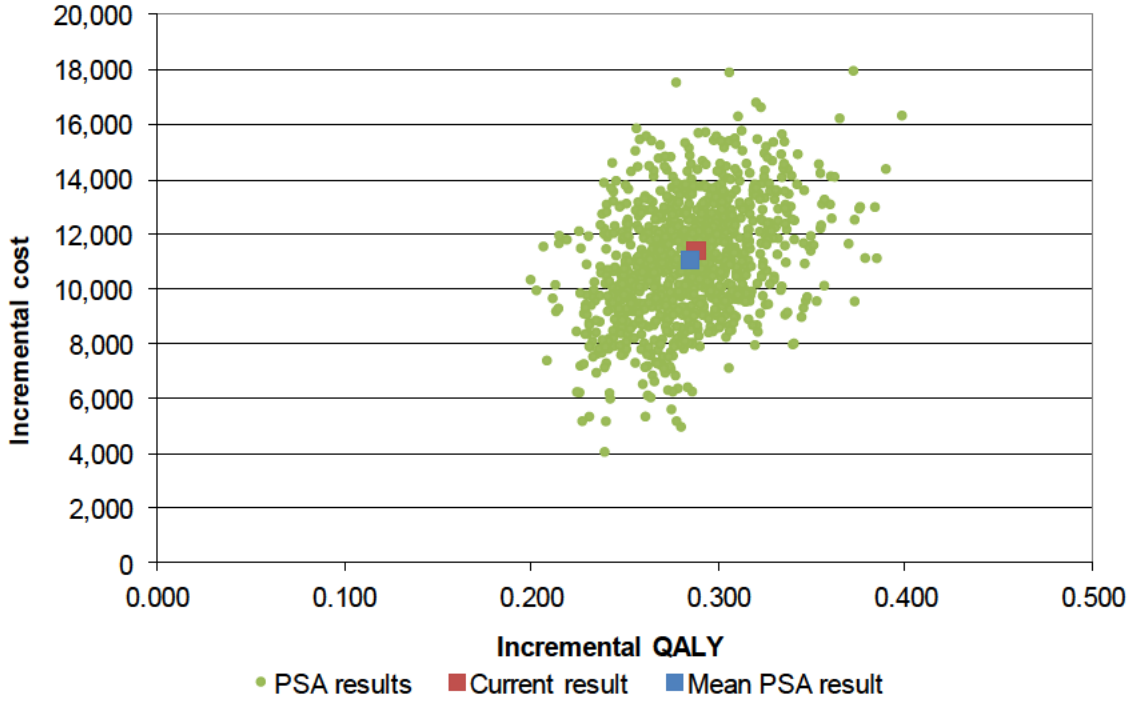
A cost-effectiveness acceptability curve (CEAC) at a willingness to pay of £20,000 is presented for the base case scenario of teriflunomide versus a blended comparator in Figure B7.7.4. The probability of teriflunomide being cost-effective at a willingness to pay of £20,000 is 38%.

Figure B7.7.4 CEAC of teriflunomide versus blended comparator



As illustrated in Figure B7.7.2, hazard ratios on disability progression are the key drivers within the cost-effectiveness model. The range of uncertainty in the probabilistic results (Figure B7.7.3) is a consequence of the relatively wide confidence intervals in hazard ratios of 3 month disability progression obtained from the MTC. Performing PSA with 1,000 simulations whilst fixing hazard ratios on disability progression results is much less variation in the cost-effectiveness of teriflunomide versus the blended comparator (Figure B7.7.5), resulting in a mean PSA ICER of £[redacted] which is much closer to the deterministic result.

Figure B7.7.5 Scatter plot of teriflunomide versus blended comparator PSA with fixed hazard ratios on 3-month disability progression scatter plot



In addition, probabilistic sensitivity analysis was conducted with incremental results against all bet-interferons and glatiramer acetate for completeness. Figure B7.7.6 shows the resulting multi-CEAC; the corresponding CEAF is presented in Figure B7.7.7 to clearly show the most probable cost-effective treatments at a willingness to pay threshold of £20,000.

Figure B7.7.6 Multi-CEAC of terilflunomide versus all beta-interferons and glatiramer acetate

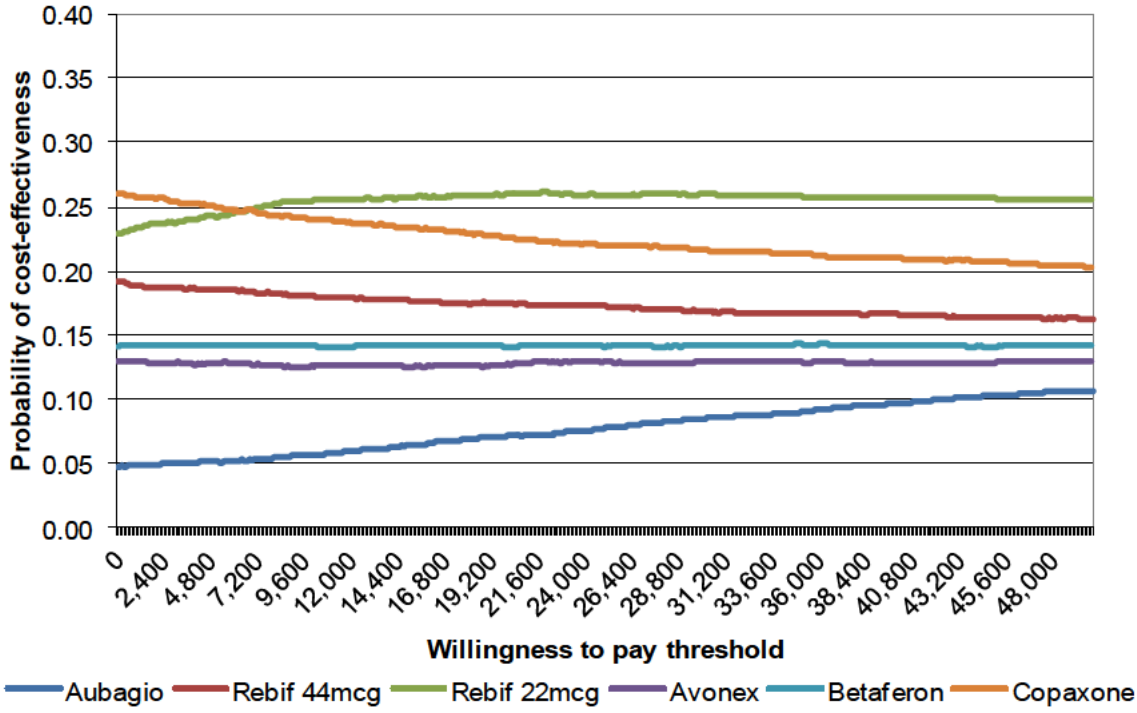
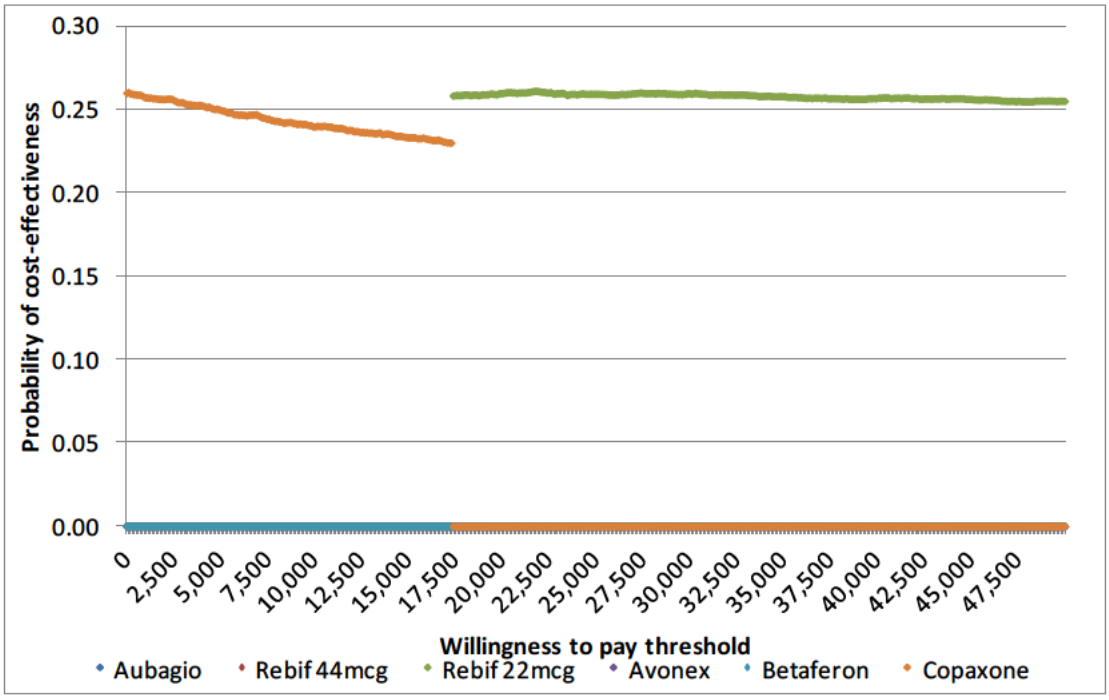


Figure B7.7.7 CEAF of teriflunomide versus all beta-interferons and glatiramer acetate



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

As described in Section B7.6.1, deterministic scenario sensitivity analyses were run with feasible treatment sequencing scenarios to reflect clinical practice (Table B7.7.18). Additionally, scenario analyses were run for the base case of teriflunomide versus a blended comparator (Table B7.7.19) and teriflunomide versus all comparators used in the treatment of SPMS (Table B7.7.20).

Table B7.7.18 Treatment sequencing scenario analysis deterministic results

Sequencing scenario (see Section B7.6.1)	Treatment sequence total costs (£)	Treatment sequence total QALYs	Comparator sequence total costs (£)	Comparator sequence total QALYs (£)	Inc costs (£)	Inc QALYs	ICER (£) inc (QALYs)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 with possible fingolimod price of £13,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 with possible fingolimod price of £11,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 with possible fingolimod price of £13,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 with possible fingolimod price of £11,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inc, incremental, QALY, quality adjusted life-year, LY, life year							

Table B7.7.19 Deterministic structural scenario analysis results of teriflunomide versus blended comparator

Scenario	Teri total costs (£)	Teri total QALYs	Blended comparator total costs (£)	Blended comparator total QALYs (£)	Inc costs (£)	Inc QALYs	ICER (£) inc (QALYs)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect reduction by 50% after 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect reduction by 25% after 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

No waning of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate of discontinuation reduction by 75% after year 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural history transition probabilities for Active RRMS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment effect on relapses or proportion leading to hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No discount rate costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No discount rate outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6% discount rate costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6% discount rate outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inc, incremental, QALY, quality adjusted life-year, LY, life year, Teri, teriflunomide							

Table B7.7.20 Deterministic structural scenario analysis results of teriflunomide versus all comparators with treatment in SPMS of licensed beta-interferons

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc costs (£)	Inc LYs	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) Inc (QALYs)
IFNβ-1a 44µg (Rebif)	[redacted]	[redacted]	[redacted]					
IFNβ-1a 22µg (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inc, incremental, QALY, quality adjusted life-year, LY, life year								

7.7.10 What were the main findings of each of the sensitivity analyses?

The deterministic sensitivity analysis results indicated that the model was most sensitive to the hazard ratio of 3-month disability progression, when using the 95% upper and lower confidence intervals from the MTC. The model was also very sensitive to the inclusion criteria applied in the derivation of MTC results in terms of disability progression, ARR and withdrawal. The impact of the wider inclusion criteria, (not limiting to post-2000 studies) needs to be interpreted in light of the increased study heterogeneity as outlined in Section B6.7.8 and Additional Appendix 2.

The model was also sensitive to: the withdrawal rate derived from the MTC; the discount rate of outcomes when using lower and upper and limits of 0% and 6%; and the use of natural disease costs from Karampampa et al. The model was slightly sensitive to discount rates in costs when varied between 0% and 6%, natural history costs, EQ-5D utilities and the ARR derived from the MTC. The model was insensitive to: adverse event disutilities; relapse costs; administration costs; monitoring costs; adverse event costs; proportion of relapses leading to hospitalisation; caregiver relapse disutility' and published sources for relapse costs and disutility.

The probabilistic results show there was significant correlation between costs and outcomes. The corresponding CEAC show that there was a higher probability of the blended comparator being more cost-effective than teriflunomide.

The scenario analyses with treatment sequencing showed that modelling a realistic treatment pathway incurs more costs but also more QALYs. The patient would receive treatment for longer, as following withdrawal from the first treatment, they would move to another DMT rather than BSC, which meant they will incur greater costs of drugs, monitoring and adverse events but would receive the benefit of slowed disability progression and reduced number of relapses. The ICER increased in each of the treatment sequencing scenarios.

Applying assumptions to the duration of treatment effect also had relatively little impact on the cost-effectiveness results. This would suggest extrapolation of the clinical outcomes over the full time horizon of the model was a reasonable assumption. Using natural history transitions for active RRMS patients lowers the ICER of teriflunomide versus blended comparator. Assuming no treatment effect on relapses to avoid double-counting has virtually no effect on the ICER. Including treatment within SPMS populations for licensed indications favours teriflunomide (Table B7.7.15).

7.7.11 What are the key drivers of the cost-effectiveness results?

As discussed in Section B7.7.10, the model was most sensitive to the hazard ratios of disability progression sourced from the MTC. The ICER ranged from approximately £5,000 to £559,000 when using the upper and

lower 95% confidence intervals of disability progression. The effect of fixing hazard ratios on disability progression within the PSA is explored in Section B7.7.8

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Quality assurance of the model included two independent health economists involved in the design and build, as well as clinical expertise ratifying plausibility of results. The model outputs have been compared to published literature to validate outputs (see Section B7.7.1); although differences were observed there were reasonable justifications particularly in terms of the variation in severity of observed versus modelled cohort.

7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section B6.3.7.

Subgroup analyses were undertaken to align with the requirements of the NICE scope. A comparison of teriflunomide vs. fingolimod in HAD and teriflunomide vs. natalizumab in RES were performed.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

HAD and RES have been defined in Sections B6.3.7 and B6.10.3. For HAD, only the TEMSO study recorded patients who had at least one relapse within one year before randomization, and with previous DMT intake (only Interferon) for at least 12 months, gap from last DMT to randomisation lower or equal to 12 months, and at least one gadolinium-enhanced lesion at baseline. For RES, only the TEMSO study recorded patients who had at least two relapses within one year before randomization, and at least one gadolinium-enhanced lesion at baseline.

7.9.3 Please describe how the statistical analysis was undertaken.

Indirect comparisons were performed to determine the relative effectiveness of teriflunomide, fingolimod and natalizumab for the respective subgroups.

Teriflunomide was associated with a ARR of [redacted] and a 3-month SAD HR of [redacted] compared to placebo; the large confidence intervals was due to the fact that only 11 (3%) had HAD as defined by NICE [Sanofi, 2013]. Fingolimod was associated with a ARR of 0.57 [0.28-1.16] and a 3-month SAD HR of 0.69 [0.25-1.89] based on the EPAR subgroup analysis considering patients who had at least one relapse within one year before randomization, had a MS drug for at least 6-months, were still on treatment in the year before starting study drug and at least [Gilenya EPAR, 2005]. Discontinuation was unavailable for fingolimod and consequently the probability of withdrawal with fingolimod and teriflunomide were assumed to be the same as the RRMS MTC.

Teriflunomide was associated with a ARR [redacted] and a 3-month SAD HR [redacted] compared to placebo; the large confidence intervals was due to the fact that only 33 (9%) had HAD as defined by NICE [Sanofi, 2013]. Natalizumab was associated with a ARR of 0.81 [0.70-0.88] and a 3-month SAD HR of 0.47 [0.24-0.93] based on the NICE manufacturers submission considering patients who had at least two relapses within one year before randomization, and at least one GAD lesion at baseline [Biogen, 2006]. Discontinuation was unavailable for natalizumab and consequently the probability of withdrawal with natalizumab and teriflunomide were assumed to be the same as the RRMS MTC.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section B7.7.6 (Base-case analysis).

As discussed in Section 7.7.6, the most appropriate results to present as the base case are probabilistic rather than deterministic. Stochastic hazard ratios used to obtain the results presented in Section 7.7 were sampled using a gamma distribution. Due to the large beta derived from the HAD 3-month SAD confidence interval detailed in Section B7.9.3, values could not be sampled from the gamma distribution and consequently a lognormal distribution was used to sample variation in hazard ratios for HA disease. The probabilistic results of the HA cost-effectiveness analysis are presented in Table B7.9.1.

The RES subgroup analysis was performed using the same variation in parameters as the RRMS analysis. The probabilistic results of the RES subgroup analysis are presented in Table B7.9.2.

Table B7.9.1 Subgroup results for HA RRMS

Treatment	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Teriflunomide	[redacted]	[redacted]			
Possible Fingolimod PAS price of £11,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Possible Fingolimod PAS price of £13,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod list price	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table B7.9.2 Subgroup results for RES RRMS

Treatment	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Teriflunomide	[redacted]	[redacted]			
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

All populations mentioned in the NICE scope were considered in this STA. Hence, no obvious subgroups were not considered.

7.10 Interpretation of economic evidence

7.10.1 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?

N/A. No published literature for the cost-effectiveness of teriflunomide.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes.

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

Table B7.10.1 Strengths and limitations of the evaluation

Strength	Limitation
• The model is based on the model developed by ScHARR to assess the cost effectiveness of beta-interferons • The ScHARR model was also used in STA submissions for fingolimod and natalizumab and accepted by NICE [Novartis, 2011; Biogen, 2006]	
• Treatment sequencing has been incorporated into the model structure to model scenarios reflective of clinical practice	• The model has become more complex
• Clinical parameters have been derived from comprehensive MTC	• MTC did not include all clinical parameters for Rebif 22µg • HAD and RES subgroup clinical parameters were derived from indirect comparisons
	• London Ontario data set has been used which has a number of limitations; however, it was the best source available at time of analysis

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

None.

Section C – Implementation

8 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.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Teriflunomide (Aubagio) is licensed for the treatment of relapsing-remitting multiple sclerosis (RRMS) in adult patients [Teriflunomide SmPC, 2013]. Specifically, the target populations for teriflunomide are patients with previously untreated RRMS (treatment-naïve) and patients with RRMS who have experienced a lack of tolerability on another disease-modifying therapy DMT (treatment-experienced).

As detailed in Section A2.2, there are approximately 89,000 MS patients in England and Wales [MS Trust, 2012; ONS, 2012]. It is estimated that 35.5% of MS patients will be diagnosed with RRMS [Kobelt et al. 2006]. Therefore, the estimated prevalence of patients with RRMS in England and Wales in 2013 will be a 31,512. Of the prevalent RRMS patients, 31% will be prevalent treated or treated within the last 12 months (treatment-experienced), and could potentially receive teriflunomide [Zajicek et al. 2010]. It is estimated that 20% of patients eligible to receive a DMT will be resistant to treatment with injectables and therefore receive no treatment (treatment-naïve) [Genzyme KOL Advisory board report, 2011]. However, since teriflunomide is an oral treatment, these patients are eligible to be treated. Therefore, the 9769 treatment-experienced patients make up only 80% of the population eligible to receive a DMT. The 20% of patients resistant to treatment with injectables (treatment-naïve) are therefore calculated as 25% of the 80% treatment-experienced. Table C8.1 provides full details of assumptions regarding eligible patient populations.

Table C8.1 Derivation of patient populations eligible for treatment with teriflunomide

	Percentage	Number	Reference
Prevalence of multiple sclerosis (MS)	0.16%	88766	[MS Trust, 2012; ONS, 2012]
Number with relapsing remitting MS (RRMS)	35.5%	31512	[Kobelt et al. 2006]
Prevalent treated / treated in previous 12 months	31%	9769	[Zajicek et al. 2010]
Assumed patients not receiving drug treatment because they are resistant to receiving injectable treatments as a ratio of those receiving drug treatment	25%	2442	[Genzyme KOL advisory board report, 2011]

The greatest uncertainty regarding treatment uptake relates to patients, who in the absence of teriflunomide, would be untreated with a DMT. A range of potential uptake values are therefore provided for those who in the absence of teriflunomide would not receive treatment group. The higher end of this range assumes uptake in this group equals uptake in patients where teriflunomide substitutes for an alternative treatment; the lower end of the range equates an uptake of 25% of the the substituting for alternative treatment group.

The sum of these two groups are combined with estimated market uptake to give the total estimated patients eligible for teriflunomide (Table C8.2). Given that NICE will be assessing the evidence for teriflunomide from June 2013, it is assumed in 2013 there would be negligible market uptake. Assuming a [redacted] equal market uptake for both groups in 2014 (Year 1), [redacted] patients would be eligible for treatment with teriflunomide, and by 2018 (Year 5) market uptake would increase to [redacted] resulting in [redacted] patients eligible for treatment with teriflunomide. At the lower end of the market uptake range [redacted] market uptakes for the two groups respectively in 2014 (Year 1), 311 patients would be eligible for treatment with teriflunomide, and by 2018 (Year 5) market uptake would increase to [redacted]% [redacted]% respectively, resulting in [redacted] patients eligible for treatment with teriflunomide.

Table C8.2 Derivation of patient numbers expected to be treated with teriflunomide

	2013	**2014**	**2015**	**2016**	**2017**	**2018**
Total patients who could potentially receive teriflunomide, who in its absence would receive a different DMT drug	9769	9769	9769	9769	9769	9769
% uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with teriflunomide who in its absence would receive a different DMT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Total patients estimated to not be on treatment because resistant to injectable treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower range of % uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower range of patients treated with teriflunomide who in its absence would receive no treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower range of total estimated patients who would receive teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper range of % uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper range of patients treated with teriflunomide who in its absence would receive no treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper range of total estimated patients who would receive teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimated patient numbers are not presented separately for patients with RES disease that might receive teriflunomide in place of natalizumab nor those where teriflunomide might substitute fingolimod in patients that have failed to respond to a full course of interferon treatment (where fingolimod is used in line with its license / NICE guidance). Although the NICE Final Scope for teriflunomide does detail fingolimod and natalizumab as relevant comparators in these subgroups, clinical opinion supports the view that use in such populations would be negligible.

It is recognised that teriflunomide uptake will be from both incident and prevalent patients but a simplified approach was taken to model uptake from prevalent patients only. Such a simplified approach has been used by NICE in its costing template for fingolimod [NICE, 2012(b)].

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

The relevant direct comparators for teriflunomide are beta-interferons and glatiramer acetate as illustrated in the NICE Final Scope (see also Section 7.2.7). The market share of beta-interferons and glatiramer acetate has been sourced to be consistent with the blended comparator used in the cost-effectiveness analysis (see Section 7.2.7) and is assumed not to change over the next 5 years. The comparators within subgroups are natalizumab (for patients with RES RRMS) and fingolimod (for patients with HA RRMS who have received treatment with

beta-interferon). Furthermore, it is assumed that 20% of RRMS patients eligible for disease-modifying treatment are intolerant to injectibles and are therefore not receiving any disease-modifying treatment.

8.3 What assumption(s) were made about market share (when relevant)?

Market share for the treatment-experienced population (who in the absence of teriflunomide would receive a DMT) was assumed to be [redacted] years 3 to 5. As discussed in C8.1, there is significant uncertainty associated with the market uptake in otherwise untreated patients (who in the absence of teriflunomide would received no DMT) so a range of market shares have been assessed. The market shares of the otherwise untretaed population vary between 25% and 100% of the market shares of the substituting for an alternative treatment population.

8.4 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).

In addition to the differences in technology acquisition costs between teriflunomide and comparators, there are savings in administration costs and adverse event costs but additional costs from monitoring. These costs are in line with those used in the cost-effectiveness analysis (see Section B7.5.1).

The average cost of the UK Risk-sharing scheme (RSS) displaced treatments when split between the market shares is £7,712 (see Table C8.3). The anticipated annual acquisition cost of teriflunomide is £13,529, resulting in an additional cost of £5,817 per patient per year.

Table C8.3 Acquisition costs associated with beta-interferons and glatiramer acetate

Treatment	Annual cost	% split	Reference
IFNβ-1a (Avonex)	£8,502	29%	[DoH HSC 2002/004]
IFNβ-1b (Betaferon)	£7,259	9%	[DoH HSC 2002/004]
Glatiramer acetate	£5,823	23%	[DoH HSC 2002/004]
IFNβ-1a 44µg (Rebif)	£8,942	23%	[DoH HSC 2002/004]
IFNβ-1a 22µg (Rebif)	£7,513	14%	[DoH HSC 2002/004]
IFNβ-1b (Extavia)	£7,259	2%	[BNF Extavia, 2013]

There are no administration costs associated with teriflunomide since it is assumed no resource use is associated with the administration of oral treatments. As detailed in Table C8.4, administration costs of displaced

treatments split by market share are £174 per patient in the first year and £0 in subsequent years resulting in a saving of £174 per patient in year 1 when using teriflunomide rather than current practice.

Treatment with teriflunomide requires slightly greater monitoring resource in terms of additional liver function tests and full blood counts required as per the SmPC [Teriflunomide SmPC, 2013]. As detailed in Table C8.5, monitoring costs of displaced treatments when split between the market shares were £351 per patient in year 1 and £345 per patient in each subsequent year. The monitoring costs for teriflunomide were £407 per patient in year 1 and £368 per patient in each subsequent year resulting in additional costs of £56 in year 1 and £24 in each subsequent year when using teriflunomide rather than current practice.

Table C8.4 Administration costs associated with teriflunomide, beta-interferons and glatiramer acetate

Treatment	Treatment regimen	Resource use Year 1	Resource use Subsequent years	Year 1	Assumptions / reference
Teriflunomide	Once daily in oral form	None	None	£0	No resource use associated with administration of oral treatments
Beta-interferon	Self-injection	3 hours required for nurse to teach self-administration	None	£174	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)
Glatiramer acetate	Self-injection	3 hours required for nurse to teach self-administration	None	£174	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)

Table C8.5 Monitoring costs associated with teriflunomide, beta-interferons and glatiramer acetate

	Liver function test	Full blood count	Neurology visit	Total Cost
Unit Cost	£1.23	£3.09	£169.00	
Reference	NHS Reference costs 2011-12, Pathology services, Biochemistry DAP841	NHS Reference costs 2011-12, Pathology services, Haematology [Excluding Anti-Coagulant Services] DAP823	NHS Reference costs 2011-12, Outpatient Attendances, Neurology 400	
Teriflunomide (year 1)	16	16	2	£407.12
Beta-interferons (year 1)	4	4	2	£355.28

Glatiramer acetate (year 1)	0	0	2	£338.00
Teriflunomide (subsequent years)	7	7	2	£368.24
Beta-interferons (subsequent years)	2	2	2	£346.64
Glatiramer acetate (subsequent years)	0	0	2	£338.00

The costs incurred through the treatment of adverse events associated with teriflunomide are lower than the costs of treating adverse events of beta-interferons and glatiramer acetate as shown in Table C8.6. The costs of treating adverse events are estimated per patient and were adjusted for probability of occurrence. The costs of treating adverse events of displaced treatments when split between the market shares were £5.72 in year 1 and £5.44 in subsequent years. The average costs of treating the adverse events associated with teriflunomide were £4.88 in year 1 and £4.03 in subsequent years. Therefore, treatment with teriflunomide results in a saving per patient of £0.84 in year 1 and £1.41 in subsequent years.

Table C8.6 Costs associated with the treatment of adverse events from with teriflunomide, beta-interferons and glatiramer acetate

Drug	Year 1	Subsequent years	Source
Teriflunomide	£4.88	£4.03	See Table 7.3.18 and 7.5.4
IFNβ-1a (Avonex)	£3.71	£3.71	See Table 7.3.18 and 7.5.4
IFNβ-1b (Betaferon)	£5.68	£3.13	See Table 7.3.18 and 7.5.4
Glatiramer acetate	£3.05	£3.05	See Table 7.3.18 and 7.5.4
IFNβ-1a 44µg (Rebif)	£9.46	£9.46	See Table 7.3.18 and 7.5.4
IFNβ-1a 22µg (Rebif)	£8.19	£8.19	See Table 7.3.18 and 7.5.4
IFNβ-1b (Extavia)	£5.68	£3.13	Assumed same as Betaferon
Average adverse event costs of displaced medicines	**£5.72**	**£5.44**	

8.5 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?

Unit costs of treatment were sourced from the UK Risk-sharing scheme and the British National Formulary [DoH HSC 2002/004; BNF Extavia, 2013]. Administration and monitoring costs were sourced from National reference costs and the PbR tariff. See Section B7.5.1 for details.

8.6 Were there any estimates of resource savings? If so, what were they?

As described in section 8.3, teriflunomide requires no resource in training patients to administer treatments as it is an oral treatment. This resulted in a cost saving of £174 per patient. Furthermore, there are resource savings included within the cost savings associated with adverse events which largely comprise MS nurse and GP consultations.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

As illustrated in Tables C8.7 and C8.8, the estimated budget impact in England and Wales may range between [redacted] in 2014 (Year 1) and is anticipated to increase up to between [redacted] in 2018 (Year 5), depending on uptake in treatment-naïve patients.

Table C8.7 Lower net budget impact of introducing teriflunomide into England and Wales

	2013	2014	2015	2016	2017	2018
Patients treated with teriflunomide who in its absence would receive a different DMT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assumed uptake from those receiving an interferon or glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (acquisition, administration and monitoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients treated with teriflunomide who in its absence would receive no treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assumed uptake from those receiving no treatment at present	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (acquisition, administration and monitoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total net drug budget cost associated with teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table C8.8 Upper net budget impact of introducing teriflunomide into England and Wales

	2013	2014	2015	2016	2017	2018
Patients treated with teriflunomide who in its absence would receive a different DMT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assumed uptake from those receiving an interferon or glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (acquisition, administration and monitoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with teriflunomide who in its absence would receive no treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assumed uptake from those receiving no treatment at present	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (acquisition, administration and monitoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total net drug budget cost associated with teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No opportunities for additional savings have been identified.

9 References

Please use a recognised referencing style, such as Harvard or Vancouver.

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