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Comparative Clinical and Cost-Effectiveness of Drug Therapies for Relapsing-Remitting Multiple Sclerosis

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Note regarding changes to the report following stakeholder feedback:
Following feedback received in response to the previous draft of this report, several modifications were made to the text and data tables. These modifications were minor changes and did not alter the results of the main analyses or the conclusions of the report. The most notable changes to the report include: addition of the results of subgroup analyses from the CONFIRM study, updates to the prices of the RRMS treatments, change in the probabilistic distribution of utilities from log-normal to beta, modification of the discontinuation rate in the base-case economic model from 10% to 15% annually, the addition of a value of information analysis, the addition of exploratory sensitivity analyses examining different discontinuation rates for orals versus injectables, and sensitivity analyses regarding the natural history of the disease.

Note regarding changes to the report following posting in October 2013:
In March 2014, minor punctuation corrections were made on page ix in the second bullet under “Key Findings of the Economic Analysis.” These modifications did not alter the results of the main analyses or the conclusions of the report.

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). It was prepared with the advice and assistance of economic, methodological, and clinical experts, and is a comprehensive review of the public literature available to CADTH.

Canadian Agency for Drugs and Technologies in Health

Comparative Clinical and Cost-Effectiveness of Drug Therapies for Relapsing-Remitting Multiple Sclerosis

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Authorship

Khai Tran wrote the protocol for the clinical review, selected and extracted data from included studies, designed and conducted the systematic review and meta-analysis, and wrote the clinical sections of the report.

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Anita G. Carrie assisted in the interpretation of results of pairwise and network meta-analyses, and assisted in the writing and editing of the clinical sections of the report.

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ABBREVIATIONS

ARR	annualized relapse rate
CI	confidence interval
CIS	clinically isolated syndrome
CrI	credible interval
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
EVPPI	expected value of partial perfect information
GdE	gadolinium-enhancing
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
IFN	interferon
ITT	intention to treat
JC Virus	John Cunningham virus
MCS	Mental Component Summary
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
NMA	network meta-analysis
OR	odds ratio
PML	progressive multifocal leukoencephalopathy
PPMS	primary-progressive multiple sclerosis
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PRMS	progressive-relapsing multiple sclerosis
QALY	quality-adjusted life-year
RCTs	randomized controlled trial
RR	relative risk
RRMS	relapsing-remitting multiple sclerosis
ScHARR	School of Health and Related Research
SIP	Sickness Impact Profile
SPMS	secondary-progressive multiple sclerosis
VAS	visual analogue scale

EXECUTIVE SUMMARY

Context and Policy Issues

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system[1] that is more common in women than in men, by a factor of approximately 3:1.[2,3] Canada has the fifth-highest worldwide prevalence at 240 per 100,000 persons.[4]

MS is classified into four subtypes, with approximately 85% to 90% of MS patients having the relapsing-remitting type of MS (RRMS).[5] In MS, the frequency of relapse is highly variable, but tends to be more frequent in the first few years of disease onset.[5] The therapeutic aims of MS drugs are to lower the frequency of relapses, decrease the lasting effects of relapses, prevent or decrease disability that is the result of disease progression, and promote tissue repair.[1,6]

In Canada, the earliest available disease-modifying treatments for MS include interferons (interferon beta-1a and interferon beta-1b) and glatiramer acetate, approved by Health Canada in the 1990s. Natalizumab, administered via intravenous infusion, was approved by Health Canada in 2006 for the treatment of RRMS; however, there are some safety concerns regarding natalizumab because of its association with progressive multifocal leukoencephalopathy (PML), a rare demyelinating neurological disorder caused by the reactivation of the JohnCunningham virus (JC Virus).[7,8] More recently, fingolimod — the first oral agent for the treatment of RRMS — was approved by Health Canada in 2011. Patients express a desire for oral agents over injectables; however, the price of fingolimod is considerably higher than that of either the interferons or glatiramer acetate and this drug has not been considered to be cost-effective in all patients studied. In addition, Health Canada monographs for both natalizumab and fingolimod indicate that these agents are generally recommended for patients with inadequate response or intolerance to other therapies for MS.

Dimethyl fumarate, a new oral agent, was approved by Health Canada for the treatment of RRMS during the undertaking of this systematic review in 2013. In addition, a number of new disease-modifying therapies (both oral and injectable) for the treatment of MS are in development. These include alemtuzumab (injectable) and teriflunomide (oral), which are soon expected to enter the Canadian market.

The effectiveness and safety of available MS treatments, relative to other active comparators, are not well-established. The emergence of novel oral and injectable agents necessitates consideration of their place in therapy, including the potential for combination therapy. Thus, the comparative clinical and cost-effectiveness of currently available and emerging disease-modifying agents for RRMS, both alone and in combination, need to be determined.

Objectives

The objective of this Therapeutic Review was to conduct a systematic review to assess the comparative clinical and cost-effectiveness of drug therapies for the treatment of RRMS, based on the following research questions:

1. What is the comparative efficacy and safety between individual disease-modifying agents in RRMS?
2. What is the comparative cost-effectiveness between individual disease-modifying agents in RRMS?
3. What is the comparative efficacy and safety of combination therapy (two or more disease-modifying agents compared with individual agents or other combinations) in RRMS?

4. What is the comparative cost-effectiveness of combination therapy (two or more disease-modifying agents compared with individual agents or other combinations) in RRMS?

Methods

Randomized controlled trials (RCTs) of pre-specified disease-modifying agents in RRMS were identified through electronic databases, grey literature, and stakeholder consultation. Two reviewers independently screened the titles and abstracts and independently evaluated the full-text publications for final article selection. RCTs were considered for inclusion if they compared at least two of the drug therapies under review and reported outcomes related to clinical efficacy and safety, as pre-specified in the review protocol. Drug therapies specified in the protocol included interferon beta-1a and interferon beta-1b, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, and alemtuzumab. For drug therapies currently approved by Health Canada for the treatment of RRMS, only approved formulations and doses were included. Drug therapies not yet approved by Health Canada for the treatment of RRMS were not restricted to specific doses or formulations. Outcomes specified in the review protocol included relapse, disability, magnetic resonance imaging (MRI) changes, quality of life, mortality, adverse events, serious adverse events, and withdrawal because of adverse events.

Direct pairwise meta-analyses were conducted for all outcomes where statistical heterogeneity was deemed sufficiently low, using Review Manager 4.2 software. Indirect comparisons were made using Bayesian network meta-analyses (NMAs), using WinBUGS software for outcomes for which sufficient data were available to form stable networks; specifically, annualized relapse rate (ARR) and proportion of patients with sustained disability progression, based on Poisson and binomial distributions, respectively. Sensitivity analyses were conducted through a series of meta-regression and subgroup analyses to explore potential sources of heterogeneity.

An economic model was developed in the form of a cost-utility analysis. The primary outcome was the number of quality-adjusted life-years (QALYs), with treatments compared in terms of the incremental cost per QALY (incremental cost-utility ratio [ICUR]).Treatment effect estimates were obtained from the CADTH systematic review of clinical evidence. Other inputs for the model were derived from published sources and clinical experts' opinions. Drug costs for agents available in Canada were obtained from the Ontario Drug Benefit Formulary (2013) or directly from manufacturers. For drugs for which pricing in Canada was not available at the time the analyses were conducted, information was obtained from US pricing, where the ratio of prices for the new agents compared with existing treatments was calculated and used to determine the hypothetical price for the new drugs, or assumptions were made. Extensive sensitivity analyses were conducted to test the effect of changes in underlying parameter values (parameter uncertainty) and assumptions within the models (structural uncertainty).

This report was peer-reviewed by methodologists, MS clinical experts, and health economists.

Patient Input

The Multiple Sclerosis Society of Canada provided input relevant to the Therapeutic Review, based on its online survey. Progression of disability and frequency of relapse were the symptoms that were most frequently stated by patients as being important to control, and these outcomes were included in the present systematic review and economic analyses. A number of symptoms common to MS that patients indicated had major impacts on their lives — such as fatigue, difficulty walking, and memory and attention problems — could not be captured in the systematic review or economic analyses because of a general lack of reporting from the included trials. However, they were captured through the patient input with regards to multiple

impacts these symptoms have in the lives of people living with MS (i.e., work, sleep, school, socialization, mobility, living independently, driving a car, self-care, family relationships, and recreational activities).

Patients expressed a desire for oral agents over injectables. Their preference stems from a variety of reasons, including anxiety associated with needles, issues with rotation of sites, inability to use a needle because of coordination issues, side effects (injection site reactions, lipoatrophy, and bruising on the skin), and inconvenience with refrigeration/travel. Patients noted that having options that match a person's life and situation are important considerations.

Key Findings of Systematic Review

The systematic review included 30 individual RCTs.[9-38] Twenty-seven trials provided monotherapy comparisons,[9-35] and four trials provided comparisons between monotherapy and combination therapy.[35-38]

Monotherapy

Evidence was available for the following drug therapies: alemtuzumab (three RCTs), dimethyl fumarate (two RCTs), fingolimod (three RCTs), glatiramer acetate (eight RCTs), interferon beta-1a subcutaneous (nine RCTs), interferon beta-1a intramuscular (nine RCTs), interferon beta-1b (five RCTs), natalizumab (one RCT), and teriflunomide (two RCTs). NMAs were conducted only for those outcomes for which sufficient data were available to allow for a stable network, ARR, and proportion of patients with sustained disability. For the remaining outcomes, direct pairwise results only are presented.

Direct evidence

- Compared with placebo, all active treatments (excepting alemtuzumab and interferon beta-1a 60 mcg, for which there were no placebo-controlled trials) resulted in statistically lower ARRs; rate ratios (95% confidence intervals [CI]) ranged from 0.32 (0.27, 0.37) for natalizumab to 0.81 (0.67, 0.96) for interferon beta-1a 30 mcg. Among active comparisons, ARRs were statistically lower for interferon beta-1b 250 mcg (0.69 [0.54 to 0.87]), interferon beta-1a 44 mcg (0.76 [0.59 to 0.98]), and fingolimod (0.49 [0.38 to 0.63]) compared with interferon beta-1a 30 mcg. In addition, ARRs were statistically lower for alemtuzumab at both 12 mg (0.44 [0.34 to 0.55]) and 24 mg (0.22 [0.14 to 0.35]) compared with interferon beta-1a 44 mcg, and for dimethyl fumarate (0.76 [0.62 to 0.93]) compared with glatiramer acetate.
- Compared with placebo, all active treatments exhibited a numerically lower risk of sustained disability progression, but results were only statistically significant for interferon beta-1a (both 44 mcg and 30 mcg), natalizumab, fingolimod, teriflunomide 14 mg, and dimethyl fumarate; relative risk (95% CI) for these agents ranged from 0.59 (0.46 to 0.75) for natalizumab to 0.74 (0.57 to 0.96) for teriflunomide 14 mg. Among active comparisons, the risk of sustained disability progression was statistically lower for alemtuzumab at both 12 mg (0.59 [0.40 to 0.86]) and 24 mg (0.42 [0.21 to 0.84]) compared with interferon beta-1a 44 mcg, and for interferon beta-1b 250 mcg (0.44 [0.2 to, 0.80]) compared with interferon beta-1a 30 mcg.
- Among active comparisons, MRI findings were more favourable for alemtuzumab compared with interferon beta-1a 44 mcg; and more favourable for all three of fingolimod, interferon beta-1b 250 mcg, and interferon beta-1a 44 mcg compared with interferon beta-1a 30 mcg. Compared with glatiramer acetate, dimethyl fumarate resulted in a statistically lower mean number of T2 lesions, but the mean number of gadolinium-enhancing (GdE) lesions was not statistically different between these two treatments.

- Health-related quality of life findings were reported in only two trials, and the clinical significance of reported results was uncertain.
- The incidence of serious adverse events and treatment discontinuation did not differ statistically between treatments in the majority of trials, excepting a higher incidence of treatment discontinuation for interferon beta-1a 44 mcg compared with both placebo and alemtuzumab 12 mg. Adverse events of note were treatment-specific and included influenza-like symptoms for interferons, injection site reactions and hypersensitivity for glatiramer acetate, cardiovascular disorders for fingolimod, infusion reactions and skin disorders for natalizumab, flushing for dimethyl fumarate, thyroid disorders for alemtuzumab, and alopecia for teriflunomide.

Indirect evidence

- There was considerable agreement between direct and indirect evidence for the outcome of ARR. Based on the NMA, alemtuzumab and natalizumab had the greatest activity, reducing the ARR by approximately 70% compared with placebo. Fingolimod and dimethyl fumarate had similar activity to each other, reducing the ARR by approximately 50% compared with placebo. Finally, subcutaneous interferons, glatiramer acetate, and teriflunomide appear to have similar activity to each other, reducing the ARR by approximately 30% compared with placebo. Intramuscular interferon beta-1a had the lowest activity of all active agents.
- Compared with placebo, all treatments exhibited a trend toward a reduced risk of sustained disability progression. Estimated effect sizes were greatest for alemtuzumab and natalizumab, followed by dimethyl fumarate and interferon beta-1b, and lowest for interferon beta-1a, glatiramer acetate, and teriflunomide. However, credible intervals were wide and there was considerable overlap of credible intervals among all agents, resulting in unclear distinction between treatments.

Combination Therapy Versus Monotherapy

One RCT provided evidence for each of the following comparisons in treatment-experienced patients: natalizumab plus interferon beta-1a 30 mcg versus interferon beta-1a 30 mcg, natalizumab plus glatiramer acetate versus glatiramer acetate, and teriflunomide plus interferon beta versus interferon beta. One additional RCT in treatment-naive patients compared interferon beta-1a 30 mcg plus glatiramer acetate to both agents alone.

- Compared with interferon beta-1a 30 mcg alone, natalizumab plus interferon beta-1a 30 mcg resulted in a statistically lower ARR and a lower proportion of patients with sustained disability progression during the two-year trial. Two patients in this trial developed PML.
- The two studies comparing natalizumab plus glatiramer acetate versus glatiramer acetate alone, and teriflunomide plus interferon beta versus interferon beta alone reported no improvements in measures of relapse or disability with combination therapy; however, both 24-week trials did report more favourable MRI findings with combination therapy.
- The combination of glatiramer acetate plus interferon beta-1a 30 mcg was not superior to either agent alone for most outcomes over the three-year trial, with the exception of a lower ARR for patients treated with the combination compared with interferon beta-1a alone.
- There were no apparent differences between combination therapy and monotherapy in the incidence of death, serious adverse events, and discontinuation of treatment because of adverse events in the reviewed trials.

Key Findings of Economic Analysis

- The base case analysis included only treatments for which regulatory approval has been granted. Compared with no treatment, the base case results show that treatment with any of the interferon therapies, glatiramer acetate, or dimethyl fumarate dominates no treatment; i.e., treatment is less costly and more effective than no treatment. The ICUR of fingolimod versus no treatment is $18,234, and the ICUR of natalizumab versus no treatment is $121,456.
- With respect to comparative cost-effectiveness of the treatments, glatiramer acetate was likely to be the most cost-effective treatment choice, assuming a decision-maker willingness-to-pay threshold is lower than $118,242 per QALY. For willingness to pay between $118,242 and $425,655, interferon beta-1b 250 mcg (Extavia) is the cost-effective treatment. For willingness to pay between $425,655 and $872,972, dimethyl fumarate is the cost-effective treatment. If willingness to pay is above $872,972, then natalizumab is the cost-effective treatment. Interferon beta-1b 250 mcg (Betaseron) was dominated by interferon beta-1b 250 mcg (Extavia); interferon beta-1a 44 mcg was dominated by interferon beta-1b 250 mcg (Extavia), dimethyl fumarate, and glatiramer acetate; and all other interferon therapies were dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate, as they produced fewer QALYs at a higher cost. Fingolimod was dominated by dimethyl fumarate.
- Based on the sensitivity analyses that were conducted on the model input parameters and the structural uncertainty, the cost-effectiveness results were robust to variations in model inputs and assumptions. Although ICURs did vary, none of these analyses, with the exception of cost per treatment, changed the conclusions of the analysis.

Strengths and Limitations

Strengths of the current review include its systematic approach to collecting evidence, performing data extraction, quality assessment, and analysis. Patient-relevant outcomes such as disability progression and relapse were included in the review. Available data were analyzed and presented using both direct pairwise meta-analyses and an NMA. The robustness of the NMA was supported by the consistency between direct and indirect evidence, and numerous sensitivity analyses demonstrated the robustness of the base case analysis. A comprehensive economic evaluation was conducted using available cost data and the results of the NMAs.

A key limitation of the review is the inability to estimate relative treatment effects based on prior-treatment history, as in the majority of monotherapy trials, either the patients' prior-treatment history was unclear or the trial included a mixture of treatment-naive and treatment-experienced patients. In addition, none of the monotherapy trials explicitly included patients who had inadequate response or intolerance to prior treatment; thus, it is uncertain to what extent the results of the current review are applicable to this patient population. Similarly, in the three combination trials that enrolled patients previously treated with monotherapy, it was unclear to what extent patients could be considered to have had an inadequate response to treatment. In addition, these trials do not provide evidence that an add-on (combination) strategy is superior to a drug switch strategy.

Additional limitations were related to the availability of data and suitability of data for pooling. There is a paucity of direct comparative evidence between treatments, given that the majority of trials compared active treatments with placebo. Indirect treatment comparisons via NMA of studies conducted over a 20-year time period were complicated by the heterogeneity of study and patient characteristics. Most notably, the NMA results for sustained disability, which was not consistently defined between trials, exhibited less precision than those for ARR, and there was less consistency between the direct and indirect evidence for this outcome.

An additional limitation involved the relatively short duration of the included trials and the selection of primary outcome. Specifically, many trials selected short-term outcomes (e.g., relapse and MRI findings) as their primary outcome, which have an uncertain link to long-term disability. Based on the NMA, there is a lack of clear distinction between treatments regarding effects on disability, which might be attributed to the short duration of the trials, or the insensitivity of the scale used to measure disability. Health-related quality-of-life data were seldom reported, and many outcomes of particular interest to patients were not reported, such as fatigue, difficulty walking, memory or attention problems, and impact on work life. Finally, clinical trials are generally inadequate in size and duration to identify infrequent or rare adverse events, and the identification of important safety issues may not occur until the post-market period.

Conclusions and Implications for Decision- or Policy-Making

Results from the systematic review and NMA suggest that all active treatments produce statistically significant reductions in the ARR compared with no treatment, and that there are clear between-treatment differences. Specifically, compared with no treatment, reductions in the ARR are approximately 70% for natalizumab or alemtuzumab; 50% for fingolimod or dimethyl fumarate; and 30% for subcutaneous interferons, glatiramer acetate, or teriflunomide. Between-treatment differences were less apparent regarding the risk of sustained disability progression. Given the wide credible intervals observed in the NMA, small between-treatment differences observed in the NMA should be interpreted with caution.

Adverse events were treatment-specific and may be an important consideration in treatment selection. Given that the included studies were limited in their ability to identify infrequent or rare adverse events, decision-makers may consider that older agents such as the interferons and glatiramer acetate have the benefit of a longer post-market period.

Patient-group input suggests that patient experience is variable, and that having options that match a person’s life and situation are important considerations in treatment selection.

Results from the base case economic analysis suggest that when compared with no treatment, treatment with any of the interferon therapies, glatiramer acetate, or dimethyl fumarate dominates no treatment (less costly and more effective). The ICUR of fingolimod versus no treatment is $18,234, and the ICUR of natalizumab versus no treatment is $121,456. With respect to comparative cost-effectiveness across active treatments, based on the base case, glatiramer acetate is the most cost-effective treatment; unless willingness to pay exceeds $118,242 per QALY, at which point interferon beta-1b 250 mcg (Extavia) is the cost-effective treatment; unless willingness to pay exceeds $425,655, at which point dimethyl fumarate is the cost-effective treatment; unless willingness to pay exceeds $872,972, at which point natalizumab is the cost-effective treatment. Base case results were little affected by varying model assumptions in sensitivity analyses.

The review was limited in its ability to assess the clinical and cost-effectiveness of sequential treatment given that none of the reviewed trials specifically included patients with inadequate response or intolerance to previous treatments. The review was likewise limited by the paucity of data related to quality of life and many of the outcomes of importance to patients.

The development of novel treatments for MS is an area of active research given the unmet need of patients for acceptable, safe, and effective treatments. New oral agents for the treatment of RRMS have recently been approved by Health Canada and additional agents are expected to enter the Canadian market shortly. Further research is needed that addresses outcomes of importance to patients, and that establishes the value for money of existing and emerging treatments for MS.

1 CONTEXT AND POLICY ISSUES

1.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system.[1] It is a demyelinating disease for which the course is variable, it is more common in women by a factor of approximately 3:1 compared with men,[4] and it is the leading cause of disability in young adults.[39] The prevalence of MS varies geographically and is more common in the northern hemisphere. Canada has the fifth-highest worldwide prevalence, at 240 per 100,000 persons.[5,40]

MS is classified into four subtypes: primary-progressive, secondary-progressive, progressive-relapsing, and relapsing-remitting (RRMS). Approximately 85% to 90% of MS patients have RRMS,[5] which is characterized by clearly defined relapses of impairment, followed by remissions with full recovery or with sequelae and residual deficit. Relapses are defined as acute or subacute onset of clinical dysfunction, followed by a remission. Frequency of relapse is highly variable, but tends to be more frequent in the first few years after disease onset.[5] Patients with RRMS typically have earlier onset of disease compared to those with primary-progressive, between 25 and 29 years, which may convert to secondary-progressive disease — typically at a mean age between 40 and 44.[41]

Early diagnostic criteria for MS required two neurological events to establish a diagnosis of MS;[9,42,43] however, the revised criteria currently in use allow for a diagnosis of MS after one neurological event in combination with MRI findings.[12,44,45] Markers of MS on MRI are gadolinium-enhancing (GdE) and T2 lesions, which are seen at the early stage of disease.[8] T2 lesions represent burden of disease, while GdE lesions are indicative of active inflammation in conjunction with blood-brain barrier disruptions. Biopsy and autopsy histological findings in patients with MS show inflammatory T-cells, B-cells, and macrophages.

MS is a slowly progressing disease, although it can be difficult to determine both the natural history and time to progression of disease because of difficulty in determining the “start time” of the disease — the onset of symptoms as defined by the patient, or the date of diagnosis.[46] The natural history in mostly untreated Canadian MS populations has been examined in both Ontario[47] and British Columbia.[46] Weinshenker et al. followed 1,099 untreated patients in London, Ontario, between 1979 and 1984.[47] Sensory impairment was the most common presenting symptom of MS. The median time of sustained progression to mild disability was 7.7 years; to the need to use a cane or other walking aid was 15 years; and to being restricted to a wheelchair or bed was 46 years. The percentage of patients who converted from RRMS to secondary-progressive disease increased steadily over time, with more than half of patients entering the secondary-progressive phase within the first 10 years following the MS diagnosis.

The study from British Columbia by Tremlett et al. examined prospectively collected data from patients at MS clinics in British Columbia.[46] The authors followed 2,837 patients, 70% of whom were women, for 22,723 patient-years, and measured disability every 1.1 years; a small number (7.5% of active follow-up) received immunomodulatory drug treatment. Fifteen years after the onset of disease, 21% of their patient population required the use of a cane, and after 40 years, 69% needed a walking aid. The median time of sustained progression requiring a cane was 27.9 years, with 52% of the population requiring a walking aid at age 60.

The longer time to sustained progression (Expanded Disability Status Scale [EDSS 6]) in the population in British Columbia (27.9 years) compared with that of the Ontario population (15.0 years) may have been because of a higher percentage with progressive disease in Ontario (20% versus 12%), which results in more rapid progression.[46] Tremlett et al.[46] also found that older onset of disease and male sex were not associated with poorer disease outcomes.

1.2 Therapeutic Options

The therapeutic aims of MS drugs are to reduce the frequency of relapses, decrease the lasting effects of relapses, prevent or decrease disability that is the result of disease progression, and promote tissue repair.[1,6] In Canada, the earliest available disease-modifying treatments for MS included interferons (interferon beta-1a and interferon beta-1b) and glatiramer acetate, which were approved by Health Canada in the 1990s.

Natalizumab, administered via intravenous infusion, was approved by Health Canada in 2006 for the treatment of RRMS; however, natalizumab treatment is thought to increase the risk for progressive multifocal leukoencephalopathy (PML), a rare demyelinating neurological disorder caused by the reactivation of the JC Virus.[7,8] Post-marketing data have estimated the risk of developing PML to be 1 in 500 patients treated with natalizumab.[48] The three factors that are known to increase the development of PML are the presence of anti-JC Virus antibodies, longer treatment duration (particularly beyond 24 months), and prior immunosuppressant treatment.[49] The Health Canada-approved product monograph for natalizumab states that natalizumab is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, other therapies for MS.[49]

Fingolimod, the first oral agent for the treatment of RRMS, was approved by Health Canada in 2011. The Health Canada-approved product monograph for fingolimod states that fingolimod is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for multiple sclerosis.[50] More recently (2013), dimethyl fumarate, another oral agent for the treatment of relapsing-remitting MS, was approved by Health Canada during the conduct of this Therapeutic Review.

While only the interferons have specific product monograph contraindications for pregnancy, animal studies of fingolimod show potential teratogenicity.[50] It is unclear as to whether natalizumab is safe during pregnancy;[49] and although it is unclear whether glatiramer acetate is safe during pregnancy, it is not recommended for use in pregnant women.[51] Further details regarding the approved therapeutic options for the treatment of RRMS, according to their Health Canada product monographs, are included in Table 1.

Table 1: Summary of Health Canada-Approved Therapeutic Options of Interest Based on Product Monographs						
	Interferon beta-1a[52,53]	**Interferon beta-1b**[54,55]	**Glatiramer acetate**[51]	**Natalizumab**[49]	**Fingolimod**[50]	**Dimethyl fumarate**[56]
Mechanism of Action	Not completely understood; likely the upregulation of IL-10	Not completely understood; likely mediated by binding to cell surface receptors	Likely modifies the immune processes responsible for pathogenesis of MS	Blocks interaction of alpha-4 beta-7 integrin with the mucosal address in cell adhesion molecule-1. Reduces formation or enlargement of MS lesions	Not known; likely reduces lymphocyte migration in the CNS	Not completely understood; activates the Nrf2 pathway
Approved Indications	RRMS; SPMS with relapses; single demyelinating event, accompanied by abnormal MRI scans, with lesions typical of MS	RRMS; SPMS; single demyelinating event accompanied by at least two clinically silent lesions typical of MS	RRMS; single demyelinating event, accompanied by abnormal MRI scans and considered to be at risk of developing CDMS	RRMS	RRMS	RRMS
Route of Administration	IM injection (Avonex) SC injection (Rebif)	SC injection (Betaseron, Extavia)	SC injection (Copaxone)	IV infusion (Tysabri)	Oral capsule (Gilenya)	Oral capsule (Tecfidera)
Recommended Dose	IM: 30 mcg/week (increase up to 60 mcg/week if needed)[a] SC: 22 mcg or 44 mcg 3 times/week	0.25 mg every other day	20 mg/day	300 mg every 4 weeks	0.5 mg/day	240 mg twice daily[b]
Contraindications (according to product monograph)	Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, pregnant women	Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, pregnant women	Contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol	Contraindicated in patients who have had PML, at risk for PML; hypersensitive to this drug or to any ingredient in the formulation or any component of the drug; immunocompromised, including those immunocompromised due to immunosuppressant or antineoplastic therapies, or immunodeficiencies	Contraindicated in patients who are hypersensitive to fingolimod, who are at risk for an opportunistic infection (immuno-compromised due to treatment or to disease), have hepatic insufficiency, active severe infections, or known active malignancies	Contraindicated in patients who are hypersensitive to dimethyl fumarate

Table 1: Summary of Health Canada-Approved Therapeutic Options of Interest Based on Product Monographs						
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Warnings and Precautions (according to most recent product monograph)	Should be used under supervision of a physician or qualified health care professional. May cause depression and severe liver injury.	Caution to patients with history of suicidal ideation, cardiac disease, thyroid disorders, and seizure disorders. May cause hypersensitivity reactions, liver injury, and pancreatitis.	May cause transient chest pain and immediate post-injection reactions.	MRI scan is required for diagnosis of PML. Risk of PML increases with increasing treatment duration, history of previous exposure to immunosuppressive therapy, and presence of anti-JC Virus antibodies.	Delay treatment in patients with active severe infection. Varicella zoster vaccination recommended. Should not be used in patients with history of cardiovascular disease, cerebrovascular disease, severe sleep apnea, or uncontrolled hypertension. May cause macular edema and may increase liver transaminases.	Should not be used simultaneously with other fumaric acid derivatives or in patients with signs and symptoms of serious infection. A complete blood count, liver transaminase test, and urinalysis should be available before initiating treatment. Caution should be given when treating patients with severe active gastrointestinal disease.

CDMS = clinically definite multiple sclerosis; CNS = central nervous system; IL-10 = immunosuppressive cytokine interleukin-10; IM = intramuscular; IV = intravenous; mg = milligram; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis; mcg = microgram.

[a] Patients with relapsing progressive MS or secondary-progressive MS with recurrent attacks of neurological dysfunction could benefit from an increase of their dose of Avonex up to 60 mcg.

[b] The starting dose is 120 mg twice a day. After seven days, the dose should be increased to 240 mg twice a day. A temporary reduction (up to one month) to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse effects.

1.3 Emerging Treatments

Currently, a number of new disease-modifying therapies are in development for the treatment of MS (both oral and intravenous), including alemtuzumab (intravenous) and teriflunomide (oral), which are expected to enter the Canadian market shortly.

Alemtuzumab, an emerging injectable agent, is a humanized monoclonal antibody that causes depletion of certain T-cells, natural killer cells, and monocytes.[14] Teriflunomide, an emerging oral agent for the treatment of RRMS, is a pyrimidine biosynthesis that disrupts the interaction of T-cells with antigen-presenting cells.

1.4 Issue

The comparative effectiveness and safety of current MS treatments is not well-established.[1] With the emergence of novel oral and injectable agents, and the uncertainty in the comparative effectiveness of current treatments, the landscape of disease-modifying treatments is evolving and becoming more complex for health care decision-makers. It is therefore important to determine the comparative clinical and cost-effectiveness of currently available and emerging disease-modifying agents for MS, both as monotherapy and in combination. While oral agents may be preferred by patients, their clinical benefit and cost-effectiveness compared with older injectable agents requires evaluation.

2 RESEARCH QUESTIONS

1. What is the comparative efficacy and safety between individual disease-modifying agents in RRMS?
2. What is the comparative cost-effectiveness between individual disease-modifying agents in RRMS?
3. What is the comparative efficacy and safety of combination therapy (two or more disease-modifying agents compared with individual agents or other combinations) in RRMS?
4. What is the comparative cost-effectiveness of combination therapy (two or more disease-modifying agents compared with individual agents or other combinations) in RRMS?

3 METHODS

3.1 Systematic Review

3.1.1 Literature search strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy (APPENDIX 3).

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; Embase via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were relapsing-remitting multiple sclerosis and interferon beta-1a/1b, natalizumab, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, and alemtuzumab.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and safety studies. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year but was limited to English language results. Conference abstracts were excluded from the search results.

The initial search was completed on November 9th, 2012. Regular alerts were established to update the search until October 2013. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, clinical trial registries, and professional associations. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

3.1.2 Selection criteria and methods

Trials were included in the systematic review based on the pre-specified selection criteria (Table 2). Active and placebo-controlled trials were selected for inclusion if they were published in English, involved patients with RRMS, had treatment arms consisting of currently available or emerging disease-modifying agents, and reported any of the specified outcomes related to clinical efficacy and safety. Trials that included mixed populations of MS were also included if the proportion of RRMS patients was more than 50% of the total population. For interventions currently approved by Health Canada for the treatment of RRMS, only approved formulations and doses were included in the systematic review. Interventions not yet approved by Health Canada for the treatment of RRMS, but expected to enter the Canadian market shortly, were not restricted to specific doses or formulations.

Two reviewers independently screened titles and abstracts relevant to the clinical research questions regarding available and emerging agents for the treatment of patients with RRMS. Full texts of potentially relevant articles were retrieved and independently assessed for possible inclusion based on the pre-determined selection criteria. The two reviewers then compared their chosen included and excluded studies; disagreements were discussed until consensus was reached. The study selection process was presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (APPENDIX 6).

Table 2: Inclusion and Exclusion Criteria for Primary Studies	
Inclusion Criteria	
Design	Published RCTs
Population	Patients diagnosed with RRMS[a]
Intervention	• Disease-modifying agents ▪ Currently available (formulations and doses approved and available in Canada only will be included) o Fingolimod — oral o Interferon beta-1a — injectable o Interferon beta-1b — injectable o Natalizumab — injectable o Glatiramer acetate — injectable ▪ Emerging o Teriflunomide — oral o Dimethyl fumarate — oral o Alemtuzumab — injectable • Placebo
Outcomes	• Relapse • Disability • MRI changes • Quality of life • Deaths • Serious adverse events • Discontinuation of treatment because of adverse events • Adverse events
Exclusion Criteria	
Studies in languages other than English Non-randomized studies Follow-up or extension studies Preliminary results in abstract form	

MRI = magnetic resonance imaging; MS = multiple sclerosis; RCT = randomized controlled trials; RRMS = relapsing-remitting MS.
[a]RCTs having a mixed population (i.e., persons with primary-progressive or secondary-progressive MS in addition to persons with RRMS) will be included for completeness if the RRMS population is greater than 50% of the total population.

3.1.3 Data extraction strategy and critical appraisal of included studies

One reviewer performed data extraction for each article, using a pre-drafted data extraction form covering the following items:

- baseline characteristics of trial participants
- interventions evaluated, including dose, duration, and mode of administration
- efficacy and safety results for specified outcomes
- type of analysis (intention to treat [ITT] or per-protocol).

All extracted data were checked for accuracy by a second reviewer. Any disagreements were resolved through discussion until consensus was reached. A quality assessment of RCTs was performed independently by two reviewers using a standardized table based on major items from the SIGN-50 instrument for internal validity. Additional critical appraisal was performed based on input from clinical experts.

Clinical outcomes included relapse (annualized relapse rate [ARR] and proportion of patients remaining relapse-free) and disability (proportion of patients with sustained disability progression, mean change of EDSS, and mean change of Multiple Sclerosis Functional Composite [MSFC]). Disability is measured by EDSS change. The definitions of relapse and sustained disability progression from individual studies are presented in APPENDIX 9. MSFC comprises the average of the scores on the timed 25-foot walk, the nine-hole peg test, and the paced auditory serial-addition test with a three-second interstimulus interval, with higher scores (Z-score) representing improvement.[57]

MRI outcomes included a proportion of patients with GdE lesions, mean number of GdE lesions, proportion of patients with new or enlarging T2-hyperintense lesions, and mean number of new or enlarging T2-hyperintense lesions.

Safety outcomes included serious adverse events, discontinuation of treatment because of serious adverse events, total withdrawal, and common adverse events.

3.1.4 Data analysis methods

Direct pairwise meta-analyses were performed for all outcomes to assess consistency with network meta-analysis (NMA) results when NMA was undertaken, and to obtain summary estimates for outcomes that were not analyzed by NMA.

Review Manager 4.2 was used for all statistical analyses of direct comparisons of dichotomous and continuous outcomes in the clinical review. Where the quantitative pooling of results was appropriate, the random-effects model was used to compute treatment efficacy between interventions across studies, based on the assumption that treatment effects follow a distribution across studies.

Dichotomous data were summarized using relative risk (or risk ratio), which compares the proportion of patients having the event between two treatment groups. In our study, the dichotomous outcomes that were measured included:

- proportion of patients who were relapse-free
- proportion of patients with sustained disability progression
- proportion of patients with GdE lesions
- proportion of patients with new or enlarging T2-hyperintense lesions.

Continuous data with means and standard deviations were summarized using mean differences. Where standard deviations were not reported, they were obtained from standard errors, confidence intervals, t values, or *P* values.[58] Where no variance was reported, a value of standard deviation was imputed using the coefficient of variation, which was calculated based on studies with similar population, study design, and intervention.[59] The continuous outcomes that were measured in this study included:

- mean change in EDSS from baseline
- mean change in MSFC from baseline
- mean number of GdE lesions
- mean number of new or enlarging T2-hyperintense lesions.

Relapses were considered as count data and were summarized using a Poisson approach to obtain the relative ARR or rate ratio from the total number of relapses and patient-years. The analyses were performed using the Comprehensive Meta-Analysis software.

The heterogeneity between studies was assessed using I^2 statistics, which quantifies the percentage of variation across studies that is because of heterogeneity rather than chance.[60] Heterogeneity is considered to be low when I^2 is less than or equal to 25%, moderate when I^2 is between 25% and 75%, and high when I^2 is greater than or equal to 75%. Attempts were made to explain substantial statistical heterogeneity ($I^2 \geq 50\%$) by subgroup analyses or elimination of outliers. Where statistical heterogeneity remained present in the subgroup analyses, clinical outcomes were presented separately for each study and were reviewed qualitatively. The I^2 statistics, however, do not provide evidence about clinical heterogeneity in study design, treatments, and baseline demographics and characteristics of patient population.

The planned subgroup analyses included age (≤ 40 years or > 40 years), baseline EDSS score (0 to 3, or > 3), GdE lesions at screening (0 ≥ 1), gender (female or male), and number of relapses in the previous year before screening (1, 2, or ≥ 3).

3.2 Indirect Comparisons

Bayesian NMAs were conducted for two outcomes: relapse and disability. The selection of the outcome-specific measures for the NMA (ARR and the proportion of patients with sustained disability progression) was based on input from clinical experts. NMAs were not conducted for other efficacy outcomes (MRI findings and health-related quality of life) because data were sparsely reported, and, in the case of MRI, eight out of 14 studies reporting MRI outcomes were subsets of randomized populations with unclear selection criteria for MRI scans (Table A10.2). NMAs were not conducted for adverse events data (serious adverse events, and withdrawal because of adverse events) because the occurrence of events was low.

WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) was used for all NMAs. Posterior densities for all unknown parameters were estimated using Markov Chain Monte Carlo methods. Prior distributions for overall effects of interest and study-specific effect estimates were assigned vague normal prior distributions centred at zero, with adequately large variances to allow the collected data to drive the calculation of pooled estimates. Model diagnostics including trace plots, autocorrelation plots, and the Brooks-Gelman-Rubin statistic were assessed to ensure model convergence. Assessment of model fit for NMA comprised the assessment of deviance information criterion and comparison of residual deviance to the number of unconstrained data points. Measures of effect were estimated according to the WinBUGS routine developed by the Evidence Synthesis Group, consisting of experts from the universities of Bristol and Leicester (the code is available from the website). Median estimates were reported, along with corresponding 95% credible intervals ([CrI]; Bayesian confidence interval). For comparative purposes, both fixed-effects and random-effects NMAs were conducted.

Regarding the interpretation of NMA estimates, if a 95% CrI for a risk ratio comparing two interventions did not include the value 1, this was interpreted as an indication that there is a less than 5% probability that there was no difference in effect between treatments.

3.2.1 For ARR

The Poisson distribution is a discrete distribution and is appropriate for modelling counts of observations or events that occur in a given interval of time (or space). In this review, ARR was modelled as a Poisson outcome based on the total number of relapses observed within a treatment group and the total number of person-years of follow-up for that treatment group as the input data.

Where studies did not report the total number of relapses or exposure time (person-years) directly in the publication, imputations were performed to derive the respective values. Missing total number of relapses were derived using exposure time (in person-years) and the reported mean ARR values. For missing exposure time (in person-years), the values were imputed using treatment duration and number of patients completing the study (100% was assumed in cases where the percentage of completers was not reported).

3.2.2 For sustained disability progression

Patient sustained disability progression was analyzed as a binomial outcome, with the total number of patients with the event within a treatment group and the total number of patients randomized for that treatment group as the input data.

3.2.3 Exploring heterogeneity

NMA requires that studies be sufficiently similar in order for their results to be pooled. A wide range of patient and trial characteristics were recorded to allow for a qualitative assessment of the heterogeneity of included trials. However, the methodological limitations with this approach are recognized; assessment of heterogeneity is naturally limited to reported characteristics. For example, older trials did not report or indicate whether the patient population consisted solely of treatment-naïve patients or was inclusive of patients with history of a prior treatment. Assumptions based on the reported information were made to that aspect; consequently, the ability to explore the impact of heterogeneity between studies regarding patient population, in terms of treatment experience, in the NMA was limited.

Heterogeneity was further explored through selected meta-regressions and subgroup analyses based on patient covariates (baseline EDSS score, time since symptom onset, number of relapses in previous year, prior-treatment history) and trial characteristics (publication date and treatment duration). Meta-regressions were performed when the variable was continuous in order to incorporate the maximum amount of information available from trials. Subgroup analyses were performed when the variable could be dichotomized (e.g., patient population was treatment-naïve or mixed). Cut-offs defining the subgroups (e.g., trial publication date or treatment duration) were selected based on currently accepted conventions and clinical expert input.

3.3 Pharmacoeconomic Analysis

3.3.1 Type of economic evaluation

The analysis was in the form of a cost-utility analysis. The primary outcome was the number of QALYs, with treatments compared in incremental cost per QALY (ICUR).

3.3.2 Target population

The target population was Canadians with RRMS. For the base case analysis, a typical patient profile from the RCTs identified in the systematic review was adopted: an average age of 36 years, 68% of patients being female, time since onset of five years, and an initial discrete distribution of EDSS score with a mean score of 2.3.

3.3.3 Treatments

The currently available treatments that are approved and available in Canada were included in the primary analysis (Table 3).

Table 3: Available Treatments Included in Primary Analysis

Treatment Comparators
Dimethyl fumarate 240 mg (Tecfidera)
Fingolimod 0.5 mg (Gilenya)
Glatiramer acetate 20 mg/mL (Copaxone)
Interferon beta-1a 30 mcg (Avonex)
Interferon beta-1a 22 mcg (Rebif)
Interferon beta-1a 44 mcg (Rebif)
Interferon beta-1b 250 mcg (Betaseron)
Interferon beta-1b 250 mcg (Extavia)
Natalizumab 300 mg/15 mL (Tysabri)

mg = milligram; mL = millilitre; mcg = microgram.

Emerging treatments in RRMS (for which regulatory approval has not been granted) were included in an exploratory analysis (Table 4). As the costs of these treatments are unknown, it was assumed that the prices would follow the same patterns as in the US for base case. Given the uncertainty of the price for unmarketed agents, this assumption was tested in sensitivity analyses.

Table 4: Emerging Treatments Included in Exploratory Analysis

Treatment Comparators
Alemtuzumab 12 mg
Alemtuzumab 24 mg
Teriflunomide 7 mg
Teriflunomide 14 mg

mg = milligram.

Due to a lack of clinical data exploring the sequential use of treatments following the failure of first-line treatment or switching, it was assumed that patients cannot switch between treatments in the model. Therefore, the only transition between interventions that is possible is from active treatment to no treatment (treatment discontinuation).

3.3.4 Perspective

This analysis was conducted from the perspective of a provincial Ministry of Health in Canada.

3.3.5 Time horizon

The analysis adopts a time horizon of 25 years as a base case, with a cycle length of three months. Alternative horizons of 10 years, 20 years, and 40 years (lifetime) were considered in sensitivity analyses. Although RRMS disease onset can occur in early life and has limited effect on life expectancy, a time horizon of 25 years has been implemented to account for the

uncertainty regarding natural history of the disease, as well as the uncertainty regarding the long-term efficacy of the treatments.

3.3.6 Model structure

A Markov cohort approach was taken for the analysis, with the model developed in MS Excel. The model was based on a series of health states that reflect the progression of patients with RRMS. Time elapses explicitly in Markov models and transition probabilities are assigned for movement between these states over the three-month cycles. By attaching estimates of resource use and health outcome consequences to the health states, and running the model over a 25-year time horizon (100 cycles), it was possible to estimate the long-term costs and outcomes associated with the various treatments.

Health states were defined according to the Kurtzke EDSS, as well as based on severity of relapse. EDSS levels were grouped into five health states for modelling disease progression (Table 5). These five EDSS levels are generally regarded as the key markers for disability of patients with RRMS.[61] This approach was implemented in other published economic models, such as Prosser,[62] and clinical experts were in agreement with the approach (Figure 1).

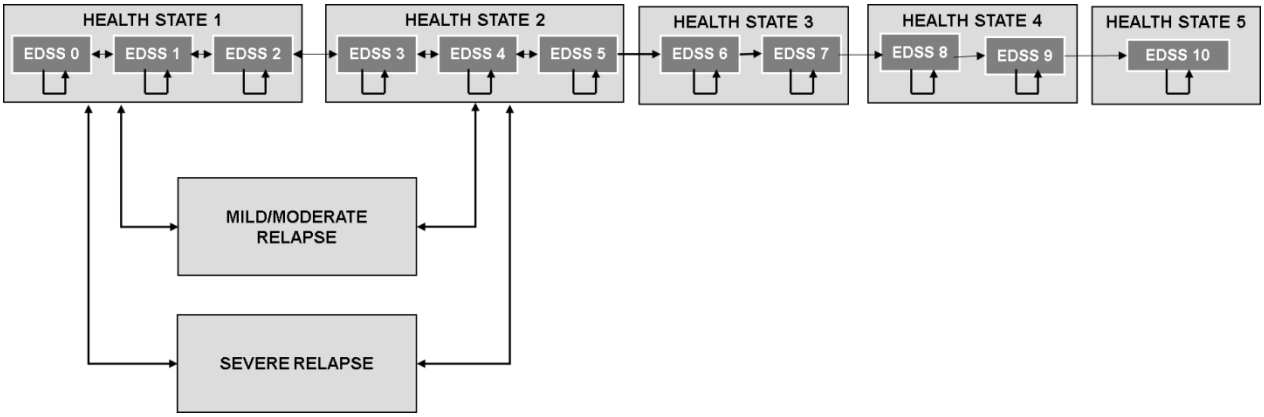
Table 5: Description of Health States

Health States	Description
Health state 1 No/few limitations (EDSS 0 to 2.5)	No MS symptoms (0) to minimal disability in two functional systems (2.5)
Health state 2 Moderate limitations (EDSS 3 to 5.5)	Moderate disability in one area or mild disability in up to four areas but still able to walk unassisted and accomplish full daily activities (3), to disability that precludes full daily activities, but still able to walk unassisted (5.5)
Health state 3 Walking aid or wheelchair (EDSS 6 to 7.5)	Requires walking aid such as cane, crutch, or brace to walk 100 metres (6), to restricted to wheelchair (7 to 7.5)
Health state 4 Restricted to bed (EDSS 8 to 9.5)	Restricted to bed with some ability to self-care (8), to requiring assistance for all activities of daily living (9 to 9.5)
Health state 5 Death (EDSS 10)	Death due to MS

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

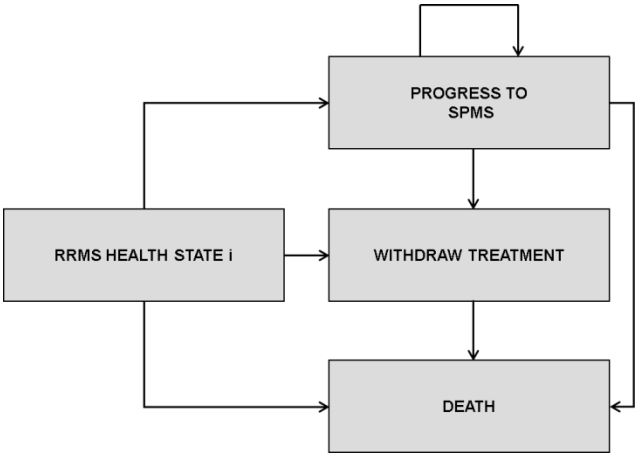
During one cycle, patients can remain in the current health state; progress to the next, more severe state; improve to a less severe state; transition to a secondary-progressive health state; withdraw treatment; or die (Figure 2).

Figure 1: Model Diagram



EDSS = Expanded Disability Status Scale.

Figure 2: Model Diagram (continued)



EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
Note: Patients progressing to SPMS will transition across SPMS EDSS scores based on SPMS transitional probabilities. Patients withdrawing treatment will transition across health states based on natural history transitional probabilities.

The progression to more severe states was based on natural history data for MS from a London, Ontario cohort study.[47] The fluctuating nature of RRMS — i.e., a possibility of patients moving in both directions along the EDSS scale — has recently been frequently recognized as a clinical phenomenon in the early stage of the disease. Therefore, improvements in lower health states (health state 1 and 2) in the EDSS score were also modelled, based on the study by Tremlett et al. that was conducted using the British Columbia MS database.[63] However, since the evidence on improvement on the EDSS scale is mixed, a scenario analysis was conducted, where no improvements on the EDSS scale were modelled (i.e., once patients progressed, they could not transition back to a less severe EDSS state, which is consistent with the older modelling studies[64]).

Based on the conclusion of the study by Wong et al.,[65] there are no significant differences in adherence among the disease-modifying agents for RRMS. Therefore, a constant annual rate of discontinuation was assumed across all treatments for the first two years of 15%, based on the withdrawal rates in the clinical trials included in the systematic review, as well as in line with some of the observations by clinical experts in Canada. After two years, the discontinuation rate was assumed to be zero, assuming that all patients who discontinue treatment would have done so by the end of the second year. Sensitivity analysis was conducted, varying the discontinuation rates and the number of years that discontinuation rates were applied to, to address the variability of discontinuation that might be present in different settings.

The stopping rules for RRMS therapies vary across Canadian public drug plans, ranging from an EDSS score of 5.5 to 7.0, as per clinical experts' opinion. For the base case scenario, a conservative assumption was made that once patients progress to an EDSS of 7.0 or secondary-progressive multiple sclerosis, they would withdraw treatment. Given the differences in stopping rules for therapies across the Canadian provincial plans, a sensitivity analysis was conducted, varying the EDSS score from 5.0 to 7.0, as well as exploring the scenario if the no-stopping rule has been implemented.

As the model assesses the cost-effectiveness of the treatments in RRMS, progression to secondary-progressive multiple sclerosis (SPMS) in the base case scenario led to treatment discontinuation. However, this assumption was also tested in the scenario analysis.

Relapses were assumed to occur only in patients in the health states 1 and 2 (EDSS 0.0 to 5.5). Although relapses may occur for states with EDSS greater than or equal to 6.0, as per clinical expert opinion, the severity of disability may prevent detection of relapses (i.e., acute increase in disability due to relapse and increase in sustained disability arising from disease progression may not be easily differentiated). Relapses were assumed to last for 45 days for mild or moderate relapses, and 90 days for severe relapses, based on clinical opinion and published literature.

A half-cycle correction was implemented to adjust both costs and QALY gains, so that they are calculated halfway through each cycle, as opposed to the end of each cycle.

3.3.7 Data inputs

To the extent that data inputs of the given model are estimated, they will be subject to uncertainty regarding their true value, known as parameter uncertainty.[66] This can be achieved by implementing an informal Bayesian approach to cost-effectiveness analysis by specifying relevant parameters as probability distributions rather than point estimates. This technique allows for the estimation of the likelihood of various output values based on a wide number of sets of input parameters generated by sampling from their probability density functions, and was implemented in the probabilistic sensitivity analysis.

a) *Natural history*

Disability progression

Ideally, the model would use transitional probabilities derived from one of the large Canadian cohort studies;[46,47] however, none of these data were directly available or easily accessible; therefore, the transitional probabilities were based on estimates reported in the published literature.

In the published literature, the most common outcome in the natural history of disease studies was time to reaching EDSS 6, which was not granular enough to be used for modelling the disability progression. The only available data reported in a format that could readily be used were from the London, Ontario cohort study reported by the Centre for Bayesian Statistics in Health Economics of the University of Sheffield, School of Health and Related Research (ScHARR) in its final report to the National Institute for Health and Care Excellence.[67] The ScHARR report contained hazard rates for disability progression within RRMS, transitioning from RRMS to SPMS, as well as disability progression within SPMS (Table 6, Table 7, and Table 8).

Hazard rates were calculated as:

$$\lambda_i = \frac{number\ of\ people\ leaving\ state\ i}{\sum_{j=1}^{n} duration\ in\ state\ i}$$

$$var(\lambda_i) = \frac{number\ of\ people\ leaving\ state\ i}{(\sum_{j=1}^{n} duration\ in\ state\ i)^2}$$

where *n* is the number of individuals, *j* is each individual leaving state *i*, and *i* = EDSS states 0 to 10.

These hazard rates were further transformed into transitional probabilities using standard methodology:

$$p_t = 1 - e^{\lambda t}$$

where *t* is the cycle length. These transitional probabilities were used to inform the model. By using quarterly transitional probabilities, it is possible for patients to transition to a maximum of four EDSS states during one year.

Table 6: Hazard Rates on Progression Rates Within RRMS Health States

EDSS	Base Estimate (Per Person-Year)	Variance	Probability Distribution
0	0.144	0.00007	Beta (253.43, 1506.49)
1	0.075	0.00003	Beta (173.36, 2138.14)
2	0.152	0.00006	Beta (326.38, 1820.88)
3	0.272	0.00025	Beta (215.17, 575.89)
4	0.450	0.00166	Beta (66.64, 81.45)
5	0.485	0.00213	Beta (56.39, 59.88)
6	0.283	0.00104	Beta (54.93, 139.17)
7	0.342	0.00450	Beta (16.76, 32.25)
8	0.105	0.00139	Beta (6.99, 59.61)
9	0.167	0.02778	Beta (8.2,40.88)

EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis.
Source: ScHARR[67]

Table 7: Hazard Rates on Progression Rates Within SPMS Health States			
EDSS	**Base Estimate (Per Person-Year)**	**Variance**	**Probability Distribution**
2	0.370	0.00370	Beta (22.94, 39.06)
3	0.385	0.00129	Beta (70.28, 112.27)
4	0.594	0.00280	Beta (50.57, 34.56)
5	0.349	0.00088	Beta (89.76,167.42)
6	0.241	0.00029	Beta (151.77, 477.98)
7	0.186	0.00024	Beta (117.15, 512.7)
8	0.107	0.00015	Beta (68.05, 567.95)
9	0.093	0.00038	Beta (20.55, 200.43)

EDSS = Expanded Disability Status Scale; SPMS = secondary-progressive multiple sclerosis.
Source: ScHARR[67]

Table 8: Hazard Rates on Progression Rates from RRMS to SPMS States			
EDSS	**Base Estimate (Per Person-Year)**	**Variance**	**Probability Distribution**
0	0.004	0.000002	Beta (7.57, 1933.82)
1	0.002	0.000001	Beta (3.23, 1792.53)
2	0.029	0.000012	Beta (72.24, 2343.92)
3	0.102	0.000094	Beta (100.21, 877.45)
4	0.199	0.000735	Beta (43.07,173.04)
5	0.256	0.001126	Beta (42.91, 125.03)
6	0.184	0.000676	Beta (40.60, 180.31)
7	0.237	0.0003116	Beta (13.50, 43.50)
8	0.066	0.000866	Beta (4.60, 65.38)
9	0.167	0.027778	Beta (8.17, 40.84)

EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.
Source: ScHARR[67]

The authors of the ScHARR model noted that, although there is some evidence that disability improvements can occur up to 12 months after the progression is observed, the improvements are not reported in the long-term natural history data used in this model.[64] Tremlett et al.[63] recently conducted a large study based on 2,961 patients in the British Columbia MS database and concluded that disability improvements in MS over one or two years are not unusual. That is, the authors of the study reported greater than or equal to 2-point improvements on the EDSS score in 2.2% EDSS intervals per year, greater than or equal to 1-point improvements in 8.3%, and greater than or equal to 0.5-point improvements in 14.9%. To capture the fluctuating nature of RRMS, which is frequently recognized as a clinical phenomenon, these were included in the model by assuming that a maximum of 2 EDSS-point improvements could be achieved. The rates of annual disability improvements were transformed into quarterly rates resulting in 0.5% of 2-point improvements and 1.49% of 1a -point improvement per quarter, and were applied only to the first two health states.

Relapse rate

Based on London, Ontario cohort data, ScHARR reported a mean relapse rate of 0.835 and 1.423 for EDSS 0 to 2 and 3+, respectively, over the first two years since onset.[67]

However, there is available evidence suggesting that the frequency of relapse is affected by a patient's age and disease duration,[68] and therefore it is time-dependent.[5] A prospective study by Patzold and Pocklington reported relapse rates over 19 years, showing a decrease over time.[69] This study reported the correlation of the mean annual relapse rate and the duration of disease through a logistic regression analysis (r = 0.9466, $P < 0.01$).

$$y = 1.613 - 0.512Log(x),$$

where *x* is the duration of disease.

Based on the regression analysis from the Patzold and Pocklington study, the estimate for relapse rate after two years since onset closely matches the estimate of relapse rate reported in the ScHARR report for patients in EDSS of 3+. Therefore, the regression analysis from the Patzold and Pocklington study was used as the basis for estimating the decrease of the relapse rate over time for patients in health state 2 (EDSS 3.0 to 5.5), adjusting such that the patients enter the model with an average time since disease onset of five years, as in the RCTs identified in the systematic review.

The base estimate from ScHARR of 0.835 for EDSS 0 to 2 in combination with the rate of decrease by Patzold and Pocklington was used to estimate the relapse rate for health state 1 (EDSS 0 to 2.5) for patients with five years since onset and onwards.

Table 9: Annual Relapse Rates

Year Since Onset	Base Estimate	Probabilistic Distribution
EDSS 0 to 2.5		
5	0.712	Gamma (4.31, 0.03)
10	0.623	Gamma (3.45, 0.04)
15	0.571	Gamma (2.97, 0.04)
20	0.534	Gamma (2.66, 0.04)
25	0.506	Gamma (2.42, 0.04)
EDSS 3 to 5.5		
5	1.255	Gamma (10.58, 0.02)
10	1.101	Gamma (8.66, 0.02)
15	1.011	Gamma (7.58, 0.03)
20	0.947	Gamma (6.84, 0.03)
25	0.897	Gamma (6.28, 0.03)

EDSS = Expanded Disability Status Scale.
Source: Patzold and Pocklington ,[69] ScHARR.[67]

Regarding the severity of relapses, it was assumed that 23% of relapses are severe.[62] The average length of mild or moderate relapse was assumed to be 45 days, while the length of severe relapse was assumed to be 90 days, based on clinical expert opinion and published literature.

b) *Treatment efficacy*

The clinical efficacy of disease-modified treatments on both disability progression and relapse rates were included in the model. The comparative data were based on the NMA conducted as part of the CADTH systematic review (Table 10, Table 11). The relative rate of annual relapse and the relative risk of disability progression versus placebo were included, as the transitional probabilities describing the natural history of the disease are based on the London, Ontario dataset of untreated patients.

Disability progression

The transition matrix for patients on treatments was derived from the transition matrix for untreated patients by multiplying the transitional probability to a higher EDSS state by the relative risk of sustained disability progression for each treatment. The relative risk is 1 for the no-treatment strategy, and there is a lower relative risk for each of the treatments, which represent the effect of slowing disability progression.

The relative risks of sustained disability progression were applied to the transitional probabilities of patients moving to a higher health state, as well as to progressing to SPMS. Once patients progressed to SPMS, the transition between health states during the SPMS phase was unaffected by the relative risks; i.e., patients transitioned as per natural history of disease transitional probabilities in the SPMS state. The probability of staying in the same health state was then increased by the percentage of patients who did not progress because of the treatment effects, so that the sum of the transitional probabilities remained 1.

Patients who discontinue treatment will progress according to rates for natural disability progression, but will retain benefits received.

Table 10: Relative Risk of Disability Progression Across Treatments

Drug/Comparator	RR of Sustained Disability Progression	2.5% CrI	97.5% CrI
Alemtuzumab 12 mg	0.557	0.321	0.865
Alemtuzumab 24 mg	0.494	0.199	0.966
Dimethyl fumarate 240 mg (Tecfidera)	0.734	0.528	0.974
Fingolimod (Gilenya)	0.763	0.521	1.036
Glatiramer acetate (Copaxone)	0.829	0.647	1.024
Interferon beta-1a 30 mg (Avonex)	0.868	0.668	1.091
Interferon beta-1a 22 mcg (Rebif)	0.889	0.577	1.231
Interferon beta-1a 44 mcg (Rebif)	0.836	0.613	1.083
Interferon beta-1b 250 mg (Betaseron)	0.744	0.504	0.967
Interferon beta-1b 250 mg (Extavia)	0.744	0.504	0.967
Natalizumab (Tysabri)	0.673	0.404	1.007
Teriflunomide 7 mg	0.847	0.535	1.192
Teriflunomide 14 mg	0.803	0.499	1.150

CrI = credible interval; mg = milligram; RR = relative risk.

Relapses
The treatment effects on the relapse rates are modelled by applying the relative rate of relapse on the average number of relapses experienced while on no treatment, as presented in Table 11. As with progression, the magnitudes of these effects differ between treatments.

Table 11: Relative Rates of Annual Relapse Across Treatments

Drug/Comparator	RR of Annual Relapse Rate	2.5% CrI	97.5% CrI
Alemtuzumab 12 mg	0.307	0.250	0.373
Alemtuzumab 24 mg	0.169	0.106	0.266
Dimethyl fumarate 240 mg (Tecfidera)	0.506	0.437	0.590
Fingolimod (Gilenya)	0.443	0.375	0.525
Glatiramer acetate (Copaxone)	0.684	0.612	0.757
Interferon beta-1a 30 mg (Avonex)	0.864	0.766	0.974
Interferon beta-1a 22 mcg (Rebif)	0.707	0.604	0.831
Interferon beta-1a 44 mcg (Rebif)	0.678	0.599	0.758
Interferon beta-1b 250 mg (Betaseron)	0.700	0.620	0.783
Interferon beta-1b 250 mg (Extavia)	0.700	0.620	0.783
Natalizumab (Tysabri)	0.315	0.263	0.378
Teriflunomide 7 mg	0.784	0.628	0.965
Teriflunomide 14 mg	0.743	0.592	0.924

CrI = credible interval; mg = milligram; RR = relative rate.

c) *Treatment safety*

Due to the transient nature of most of the adverse events related to the RRMS treatments (such as injection site reactions), as well as some of them potentially being related to the disease process (fatigue, depression), the implications of including them in the model (the costs of treating and decrements in quality of life) were expected to be negligible. Although the difference in safety profiles might be determinant for patients and physicians on choice of treatment, the costs and effects were expected to be similar among therapies.

PML has been identified by physicians and decision-makers as an important concern, and consequently the risk of PML associated with natalizumab was included in the model. Based on a recently published article by Hunt and Giovannoni,[70] there is a risk of developing PML (which is associated with a mortality rate of 18.5%) for 0.15% of patients on natalizumab.

However, given different concerns with some of the treatments, monitoring costs were included to capture some of the differences for resource use. The input for necessary monitoring associated with each of the treatments was obtained from two clinical MS experts (Table 12).

Table 12: Monitoring Associated With Treatments	
Treatment	**Monitoring**
Glatiramer acetate	No monitoring
Interferons	LFT every 6 months Thyroid test every 6 months CBC test every 6 months
Dimethyl fumarate	LFT every 6 months CBC test every 6 months
Fingolimod	Before starting treatment: CBC, antivaricela antibody test, 1 EKG + 50% chance of cardiologist visit + LFT + ophthalmology visit (funded by manufacturer) LFT every 6 months CBC test every 2 months
Natalizumab	Prior to starting treatment: CBC test + LFT + JC Virus assay (funded by manufacturer) MRI every 6 months CBC+ LFT every month
Alemtuzumab	Thyroid test every 3 months CBC test every 3 months
Teriflunomide	CBC test and LFT every month for the first 6 months; every 2 to 3 months thereafter

CBC = complete blood count; EKG = electrocardiogram; JC Virus = John Cunningham virus; LFT = liver function test; MRI = magnetic resonance imaging.
Source: Expert Opinion (April, 2013).

d) *Mortality*

RRMS is disabling, but not a life-threatening disease, and there is only a small impact on mortality, captured by EDSS = 10. Therefore, the model assumes that these treatments have no survival benefit.

All-cause mortality is calculated using the Statistics Canada life table for the data-years 2000 to 2002.[71,72]

The data include year-on-year mortality rate distinguished by sex. As the model does not take the sex of the cohort into account, a weighted average has been calculated based on the assumption that the percentage of female patients with RRMS is 68%, as per RCTs included in the CADTH systematic review. These probabilities represent the probability of dying from causes other than MS during any given cycle.

e) *Costs*

The costs included in the model are drug costs, monitoring costs, and costs associated with MS care (excluding drugs) by EDSS scores.

Drug costs were obtained from the Ontario Drug Benefit Formulary (2013). For the drugs for which Canadian prices were not available at the time the analyses were conducted, information was obtained from the US, where the ratio of prices for the new agents compared with existing treatments was calculated and used to determine the hypothetical price for the new drugs. For drugs that are not approved in Canada and for which no international price is available, a

conservative assumption was made that the cost will be equal to the highest-cost treatment. Sensitivity analysis regarding drugs costs was performed.

The annual drug cost was calculated based on recommended doses (Table 13) and detailed in a cost table (Table 44).

Table 13: Base Case Drug Costs

Drug/Comparator	Annual Drug Cost Base Estimate ($)	Reference
Alemtuzumab 12 mg	$40,281	Assumption[a]
Alemtuzumab 24 mg	$40,281	Assumption[a]
Dimethyl fumarate 240 mg (Tecfidera)	$23,019	Manufacturer's information
Fingolimod (Gilenya)	$31,170	Ontario MoH (2013)
Glatiramer acetate (Copaxone)	$16,286	Ontario MoH (2013)
Interferon beta-1a 30 mcg (Avonex)	$20,597	Ontario MoH (2013)
Interferon beta-1a 22 mcg (Rebif)	$20,210	Ontario MoH (2013)
Interferon beta-1a 44 mcg (Rebif)	$24,604	Ontario MoH (2013)
Interferon beta-1b 250 mcg (Betaseron)	$20,130	Ontario MoH (2013)
Interferon beta-1b 250 mcg (Extavia)	$18,183	Ontario MoH (2013)
Natalizumab (Tysabri)	$40,281	Ontario MoH (2013)
Teriflunomide oral 7 mg	$24,184	Assumption[b]
Teriflunomide oral 14 mg	$24,184	Assumption[b]

mcg= microgram; mg = milligram; MoH = Ministry of Health.
[a]The price of alemtuzumab is unavailable in Canada, and it was assumed to be the same as for natalizumab.
[b]The price of teriflunomide was based on the ratio between the price of fingolimod and the price of teriflunomide in the US.[73]

A systematic review of literature was conducted to identify Canadian studies reporting the cost associated with EDSS health states, as well as cost per relapse. Two major studies were found, Grima et al.[74] and Karampampa et al.[75] In addition, a study by Patwardhan reporting a systematic review of the cost of MS by level of disability was identified.[76]

The study by Grima et al. was based on a patient survey of RRMS patients recruited at MS clinics at the Montreal Neurological Institute and the London Health Sciences Centre: 153 patients in remission and 42 patients in relapse.[74] The study reported cost per EDSS scores, and it included both direct costs (outpatient resources, prescription medications) and indirect costs. This study included only ambulatory patients and, therefore, patients with an EDSS score higher than 6 were excluded.

The study by Karampampa et al. was based on a web-based questionnaire including 241 MS patients in Canada.[75] Of these, 235 patients had an EDSS score less than 7, and only six patients with an EDSS score of 7 or higher were included in the study. The costs included in the study were related to in-patient care, outpatient care, consultations, investigations, MS treatments, prescribed co-medication and OTC drugs, investments or modifications, professional care, informal care, and indirect costs.

Because this analysis was conducted from the perspective of a public payer, only direct costs were included. The study by Grima et al.[74] was used as a primary source for the health state 1 and 2. Since the study by Grima et al. included patients with an EDSS score up to 6, the costs for health states higher than 6 were calculated based on exponential extrapolation. This assumption was based on the aforementioned study by Patwardhan et al. which, based on the systematic review, concluded that costs rose at an exponential rate with increasing MS disability levels.[76] Further, the costs reported by Grima et al. did not include professional care needed for patients with more severe disability. To account for this, information was obtained from Karampampa et al.[75] and added to the total costs. Costs per health state were derived by averaging across the costs by disability levels, inflated to 2012 costs using Bank of Canada Consumer Price Index information (Table 14).

The cost of mild or moderate relapse was based on the study by Grima et al.,[74] as this study included only ambulatory patients who were interviewed during their visit. The cost per severe relapse was estimated based on the Patwardhan et al. study,[76] which reported that the cost of severe disabilities in RRMS is 240% higher than the cost of mild or moderate disability.

Table 14: Cost Estimates by Health State

Cost by EDSS	Annual Cost Estimate ($)	Probability Distribution	Source
Health State 1 (EDSS 0 to 2.5)	$1,990	Gamma (16,124.37)	Grima et al.(2000)[74]/ Karampampa et al. (2012)[75]
Health State 2 (EDSS 3 to 5.5)	$5,836	Gamma (16,364.75)	Grima et al. (2000)[74]/ Karampampa et al. (2012)[75]
Health State 3 (EDSS 6 to 7.5)	$22,780	Gamma (16,1423.77)	Extrapolated
Health State 4 (EDSS 8 to 9)	$42,452	Gamma (16,2653.25)	Extrapolated
Health State 5 (EDSS 10) (death)	$0	Fixed	Assumption
Cost per Relapse			
Mild/moderate	$6,402	Gamma (16, 87.83)	Grima et al. (2000)[74]
Severe	$15,365	Gamma (16, 960.30)	Extrapolated based on Patwardhan et al. (2005)[76]

EDSS = Expanded Disability Status Scale.

f) *Utilities*

Several sources for quality-of-life data in RRMS were identified based on a systematic review of the literature.[62,75,77-79] In the base case, the utilities values by Prosser were used,[62] because it considered the same health state definitions and was based on community-based preferences. The study collected both patients' and the general public's preferences by using the standard gamble method. Based on CADTH guidelines for economic evaluation — which state that preferences measured directly using a representative sample of the general public, who are suitably informed about the health states being valued, are preferred[80] — the results for the community-based group were used in the base case (Table 15).

Table 15: Base Case Utility Estimates				
Health State	**Utility**	**95% CI**		**Probability Distribution**
Health State 1 (EDSS 0 to 2.5)	0.954	0.936	0.971	Beta
Health State 2 (EDSS 3 to 5.5)	0.870	0.823	0.917	Beta
Health State 3 (EDSS 6 to 7.5)	0.769	0.680	0.858	Beta
Health State 4 (EDSS 8 to 9.5)	0.491	0.372	0.609	Beta
Health State 5 (EDSS 10) (death)	0.000	0.000	0.000	Fixed
Disutility associated with mild or moderate relapse	–0.091	–0.0119	–0.063	Log-normal
Disutility associated with severe relapse	–0.302	–0.366	–0.238	Log-normal

CI = confidence interval; EDSS = Expanded Disability Status Scale.
(Source: Prosser.[62])

Alternative sources were also included, such as Kobelt et al.,[77] ScHARR,[78] Earnshaw et al.,[79] and Karampampa et al.[75] (Table 16), and the impact of using these sources was tested in sensitivity analysis. It should be noted that, with the exception of Earnshaw, these alternative sources did not consider the same definitions of health states as in this model; therefore, the utility values were averaged across EDSS scores to reflect the health states in the model. Consequently, these utility estimates are used only in exploratory analysis.

Table 16: Alternative Utility Estimates					
Utility values	**Prosser[62] (Default)**	**Kobelt[77]**	**ScHARR[78]**	**Earnshaw[79]**	**Karampampa[75]**
Health State 1 (EDSS 0 to 2.5)	0.954	0.824	0.734	0.824	0.767
Health State 2 (EDSS 3 to 5.5)	0.870	0.679	0.595	0.679	0.635
Health State 3 (EDSS 6 to 7.5)	0.769	0.533	0.425	0.533	0.422
Health State 4 (EDSS 8 to 9.5)	0.491	0.533	0.232	0.491	0.275
Health State 5 (EDSS 10)	0.000	0.000	0.000	0.000	0.000

EDSS = Expanded Disability Status Scale.

3.3.8 Assumptions within the economic model

The following assumptions were made for the base case:

Assumption
Fixed discontinuation rate of 15% across treatments for the first 2 years, followed by no discontinuation thereafter
Adverse events, except PML, do not affect the ICUR (and were not included)
PML has impact on mortality rates, and no cost impact
Patients discontinue treatment once they reach EDSS = 7.0
Patients discontinue treatment once they progress to SPMS
Treatments have no effect on the transition between SPMS states
Treatment benefits are accrued only during the treatment period
Neutralizing antibodies are not included because of lack of data and confirmation from clinical experts that results are still controversial
Treatments have no survival benefit
Background costs related to EDSS states rise exponentially with increasing MS disability levels
Patients can progress by a maximum of one EDSS score per cycle (3 months)
Relapses have no residual effect
Patients cannot switch among treatments
Treatments not marketed in Canada are assumed to be in line with international pricing. Where international pricing is not available, the price is assumed to be in line with the highest-priced drug

EDSS = Expanded Disability Status Scale; ICUR = incremental cost-utility ratio; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; SPMS = secondary-progressive multiple sclerosis.

3.3.9 Sensitivity analyses

a) *Deterministic sensitivity analyses*

Extensive univariate sensitivity analyses were conducted to test the effect of changes in underlying parameter values and assumptions within the models. The analyses conducted were:

i) Parameter uncertainty —
- costs of treatments currently not marketed in Canada
- natural history of disability progression
- background MS costs
- cost of relapse
- utility values
- disutility associated with relapse
- rates of PML associated with natalizumab**.**

ii) Structural uncertainty —
- earlier discontinuation of treatment when patients progress to an EDSS score of 5.0 and 6.0 (base case assumes discontinuation upon progression to EDSS score of 7.0)
- no discontinuation of treatment because of progression to SPMS (base case assumes discontinuation because of progression to SPMS)

- time horizon of 10 years, 30 years, and 40 years (base case implements time horizon of 25 years)
- no improvements in EDSS scores (base case assumes improvements in EDSS scores)
- relapse rate being static (base case implements relapse rate as being time-dependent variable).

iii) Heterogeneity —
- baseline EDSS score
- baseline age.

b) *Probabilistic sensitivity analysis*

Probabilistic sensitivity analyses were conducted using Monte Carlo simulations, such that probability distributions related to natural history parameters, relative risks, costs, and utilities were incorporated into the analysis. The analysis adopted standard methods for defining uncertainty regarding parameters.[66] Transition probabilities were characterized by beta distributions, relapse rates were characterized by gamma, and relative risks were characterized by log-normal distributions. Utility values were characterized by beta distributions, while costs were characterized by gamma distributions. Drug costs were assumed fixed. Probability distributions were parameterized using empirical data; except for parameters where no measures of dispersion were available, in which case a coefficient of variation of 25% was assumed.

Estimates of incremental costs and QALYs were obtained by re-running the model employing values from the related probability distributions. In this study, 5,000 replications were conducted; i.e., a set of 5,000 outcome estimates was obtained. Cost-effectiveness acceptability curves were derived, which present the probability that each treatment is cost-effective given different values of willingness to pay for an additional QALY.

c) *Value of information analysis*

In addition to the deterministic and probabilistic sensitivity analyses, expected value of information analysis was conducted resulting in estimates of expected value of partial perfect information (EVPPI) for each uncertain input parameter. Expected value of perfect information is an information-based measure of the reduction in opportunity loss associated with obtaining perfect information (no uncertainty) on a parameter, and can be seen as a measure of decision sensitivity.[81] The decision sensitivity is determined by the probability that a decision based on existing information will be wrong, and the cost consequences if the wrong decision is made, as perfect information could eliminate the possibility of making a wrong decision.[82]

Therefore, the application of EVPPI is twofold. First, EVPPI can provide estimates of the value of conducting further research in this area, given the underlying uncertainty, and can be interpreted as the expected benefit by completely resolving uncertainty around an individual input parameter. Second, EVPPI can also be used as an importance measure identifying the contribution of uncertain input model parameters to output uncertainty.

In this analysis, because of the large number of input parameters, a screening method was applied which identified the input parameters that are candidates to having high EVPPI. Dominance measure was applied as a screening method.[83] Next, a novel algorithm for the calculation of a single EVPPI proposed by Sadatsafavi et al[84] has been applied. The method only relies on the data generated through Monte Carlo simulations (MCS), and one set of

simulations is enough to generate EVPPIs for each uncertain parameter of the model. The EVPPI is the approximation of the expected value of the difference between the net benefit of the optimal treatment and the maximum net benefits across all treatments.

3.3.10 Model validation

The model has extensively been validated. The face validity of the model has been confirmed by two independent clinical experts experienced in treating patients with RRMS, such that the model structure, model assumptions, and data inputs have been evaluated and confirmed that they reflect the available evidence and are consistent with the medical science. The internal validity of the model has been confirmed by an external technical reviewer consultant/health economist, with all mathematical calculations examined and confirmed to be performing correctly. As well, the model was confirmed to be free from computational errors. Cross-validation of the model has been performed by the primary modeller, with reports for other models in RRMS examined and compared. External validation tests of the model has been performed, with a specific emphasis on the natural history of disease, confirming that the outcome of the model have been consistent with the reported results of the natural history of disease studies.

4 RESULTS

4.1 Selection of Primary Studies

The original literature search identified 1,471 citations. Upon screening the titles and abstracts, 126 potentially relevant publications were retrieved for further scrutiny, as well as 45 additional references identified through other sources. Of the 171 potentially relevant reports, a total of 68 reports describing 30 unique studies were selected for inclusion. There were 27 studies[9-35] that provided comparisons of monotherapies, and four[35-38] that provided comparisons between combination therapy and monotherapy.

To be considered for inclusion, a trial needed to have at least two relevant treatment arms of employing interventions of interest. Nine studies[11,18,19,22,23,31,33-35] had at least one treatment arm excluded, as the intervention dosage was not consistent with current recommendations in Canada or the treatment arms did not meet our inclusion criteria. Of the 27 studies involving monotherapy, 14 studies[9,17-19,22-24,26-29,31,32,34] had a placebo arm. Of the combination therapy studies, three[36-38] were placebo-controlled add-on therapy trials and one[35] was a double-dummy active-controlled trial.

The trial selection process appears in a PRISMA flowchart in APPENDIX 6. Included and excluded studies are listed in APPENDIX 7 and APPENDIX 8, respectively.

4.2 Study and Patient Characteristics

4.2.1 Monotherapy

Table 17 provides a summary of the characteristics of the included studies. The 27 monotherapy studies included in this review randomized a total of 16,998 patients and, of these, 15,210 patients were assigned to a dose approved in Canada. The smallest study randomized 75 patients,[10] while the largest study randomized 1,430 patients.[18] The oldest trial was published

in 1993,[23] there were eight studies published in 2012,[12,14,15,18,19,31,31,36] and one study was published as recently as 2013.[35]

Three studies were single centre;[10,12,20] the remainder were all multi-centre trials. The largest number of centres involved was 200, in the CONFIRM study (dimethyl fumarate).[18] Of the multi-centre trials, seven were single-country,[10,12,20,25-28] while the remainder were multinational.

Table 17: Summary of Trial Characteristics

Trial Characteristics	Categories	Studies (n)
Publication status	Unique RCTs	27
Country	Multinational	19
	Single country	5
	Single centre	3
Study design	Double-blind	15
	Rater-blinded	9
	Open label	3
Sponsors	Manufacturer	21
	Manufacturer/public	2
	Public	2
	Not reported	2
Publication year		1993 to 2013
Randomized sample size		75 to 1,430
Number of sites		1 to 200

n = number; RCT = randomized controlled trial.

a) *Treatments evaluated*

Treatments evaluated included alemtuzumab (three unique RCTs),[13-15] dimethyl fumarate (two unique RCTs),[18,19] fingolimod (three unique RCTs),[22,31,33] glatiramer acetate (eight unique RCTs),[10-12,17,18,26,30,35] interferon beta-1a subcutaneous (nine unique RCTs),[12-15,20,21,24,29,30] interferon beta-1a intramuscular (nine unique RCTs),[12,16,20,21,25,27,33-35] interferon beta-1b (five unique RCTs),[10,11,20,23,25] natalizumab (one unique RCT),[9] and teriflunomide (two unique RCTs)[28,32] (Table 18).

There were 14 studies that used a placebo as a comparator.[9,17-19,22-24,26-29,31,32,34] Interferon beta-1a subcutaneous (two studies),[24,29] interferon beta-1a intramuscular (two studies),[27,34] dimethyl fumarate (two studies),[18,19] fingolimod (two studies),[22,31] teriflunomide (two studies),[28,32] glatiramer acetate (three studies),[17,18,26] interferon beta-1b (one study),[23] and natalizumab (one study)[9] had placebo as a comparator. Thirteen studies had active comparisons, and no more than two active treatments were included in any of these trials. CONFIRM was the only study to include both active and placebo comparisons; it was not designed to compare between the active treatments.[18] Dose comparative studies involved alemtuzumab (two studies),[13,15] interferon beta-1a intramuscular (one study),[16] interferon beta-1a subcutaneous (one study),[29] and teriflunomide (two studies).[28,32]

Table 18: Summary of Treatments Evaluated		
Treatment Evaluated	**Dose Specification**	**Studies (n)**
Alemtuzumab	12 mg IV infusion q.d. for 5 consecutive days at first month, 3 consecutive days at month 12	2
	24 mg IV infusion q.d. for 5 consecutive days at first month, 3 consecutive days at month 12	1
Natalizumab	300 mg IV infusion every 4 weeks	1
Interferon beta-1b (Betaseron)	250 mcg SC every other day	5
Glatiramer acetate	20 mg SC q.d.	8
Interferon beta-1a (Rebif)	22 mcg SC t.i.w.	1
	44 mcg SC t.i.w.	9
Interferon beta-1a (Avonex)	30 mcg IM q.w.	9
	60 mcg IM q.w.	1
Dimethyl fumarate	240 mg oral b.i.d.	2
Fingolimod	0.5 mg oral q.d.	3
Teriflunomide	7 mg oral q.d.	2
	14 mg oral q.d.	2

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mg = milligram; n = number; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly; mcg = microgram.

b) *Study design features*

All of the included studies were RCTs. Eleven studies were rater-blinded RCTs,[10-15,18,20,21,30,34] and three studies were open label,[25,30,34] while the remainder were all double-blind RCTs. With the exception of the EVIDENCE trial (interferon beta-1a), all of the rater-blinded trials had active comparators, as did the open-label studies. INCOMIN was rater-blinded for the MRI assessments but open label for assessment of clinical outcomes.[25]

Of the 24 studies that specified a primary end point, 13 had a primary end point of relapse,[11,18,19,21-23,25,26,29,30,32,33,35] two had disability as a primary end point,[16,27] five had an MRI outcome as a primary end point,[17,24,28,31,34] and four had co-primary end points of relapse and disability.[9,13-15] The five studies that identified MRI lesions as their primary outcome tended to have a shorter follow-up (16 weeks to nine months) and were smaller in size (N = 179 to N = 218),[17,24,28,31,34] compared with the other studies.

Sustained disability progression was confirmed over three months in 10 studies[9,11,18,19,22,23,26,32-34] and over six months in eight studies.[13-16,25,27,30,35]

c) *Follow-up duration*

The most common duration of follow-up was two years. The shortest follow-up was 16 weeks and the longest duration of follow-up was up to 3.5 years. The BEYOND study, which had the longest duration of follow-up (3.5 years), was also the largest study included in this review.[11] The study with the shortest follow-up (IMPROVE) was also a small study (N = 180).[24]

d) *Funding*

All but two studies[20,23] reported on sponsorship. Two studies were publicly funded,[25,35] two studies[26,27] disclosed public or manufacturer funding, and the remainder were manufacturer-funded.

e) *Populations*

All studies included patients with RRMS; however, one study included patients with clinically isolated syndrome (CIS) (19%),[10] one study included patients with progressive-relapsing MS (PRMS) (15%),[16] one study included patients with secondary-progressive MS (12%),[28] and one study included patients with secondary-progressive MS (5%) and progressive-relapsing MS (3%).[32] MS was diagnosed based on McDonald criteria in 16 studies[9,11,13-15,18,19,22-24,30-35] McDonald/Polman criteria in one study,[12] Poser et al. in nine studies,[16,17,20,21,25-29] and one study did not specify the criteria used.[10] Most studies specified a range baseline of EDSS scores that were acceptable for inclusion, the most common being an EDSS of 0 to 5 (11 studies),[9,11,12,15,17-20,26,27,29] or 0 to 5.5 (eight studies).[21-24,30,32,33,35] The largest EDSS range was 0 to 6.0 (three studies).[28,31,34] There were two studies that included patients with an EDSS of 0 to 3,[13,14] two studies had an EDSS of 1 to 3.5,[25,27] and one study that included patients with EDSS 2.0 to 5.5.[16] The mean baseline EDSS ranged from 2.0 to 2.7 across the studies, with the exception of the Clanet et al. study, wherein the baseline EDSS was 3.6.[16]

In all 27 studies, the majority of participants were female (range: 64% to 84% across the studies) and the mean age ranged from 29 to 41 years. These patient characteristics are consistent with MS in that patients are typically diagnosed in their late 20s or early 30s and are predominantly female. Most studies that reported ethnic background had a majority of Caucasian patients (range: 78% to 98%), with the exception of a small study conducted in Iran, where 52% of patients were Caucasian.[20]

All but two studies[24,30] reported on the number of prior relapses. Of the studies that reported relapses within the past year, most reported between 1.0 and 1.8 relapses. Etemadifar, which was a small study (N = 90), reported a mean of 2.2 relapses in the previous year.[20] Relapse rate is considered an indicator of disease activity. The time since symptom onset ranged between 1.2 and 9.2 years for those studies that reported a mean. The number of GdE lesions at baseline was reported in 13 studies.[9,11,14,15,17,19,22,30-35] Five studies reported a mean number of GdE lesions between 2.1 and 2.5,[9,11,14,15,34] six studies reported values between 1.2 and 1.7,[19,22,30-33] and two studies reported 4.3 GdE lesions at baseline.[17,35] Years since symptoms onset varied across studies, ranging from a median of 1.1 years[10] to a mean of 9.2 years.[28]

4.2.2 Combination therapy

One head-to-head, double-blind, double-dummy RCT[35] and three placebo-controlled, double-blind RCTs[36-38] were identified.

One phase 3 study (CombiRx; N = 1,008)[35] compared the combination of interferon beta-1a 30 mcg plus glatiramer acetate with either agent alone in RRMS patients, who were not previously treated with either interferon or glatiramer acetate.

One phase 2 study (Freedman et al.; N = 118)[36] evaluated the safety and tolerability of teriflunomide as add-on to an ongoing stable dose of interferon beta (Avonex, Rebif, or Betaseron) in patients with RRMS, SPMS, or PRMS. The proportion of different types of MS patients was not reported. All patients received a stable dose of interferon beta for at least 26 weeks before screening.

One phase 2 study (GLANCE; N = 110)[37] evaluated the safety and tolerability of natalizumab as add-on to glatiramer acetate in RRMS patients who were previously treated with glatiramer acetate for at least 12 months.[37]

One phase 3 study (SENTINEL; N = 1,171)[38] evaluated the safety and efficacy of natalizumab as add-on to interferon beta-1a 30 mcg in patients with RRMS, who had received treatment with interferon beta-1a for at least 12 months. Patients were excluded if they had primary-progressive, secondary-progressive, or progressive-relapsing MS, or if they had received an approved disease-modifying therapy other than interferon beta-1a 30 mcg within the 12-month period before randomization.

Treatment duration in the two phase 2 studies[36,37] was 24 weeks, and in the two phase 3 studies was two years[38] and three years.[35] Across the studies, mean age ranged from 38 to 41 years, mean baseline EDSS scores from 2.0 to 2.7, and mean number of relapses in the previous year from 0.8 to 1.7. Three of four studies reported the mean number of GdE lesions, which ranged from 0.6 in the GLANCE study[37] to 4.3 in the CombiRx study.[35]

The end points included the proportion of patients with sustained disability progression,[35,37,38] ARR,[35-38] MRI outcomes,[35-38] and adverse events.[35-38] Three studies were manufacturer-sponsored[36-38] and one received public funding.[35]

Table 19 and Table 20 provide overviews of study characteristics and patient characteristics, respectively. More details of study characteristics and patient characteristics are presented in APPENDIX 9.

Table 19: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Follow-up**	**Outcome(s)**
Monotherapy					
AFFIRM (2006)[9] DB RCT Multi-centre, multi-country (including Europe, North America)	Randomized: N = 942 Completed: N = 856 (91%)	RRMS patients (18 to 50 years), EDSS: 0 to 5.0, had MRI lesions with MS, with ≥ 1 relapse within 12 months	**Natalizumab 300 mg IV every 4 weeks** (n = 627) **Placebo** (n = 315)	2 years	Relapse Disability MRI AEs QoL
BECOME (2009)[10] Rater-blinded RCT Single centre, US	Randomized: N = 75 Completed: N = 64 (85%)	RRMS (79%) or CIS (21%) patients (18 to 55 years)	**Interferon beta-1b 250 mcg SC every other day** (n = 36) **Glatiramer acetate 20 mg SC q.d.** (n = 39)	2 years	MRI Relapse
BEYOND[a] **(2009)**[11] Rater-blinded RCT Multi-centre, 26 countries worldwide	Randomized: N = 2,244 Completed: N = 1,884 (84%)	RRMS patients (18 to 55 years), EDSS: 0-5.0, with ≥ 1 relapse within 12 months	**Interferon beta-1b 250 mcg SC every other day** (n = 897) **Glatiramer acetate 20 mg SC q.d.** (n = 448)	2 to 3.5 years	Relapse Disability MRI
Calabrese et al. (2012)[12] Rater-blinded RCT Single centre, Italy	Randomized: N = 165 Completed: N = 141 (85%)	RRMS patients (18 to 55 years), EDSS: 0-5.0	**Interferon beta-1a 44 mcg SC t.i.w.** (n = 55) **Interferon beta-1a 30 mcg IM q.w.** (n = 55) **Glatiramer acetate 20 mg SC q.d.** (n = 55)	2 years	MRI Relapse Disability
CAMMS223 (2008)[13] Rater-blinded RCT Multi-centre, multi-country (including Europe, US)	Randomized: N = 334 Completed: N = 250 (75%)	RRMS patients, EDSS: 0 to 3.0, with ≥ 2 relapses in previous 2 years	**Alemtuzumab 12 mg IV q.d. 5 consecutive days at 1st month, 3 consecutive days at months 12 and 24** (n = 113) **Alemtuzumab 24 mg IV q.d.** (n = 110) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 111)	36 months	Disability Relapse MRI AEs
CARE-MS I (2012)[14] Rater-blinded RCT Multi-centre, multi-country (including Europe, Canada, US)	Randomized: N = 581 Completed: N = 526 (91%)	RRMS patients (18 to 50 years), EDSS: 0-3.0, with ≥ 2 relapses in previous 2 years, had MRI lesions with MS	**Alemtuzumab 12 mg IV q.d., 5 consecutive days at month 0, 3 consecutive days at month 12** (n = 386) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 195)	2 years	Relapse Disability MRI AEs

Table 19: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Follow-up**	**Outcome(s)**
CARE-MS II (2012)[15] Rater-blinded RCT Multi-centre, multi-country (including Europe, Canada, US)	Randomized: N = 840 Completed: N = 715 (85%)	RRMS patients (18 to 55 years), EDSS: 0 to 5.0, with ≥ 2 relapses in previous 2 years, had MRI lesions with MS	**Alemtuzumab 12 mg IV q.d., 5 consecutive days at month 0, 3 consecutive days at month 12** (n = 436) **Alemtuzumab 24 mg IV q.d.** (n = 173) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 231)	2 years	Relapse Disability MRI AEs
Clanet et al. (2002)[16] DB RCT Multi-centre, multi-country (Europe)	Randomized: N = 802 Completed: N = 559 (70%)	RRMS patients (18 to 55 years), EDSS: 2.0 to 5.5, with ≥ 2 relapses in previous 3 years	**Interferon beta-1a 30 mcg IM q.w.**(n = 402) **Interferon beta-1a 60 mcg IM q.w.** (n = 400)	≥ 36 months	Disability Relapse MRI AEs
Comi et al. (2001)[17] DB RCT Multi-centre, multi-country (including Europe, Canada)	Randomized: N = 239 Completed: N = 225 (94%)	RRMS patients (18 to 50 years), EDSS: 0 to 5.0, with ≥ 1 relapse in previous 2 years, had MRI lesions with MS	**Glatiramer acetate 20 mg SC q.d.** (n = 119) **Placebo** (n = 120)	9 months	MRI Relapse AEs
CONFIRM[a] **(2012)**[18] Rater-blinded RCTMulti-centre, multi-country (including Europe, North America)	Randomized: N = 1,430 Completed: N = 1,127 (79%)	RRMS patients (18 to 55 years), EDSS: 0 to 5.0, with ≥ 1 relapse in previous year, had ≥ 1 Gd+ enhancing lesion 0 to 6 weeks before randomization	**Dimethyl fumarate 240 mg oral b.i.d.** (n = 359) **Placebo** (n = 363) **Glatiramer acetate 20 mg SC q.d.** (n = 350)	2 years	Relapse MRI Disability AEs
DEFINE[a] **(2012)**[19] DB RCT Multi-centre, multi-country (including Europe, Canada, US)	Randomized: N = 1,234 Completed: N = 952 (77%)	RRMS patients (18 to 55 years), EDSS: 0 to 5.0, with ≥ 1 relapse in previous year, had ≥ 1 Gd+ enhancing lesion 0 to 6 weeks before randomization	**Dimethyl fumarate 240 mg oral b.i.d.** (n = 410) **Placebo** (n = 408)	2 years	Relapse MRI Disability AEs

Table 19: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Follow-up**	**Outcome(s)**
Etemadifar et al. (2006)[20] Rater-blinded RCT Single centre, Iran	Randomized: N = 90 Completed: N = 90 (100%)	RRMS patients (15 to 50 years), EDSS: 0 to 5.0, with ≥ 2 relapses in previous 2 years, clinical- or laboratory-supported diagnosis of relapsing MS	**Interferon beta-1b 250 mcg SC every other day** (n = 30) **Interferon beta-1a 30 mcg IM q.w.** (n = 30) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 30)	24 months	Relapse Disability
EVIDENCE (2002)[21] Rater-blinded RCT Multi-centre, multi-country (including Europe, Canada, US)	Randomized: N = 677 Completed: N = 649 (96%)	RRMS patients (18 to 55 years), EDSS: 0 to 5.5, with ≥ 2 relapses in previous 2 years	**Interferon beta-1a 30 mcg IM q.w.** (n = 338) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 339)	24 weeks	Relapse Disability MRI AEs
FREEDOMS[a] **(2010)**[22] DB RCT Multi-centre, multi-country (including Australia, Canada, Europe, South Africa)	Randomized: N = 1,272 Completed: N = 1,034 (81%)	RRMS patients (18 to 55 years), EDSS: 0 to 5.5, with ≥ 2 relapses in previous 2 years	**Fingolimod oral 0.5 mg q.d.** (n = 425) **Placebo** (n = 418)	24 months	Relapse Disability AEs
IFNB-MS[a] **(**1993)[23] DB RCT Multi-centre, multi-country (Canada, US)	Randomized: N = 372 Completed: N = 250 (67%)	RRMS patients (18 to 50 years), EDSS: 0 to 5.5, with ≥ 2 relapses in previous 2 years	**Interferon beta-1b 250 mcg SC every other day** (n = 124) **Placebo** (n = 123)	3 years	Relapse Disability MRI
IMPROVE (2010)[24] DB RCT Multi-centre, multi-country (Europe)	Randomized: N = 180 Completed: N = nr	RRMS patients (18 to 60 years), EDSS: 0 to 5.5, with ≥ 1 relapse and ≥ 1 Gd+ MRI lesion in previous 6 months	**Interferon beta-1a 44 mcg SC t.i.w.** (n = 120) **Placebo** (n = 60)	16 weeks	MRI Relapse AEs
INCOMIN (2002)[25] Open-label, rater-masked RCT Multi-centre, Italy	Randomized: N = 188 Completed: N = 158 (84%)	RRMS patients (18 to 50 years), EDSS: 1.0 to 3.5, with ≥ 2 relapses in previous 2 years	**Interferon beta-1a 30 mcg IM q.w.** (n = 92) **Interferon beta-1b 250 mcg SC every other day** (n = 96)	2 years	Relapse Disability MRI AEs

Table 19: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Follow-up**	**Outcome(s)**
Johnson et al. (1995)[26] DB RCT Multi-centre, US	Randomized: N = 251 Completed: N = 215 (86%)	RRMS patients (18 to 45 years), EDSS: 0-5.0, with ≥ 2 relapses in previous 2 years	**Glatiramer acetate 20 mg SC q.d.** (n = 125) **Placebo** (n = 126)	24 months	Relapse Disability AEs
Kappos et al. [a] **(2011)**[34] Open-label, rater-masked RCT Multi-centre, multi-country (including America, Europe, Asia)	Randomized: N = 218 Completed: N = 204 (94%)	RRMS patients (18 to 55 years), EDSS: 1.0 to 6.0, with ≥ 2 relapses in previous 3 years; had ≥ 6 T2 lesions per MRI	**Interferon beta-1a 30 mcg IM q.w.** (n = 55) **Placebo** (n = 54)	24 weeks	MRI Relapse AEs
MSCRG (1996)[27] DB RCT Multi-centre, US	Randomized: N = 301 Completed: N = 278 (92%)	RRMS patients (18 to 55 years), EDSS: 1.0 to 3.5, with ≥ 2 relapses in previous 3 years	**Interferon beta-1a 30 mcg IM q.w.** (n = 158) **Placebo** (n = 143)	2 years	Disability Relapse MRI AEs
O'Connor et al. (2006)[28] DB RCT Multi-centre, Canada	Randomized: N = 179 Completed: N = 160 (89%)	RRMS or SPMS patients (18 to 65 years), EDSS: 1.0 to 6.0, with ≥ 2 relapses in previous 3 years	**Teriflunomide oral 7 mg q.d.** (n = 61) **Teriflunomide oral 14 mg q.d.** (n = 57) **Placebo** (n = 61)	36 weeks	MRI Relapse Disability AEs
PRISMS (1998)[29] DB RCT Multi-centre, multi-country (including Australia, Canada, Europe)	Randomized: N = 560 Completed: N = 502 (90%)	RRMS patients, EDSS: 0 to 5.0, with ≥ 2 relapses in previous 2 years	**Interferon beta-1a 22 mcg SC t.i.w.** (n = 189) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 184) **Placebo** (n = 187)	2 years	Relapse MRI Disability AEs

Table 19: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Follow-up**	**Outcome(s)**
REGARD(2008)[30] Open-label, rater-masked RCT Multi-centre, multi-country (Canada, South America, Europe)	Randomized: N = 764 Completed: N = 625 (82%)	RRMS patients, EDSS: 0 to 5.5, with ≥ 1 relapse in previous year	**Interferon beta-1a 44 mcg SC t.i.w.** (n = 386) **Glatiramer acetate 20 mg SC q.d.** (n = 378)	96 weeks	Relapse MRI Disability AEs
Saida et al.[a] **(2012)**[31] DB RCT Multi-centre, Japan	Randomized: N = 171 Completed: N = 147 (86%)	RRMS patients (18 to 60 years), EDSS: 0 to 6.0, with ≥ 2 relapses in previous 2 years	**Fingolimod oral 0.5 mg q.d.** (n = 57) **Placebo** (n = 57)	6 months	MRI Relapse AEs
TEMSO (2011)[32] DB RCT Multi-centre, multi-country (including Canada, Europe, US)	Randomized: N = 1,088 Completed: N = 798 (73%)	RRMS patients (18 to 55 years), EDSS: 0 to 5.5, with ≥ 2 relapses in previous 2 years	**Teriflunomide oral 7 mg q.d.** (n = 365) **Teriflunomide oral 14 mg q.d.** (n = 358) **Placebo** (n = 363)	108 weeks	Relapse Disability MRI AEs
TRANSFORMS[a] **(2010)**[33] DB RCT Multi-centre, multi-country (including Canada, Australia, Europe, and US)	Randomized: N = 1,292 Completed: N = 1,153 (89%)	RRMS patients (18 to 55 years), EDSS: 0 to 5.5, with ≥ 2 relapses in previous 2 years	**Fingolimod oral 0.5 mg q.d.** (n = 431) **Interferon beta-1a 30 mcg IM q.w.** (n = 435)	12 months	Relapse MRI Disability AEs
Combination Therapy					
CombiRx (2013)[35] Phase 3 DB RCT Multi-centre, US and Canada	Randomized: N = 1,008 Completed: N = 814	RRMS patients (18-60 years), EDSS: 0 to 5.5, with ≥ 2 relapses in previous 3 years	**Interferon beta-1a 30 mcg IM q.w. + glatiramer acetate 20 mg SC q.d.** (n = 499) **Interferon beta-1a 30 mcg IM q.w.** (n = 250) **Glatiramer acetate 20 mg SC q.d.** (n = 259)	36 months	Relapse Disability MRI AEs

Table 19: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Follow-up**	**Outcome(s)**
Freedman et al. (2012)[36] DB RCT Multi-centre, multi-country (Canada, Germany, Italy, Spain, US)	Randomized: N = 118 Completed: N = 107 (91%)	RRMS or SPMS patients (18 to 55 years), EDSS: 0-5.5, had no relapse for 8 weeks, received stable dose of interferon beta for ≥ 26 weeks	**Teriflunomide oral 7 mg q.d. + interferon beta** (n = 37) **Teriflunomide oral 14 mg q.d. + interferon beta** (n = 38) **Placebo + interferon beta** (n = 41)	24 weeks	AEs MRI Relapse
GLANCE(2009)[37] DB RCT Multi-centre, 25 countries (including Canada, US)	Randomized: N = 110 Completed: N = 95 (86%)	RRMS patients (18 to 55 years), EDSS: 0-5.0, treated with glatiramer acetate for ≥ 12 months, with ≥ 1 relapses, had MRI lesions with MS	**Natalizumab 300 mg IV every 4 weeks + glatiramer acetate 20 mg SC q.d.** (n = 55) **Placebo + glatiramer acetate** (n = 55)	24 weeks	MRI Relapse rate Disability AEs
SENTINEL (2006)[38] DB RCT Multi-centre, 25 countries (including Europe, US)	Randomized: N = 1,171 Completed: N = 1,003 (86%)	RRMS patients (18 to 55 years), EDSS: 0 to 5.0, with ≥ 1 relapse in previous year, had received treatment with interferon beta-1a	**Natalizumab 300 mg IV every 4 weeks + interferon beta-1a** (n = 589) **Placebo + interferon beta-1a** (n = 582)	2 years	Relapse MRI Disability AEs QoL

AEs = adverse events; ARR = annual relapse rate (total number of relapses divided by the number of patient-years); b.i.d. = twice daily; CIS = clinically isolated syndromes; DB = double-blind; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium; IM = intramuscular; IV = intravenous; mg = milligram; MRI = magnetic resonance imaging; MS = multiple sclerosis; nr = not reported; q.d. = once daily; QoL = quality of life; q.w. = once weekly; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis; t.i.w. = three times weekly.

[a]At least one treatment arm that did not meet the inclusion criteria was removed from that study.

Table 20: Summary of Patient Baseline Characteristics								
Study	**Age, Mean ± SD (y)**	**Sex (%)**		**Caucasian (%)**	**Years Since Symptoms Onset, Mean ± SD**	**Relapse in Previous Year, Mean ± SD**	**EDSS, Mean ± SD**	**No. of GdE Lesions, Mean ± SD**
		M	**F**					
Monotherapy								
AFFIRM[9] N = 942	36 ± 8	30	70	95	Median: 5	1.5 ± 0.9	2.3 ± 1.2	2.2 ± 4.7
BECOME[10] N = 75	36 ± nr	31	69	52	Median: 1.1	Median ARR: 1.9	Median: 2	nr
BEYOND[11] N = 2,244	36 ± nr	31	69	91	5.3 ± nr	1.6 ± nr	2.3 ± nr	2.1 ± nr
Calabrese et al. (2012)[12] N = 165	37 ± 10	30	70	nr	5.6 ± 2.4	ARR: 1.2 ± 0.7	2.0 ± 1.1	nr
CAMMS223[13] N = 334	32 ± 8	36	64	90	nr	2 y: 2.7 ± nr	2.0 ± 0.8	nr
CARE-MS I[14] N = 581	33 ± 8	35	65	95	2.1 ± 1.4	1.8 ± 0.8	2.0 ± 0.8	2.3 ± 4.8
CARE-MS II[15] N = 840	35 ± 8	33	67	89	4.5 ± 2.7	1.6 ± 0.8	2.7 ± 1.2	2.4 ± 6.4
Clanet et al. (2002)[16] N = 802	37 ± 8	32	68	98	6.6 ± 5.5	1.3 ± 0.6	3.6 ± 1.0	nr
Comi et al. (2001)[17] N = 239	34 ± 8	nr	nr	nr	8.1 ± 5.5	2 y: 2.6 ± 1.6	2.4 ± 1.2	4.3 ± 6.1
CONFIRM[18] N = 1430	37 ± 9	30	70	84	nr	1.4 ± 0.7	2.6 ± 1.2	nr
DEFINE[19] N = 1,234	38 ± 9	26	74	78	nr	1.3 ± 0.7	2.4 ± 1.2	1.3 ± 3.7
Etemadifar (2006)[20] N = 90	29 ± 7	24	76	nr	3.2 ± 2.3	2.2 ± 0.9	2.0 ± 0.9	nr
EVIDENCE[21] N = 677	38 ± nr	25	75	91	6.6 ± nr	2 y: 2.6 ± nr	2.3 ± nr	nr
FREEDOMS[22] N = 1,272	37 ± 9	30	70	nr	8.2 ± 6.7	1.5 ± 0.8	2.4 ± 1.4	1.6 ± 4.6
IFNB-MS[23] N = 372	35 ± 7	30	70	94	nr	2 y: 3.4 ± 1.6	2.9 ± 1.1	nr
IMPROVE[24] N = 180	nr	nr	nr	nr	nr	nr	nr	nr
INCOMIN[25] N = 188	37 ± 8	35	65	nr	6.3 ± 4.8	ARR: 1.5 ± 0.6	2.0 ± 0.7	nr
Johnson et al. (1995)[26] N = 251	34 ± 6	27	73	94	6.9 ± 5.0	2 y: 2.9 ± 1.2	2.6 ± 1.3	nr

Table 20: Summary of Patient Baseline Characteristics								
Study	**Age, Mean ± SD (y)**	**Sex (%)**		**Caucasian (%)**	**Years Since Symptoms Onset, Mean ± SD**	**Relapse in Previous Year, Mean ± SD**	**EDSS, Mean ± SD**	**No. of GdE Lesions, Mean ± SD**
		M	**F**					
Kappos et al. (2011)[34] N = 218	38 ± 9	35	65	96	Median: 6	nr	3.3 ± 1.4	2.5 ± 6.1
MSCRG[27] N = 301	37 ± 7	27	73	92	6.5 ± 6.6	1.2 ± 0.6	2.4 ± 0.8	nr
O'Connor et al. (2006)[28] N = 179	39 ± 9	26	74	nr	9.2 ± 7.7	Median: 1	Median: 2.3	nr
PRISMS[29] N = 560	Median: 35	31	69	nr	Median: 5.3	2 y: 3.0 ± 1.2	2.5 ± 1.2	nr
REGARD[30] N = 764	37 ± 10	29	71	94	6.2 ± 6.7	nr	2.3 ± 1.3	1.6 ± 4.8
Saida et al. (2012)[31] N = 171	35 ± 9	31	69	0	7.8 ± 6.5	1.6 ± 1.2	2.1 ± 1.8	1.4 ± 2.5
TEMSO[32] N = 1,088	38 ± 9	28	72	97	8.7 ± 6.9	1.4 ± 0.7	2.7 ± 1.3	1.7 ± 4.2
TRANSFORMS[33] N = 1,292	36 ± 9	33	67	94	7.4 ± 6.2	1.5 ± 1.0	2.2 ± 1.3	1.2 ± 3.6
Combination Therapy								
CombiRx[35] N = 1,008	38 ± 10	28	72	88	1.2 ± 3.3	1.7 ± 0.8	2.0 ± 1.2	4.3 ± 5.8
Freedman et al. (2012)[36] N = 118	40 ± 8	30	70	97	nr	0.8 ± 0.8	2.5 ± 1.4	nr
GLANCE[37] N = 110	41 ± 8	16	84	87	Median: 8	1.4 ± 0.6	2.7 ± 1.1	0.6 ± 1.5
SENTINEL[38] N = 1,171	39 ± 8	26	74	93	Median: 7	1.5 ± 0.7	2.4 ± 1.1	0.9 ± 2.2

ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; F = female; GdE = gadolinium-enhancing; M = male; N = total number of patients in the trial; nr = not reported; SD = standard deviation; y = year.

4.3 Critical Appraisal of Included Studies

4.3.1 Monotherapy

The methodological approaches to randomization and allocation concealment were generally adequate in most studies (Table A10.1). Demographic and baseline characteristics were generally balanced between-treatment groups. One study had treatment groups with different baseline characteristics.[20] In this study — a comparison between three interferon drugs (Betaseron, Avonex, and Rebif) — there was a significant difference between the Betaseron and Avonex groups in the number of participants at baseline who had an EDSS ≤ 1.5.[20] This difference in baseline disability was not discussed by the authors; however, with a sample size of 90 participants, this was one of the smallest trials included in the systematic review and thus the potential for bias in this small study is unlikely to affect our results.

Many of the included trials compared oral versus injectable agents,[18,33] intravenous versus subcutaneous,[13-15] intramuscular versus subcutaneous,[12,20,25] or different dosing schedules[10,11] that made patient blinding challenging; therefore, many of the trials were not double-blinded. Of the 27 included studies, only 15 were double-blinded RCTs,[9,16,17,19,22-24,26-29,31-33,35] while the remainder were rater-blinded (N = 9)[10-15,18,20,21] or open label (N = 3).[25,30,34] In rater-blinded trials, the assessors evaluating the treatment results were blinded to the patients' treatment allocation. The INCOMIN study was rater-blinded for the MRI assessments but open label for assessment of clinical outcomes.[25] However, in all trials, the differing side-effect profiles of the MS drugs further complicate the ability to blind.

The clinical outcome analyses in all studies, except three,[11,12,31] were performed based on the ITT approach. BEYOND was a large study but did not report whether all patients were included in the ITT analyses.[11] Calabrese et al.[12] and Saida et al.[31] were small studies and did not use the ITT approach in their analyses. In most studies, the analyses of MRI outcomes were not performed based on the ITT approach; MRI populations were usually smaller than the efficacy and safety populations, and it is unclear how the MRI populations were selected.

Treatment duration varied from 16 weeks to 3.5 years, with the majority being two years or more. There were six studies[17,24,31,36,37,85] with a treatment duration of less than one year. The patient characteristics that were similar among trials were mean age (around 35 years), mean or median number of relapse in the previous year (less than two), mean or median EDSS scores at baseline (between 2 and 3). However, the population was relatively younger in the Etemadifar et al. study,[20] with a mean age of 29 years, and the mean EDSS score at baseline was 3.6 in the Clanet et al. study.[16] Most studies included RRMS patients, while four[10,16,28,32] had small proportions of other forms of MS (CIS, SPMS, PRMS) in their patient population. In many studies, it was unclear if patients were treatment-naive or treatment-experienced. Assumptions regarding treatment history had to be made to allow for meta-regression and subgroup analyses as a means of exploring the effect of this covariate on treatment effects. The time since symptom onset was substantially heterogeneous across studies; mean or median ranged from 1.1 to 9.2 years.

Loss to follow-up varied across studies (from 0% in Etemadifar et al.[20] to 33% in IFNB-MS[23]). Treatment duration appeared to play a role in dropout, as studies with follow-up of three years or more (such as CAMMS223,[13] Clanet et al.,[16] and IFNB-MS[23]) had dropout rates ranging from 25% to 33%. Studies with marked differences between-treatment arms in the dropout rate included CAMMS223,[13] CARE-MS I,[14] and CARE-MS II.[15] In those studies, alemtuzumab was compared with interferon beta-1a 44 mcg, and total withdrawal in the interferon group was

noticeably higher than that in the alemtuzumab group. The approach used to handle missing data was not reported in the publications of those studies. The higher dropout rate in one arm compared with the other may affect the outcome assessment, although an ITT approach was used for the analyses in those studies.

Finally, the definition of sustained disability progression differed across trials in how long the reduction in the EDSS needed to be sustained: three months versus six months.

4.3.2 Combination Therapy

There were two phase 2[36,37] and two phase 3[35,38] studies that were all multi-centre and double-blinded RCTs. Randomization was adequate in all four studies (Table A10.1). Allocation concealment was adequately reported in the phase 3 studies, but not reported in the phase 2 studies. Baseline characteristics were balanced between groups in three studies[35,36,38] but not in GLANCE,[37] in which there was a higher proportion of women in the natalizumab group (91%) compared with placebo (76%). As it is possible that the different agents have differing effects based on gender, this may confound the results. An ITT approach was used for the analyses in all four studies. Loss to follow-up from these studies ranged from 6%[37] to 19%.[35]

4.4 Data Synthesis

4.4.1 Monotherapy

a) *Efficacy*

Among the 27 included trials, there were 24 direct pairwise comparisons that had data for efficacy and 24 direct pairwise comparisons for safety. There were a total of 14 treatment strategies, including placebo, alemtuzumab 12 mg, alemtuzumab 24 mg, dimethyl fumarate, fingolimod 0.5 mg, glatiramer acetate, interferon beta-1a 30 mcg, interferon beta-1a 60 mcg, interferon beta-1a 22 mcg, interferon beta-1a 44 mcg, interferon beta-1b 250 mcg, natalizumab, teriflunomide 7 mg, and teriflunomide 14 mg. Dosing regimens for these agents are described in Table 21. These 14 treatment strategies were evaluated in the direct pairwise meta-analysis and the NMAs.

Table 21: Summary of Interventions Evaluated		
Interventions	**Individual Trials (n)**	**Patients (n)**
Treatment strategies included in the NMA		
Alemtuzumab 12 mg IV	3	935
Alemtuzumab 24 mg IV	1	110
Dimethyl fumarate 240 mg b.i.d.	2	769
Fingolimod 0.5 mg oral q.d.	3	913
Glatiramer acetate 20 mg SC q.d.	8	1773
Interferon beta-1a 30 mcg IM q.w.	9	1815
Interferon beta-1a 60 mcg IM q.w.	1	400
Interferon beta-1a 22 mcg SC t.i.w.	1	189
Interferon beta-1a 44 mcg SC t.i.w.	9	1651
Interferon beta-1b 250 mcg SC q.o.d.	5	1183
Natalizumab 300 mg IV	1	627
Teriflunomide 7 mg oral q.d.	2	426
Teriflunomide 14 mg oral q.d.	2	415
Placebo	15	2863

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mg = milligram; n = number; NMA = network meta-analysis; q.d. = once daily; q.o.d. = every other day; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Pairwise meta-analyses were conducted for ARR, proportion of patients relapse-free, proportion of patients with sustained disability progression, mean change in EDSS from baseline, mean change in MSFC from baseline, proportion of patients with GdE lesions, mean number of GdE lesions, proportion of patients with new or enlarging T2 lesions, mean number of new or enlarging T2 lesions, and safety outcomes.

NMAs were conducted for ARR and a proportion of patients with sustained disability progression based on input from clinical experts that identified these as the most appropriate measures of relapse and disability (Table 22). The number of RCTs included in the evidence networks for ARR and the proportion with sustained disability progression was 27 and 19 studies, including 16,998 and 15,982 patients, respectively. NMAs were not conducted for MRI outcomes because the evidence networks were relatively unstable because of sparse connection between treatments, and the MRI populations in many studies were subsets of patients with unclear selection criteria for MRI scans (Table A10.2). Additionally, the low events of key safety outcomes, such as serious adverse events and treatment discontinuation because of adverse events, precluded the conduct of NMA.

Table 22: Overview of Evidence and Analyses Performed				
Outcomes	**No. of Treatment Strategies**	**No. of Pairwise Comparisons**	**No. of Studies and Patients**	**Type of Analysis Conducted**
Annualized relapse rate	14	24	27 RCTs (N = 16,998)	Pairwise and MTC
Proportion of patients relapse-free	14	24	26 RCTs (N = 14,274)	Pairwise
Proportion of patients with sustained disability progression	14	23	19 RCTs (N = 15,982)	Pairwise and MTC
Mean change in EDSS	10	16	13 RCTs (N = 6,045)	Pairwise
Mean change in MSFC	5	4	5 RCTs (N = 3,639)	Pairwise
Proportion of patients with GdE lesions	11	11	12 RCTs (N = 6,078)	Pairwise
Mean number of GdE lesions	11	14	14 RCTs (N = 6,815)	Pairwise
Proportion of patients with new or enlarging T2 lesions	12	14	13 RCTs (N = 5,833)	Pairwise
Mean number of new or enlarging T2 lesions	11	15	14 RCTs (N = 6,728)	Pairwise
Serious adverse events	12	17	16 RCTs (N = 13,108)	Pairwise
Treatment discontinuation because of adverse events	14	23	21 RCTs (N = 16,434)	Pairwise

EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; MSFC = Multiple Sclerosis Functional Composite; MTC = mixed-treatment comparison; RCT = randomized controlled trial.

Full results of direct pairwise meta-analyses are summarized in Table A14.1 for efficacy and Table A14.2 for safety, and full results of NMA are summarized in Table 23 and Table 24.

Annualized Relapse Rate

The annualized relapse rate (ARR) was analyzed as a Poisson outcome using the total number of relapses within a treatment group and total person-time of follow-up for that treatment group (Table A13.29). The summary results for ARR are expressed as rate ratios (Table A11.3).

Direct pairwise comparisons:

There were 10 treatments that were compared with placebo and 14 pairs of head-to-head comparisons from all 27 included studies. The 10 treatments compared with placebo were dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a 30 mcg, interferon beta-1a 22 mcg, interferon beta-1a 44 mcg, interferon beta-1b 250 mcg, natalizumab, teriflunomide 7 mg, and teriflunomide 14 mg. All treatments showed statistically significant reductions in ARR compared with placebo (Table A11.3). Rate ratios ranged from 0.32 (natalizumab) to 0.81 (interferon beta-1a 30 mcg).

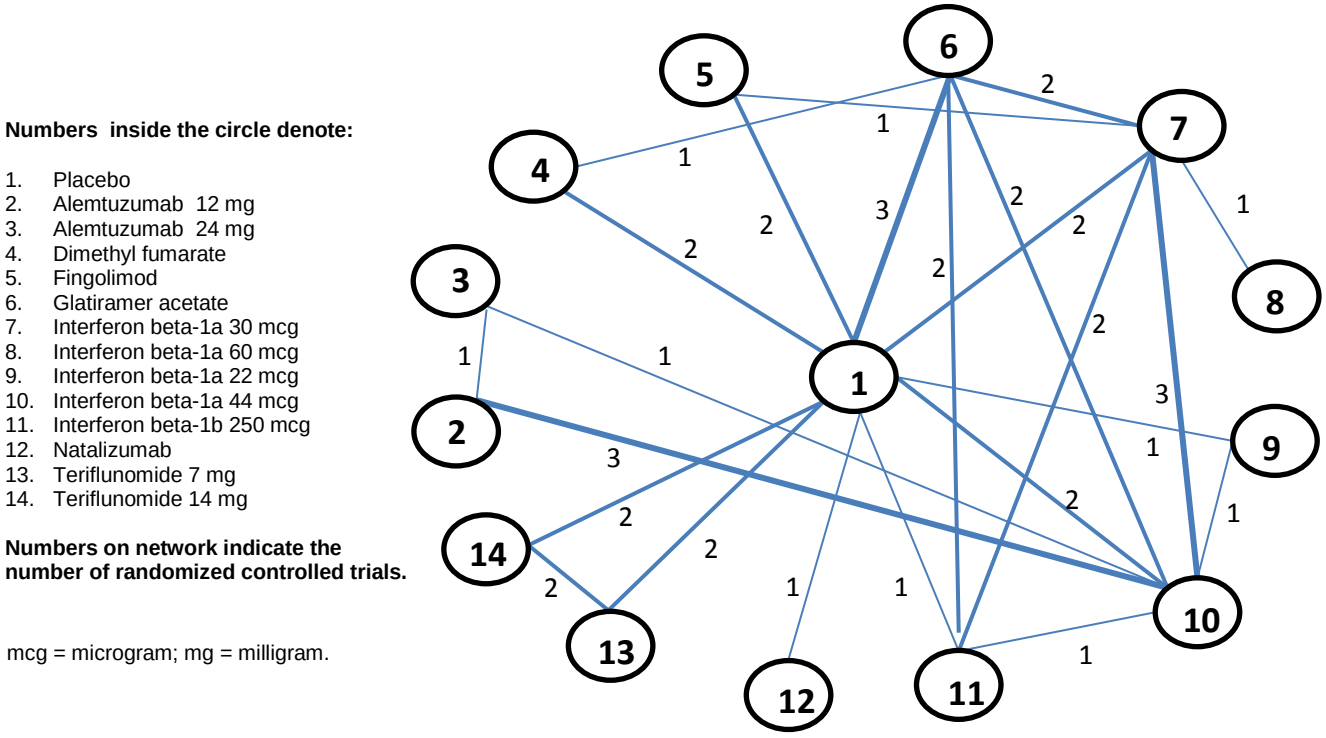
Among head-to-head comparisons, the three interferons showed no statistically significant differences compared with glatiramer acetate, although interferon beta-1a 44 mcg (rate ratio 0.76; 95% CI 0.59 to 0.98) and interferon beta-1b 250 mcg (rate ratio 0.69; 95% CI 0.54 to 0.87) resulted in statistically lower ARRs compared with interferon beta-1a 30 mcg.

Dimethyl fumarate resulted in statistically lower ARR than glatiramer acetate (rate ratio 0.76; 95% CI 0.62 to 0.93). Alemtuzumab at either 12 mg (rate ratio 0.44; 0.34 to 0.55) or 24 mg (rate ratio 0.22; 95% CI 0.14 to 0.35) resulted in statistically lower ARR compared with interferon beta-1a 44 mcg. Fingolimod resulted in statistically lower ARR compared with interferon beta-1a 30 mcg (rate ratio 0.49; 95% CI 0.38 to 0.63). There were no statistically significant differences between doses of alemtuzumab (12 mg versus 24 mg), teriflunomide (7 mg versus 14 mg), interferon beta-1a subcutaneous (SC) (22 mcg versus 44 mcg), and interferon beta-1a intramuscular (IM) (30 mcg versus 60 mcg).

Network meta-analyses:
Due to the paucity of head-to-head comparisons, indirect comparisons using an NMA approach were conducted to compare between treatments.

The evidence network for ARR with the indicated number of RCTs available for each pairwise comparison is shown in Figure 3.

Figure 3: Evidence Network for Annualized Relapse Rate



Base case: A summary of results comparing pairwise meta-analysis and random NMA for ARR from different comparisons is presented in Table A11.3. Based on qualitative assessment, the results of the direct pairwise estimates and NMA estimates are consistent; that is, they are similar in both magnitude and direction.

Figure 4 illustrates the results of the NMA for the effect of all treatments relative to a common comparator (placebo); Table 23 presents full NMA results comparing among all available treatment strategies.

Figure 4: Relative Annualized Relapse Rate for Different Treatment Strategies Compared With Placebo

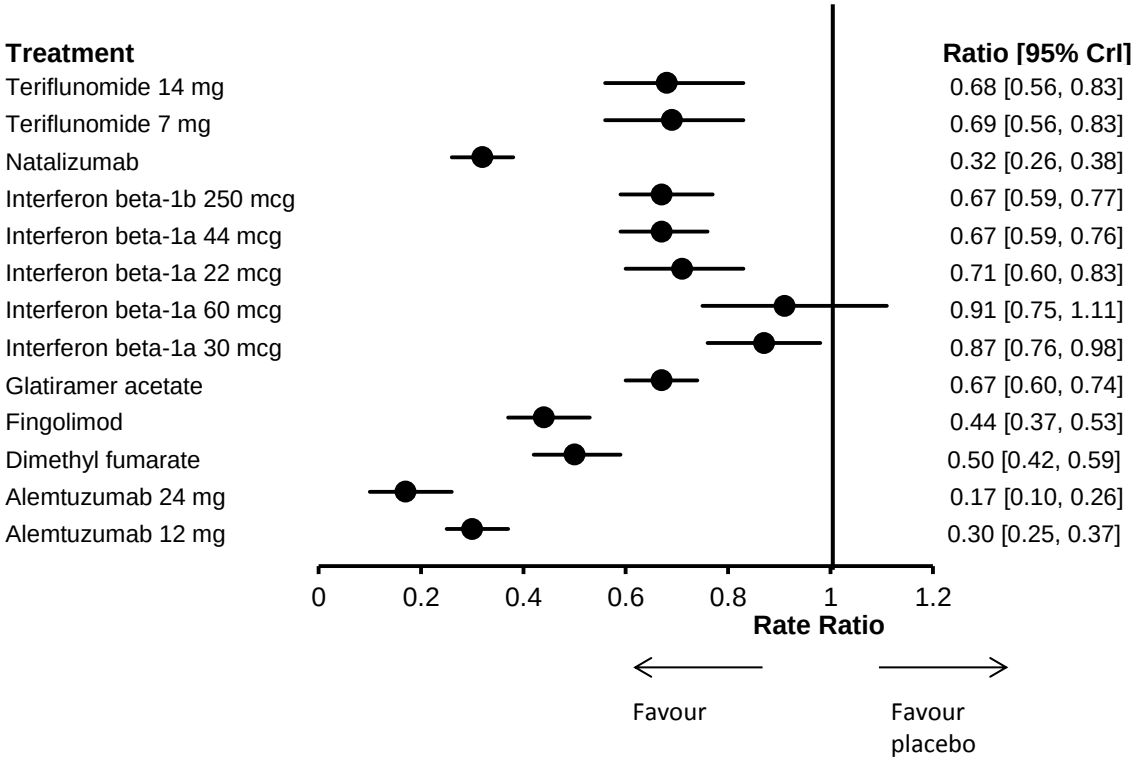


Table 23: Relative ARR From NMA (Rate Ratio [95% CrI])														
	Placebo	**Alemtuzumab 12 mg**	**Alemtuzumab 24 mg**	**Dimethyl fumarate**	**Fingolimod**	**Glatiramer acetate**	**IFN beta-1a 30 mcg**	**IFN beta-1a 60 mcg**	**IFN beta-1a 22 mcg**	**IFN beta-1a 44 mcg**	**Interferon beta-1b 250 mcg**	**Natalizumab**	**Teriflunomide 7 mg**	**Teriflunomide 14 mg**
Placebo	**1**	**3.29 [2.73, 4.04]**	**6.00 [3.84, 9.77]**	**1.99 [1.69, 2.36]**	**2.25 [1.89, 2.72]**	**1.50 [1.35, 1.68]**	**1.16 [1.02, 1.31]**	1.10 [0.90, 1.34]	**1.41 [1.20, 1.68]**	**1.48 [1.30, 1.70]**	**1.43 [1.28, 1.62]**	**3.17 [2.64, 3.84]**	**1.46 [1.20, 1.78]**	**1.46 [1.21, 1.78]**
Alemtuzumab 12 mg	**0.30 [0.25, 0.37]**	1	**1.82 [1.41, 2.42]**	**0.60 [0.58, 0.62]**	**0.68 [0.67, 0.69]**	**0.46 [0.41, 0.49]**	**0.35 [0.32, 0.37]**	**0.33 [0.33, 0.33]**	**0.43 [0.41, 0.44]**	**0.45 [0.42, 0.48]**	**0.44 [0.41, 0.48]**	**0.96 [0.95, 0.97]**	**0.44 [0.44, 0.44]**	**0.44 [0.44, 0.44]**
Alemtuzumab 24 mg	**0.17 [0.10, 0.26]**	**0.55 [0.41, 0.71]**	1	**0.33 [0.24, 0.44]**	**0.38 [0.28, 0.49]**	**0.25 [0.17, 0.35]**	**0.19 [0.13, 0.27]**	**0.18 [0.14, 0.23]**	**0.23 [0.17, 0.31]**	**0.25 [0.17, 0.34]**	**0.25 [0.17, 0.36]**	**0.53 [0.39, 0.69]**	**0.24 [0.14, 0.31]**	**0.24 [0.18, 0.31]**
Dimethyl fumarate	**0.50 [0.42, 0.59]**	**1.66 [1.62, 1.71]**	**3.02 [2.28, 4.14]**	1	**1.13 [1.12, 1.15]**	**0.76 [0.71, 0.80]**	**0.58 [0.55, 0.60]**	**0.55 [0.53, 0.57]**	**0.71 [0.71, 0.71]**	**0.75 [0.72, 0.77]**	**0.73 [0.70, 0.75]**	**1.60 [1.57, 1.63]**	**0.73 [0.71, 0.75]**	**0.74 [0.72, 0.75]**
Fingolimod	**0.44 [0.37, 0.53]**	**1.46 [1.45, 1.49]**	**2.66 [2.04, 3.60]**	**0.88 [0.87, 0.89]**	1	**0.67 [0.62, 0.71]**	**0.51 [0.48, 0.54]**	**0.49 [0.48, 0.49]**	**0.63 [0.62, 0.64]**	**0.66 [0.63, 0.69]**	**0.64 [0.61, 0.67]**	**1.41 [1.40, 1.42]**	**0.65 [0.64, 0.65]**	**0.65 [0.64, 0.66]**
Glatiramer acetate	**0.67 [0.60, 0.74]**	**2.19 [2.03, 2.41]**	**3.99 [2.86, 5.83]**	**1.32 [1.25, 1.41]**	**1.50 [1.40, 1.62]**	1	**0.77 [0.76, 0.78]**	**0.73 [0.67, 0.80]**	0.94 [0.89, 1.00]	0.99 [0.97, 1.01]	**0.97 [0.95, 0.99]**	**2.11 [1.96, 2.29]**	0.97 [0.89, 1.06]	0.97 [0.90, 1.06]
IFN beta-1a 30 mcg	**0.87 [0.76, 0.98]**	**2.85 [2.67, 3.09]**	**5.19 [3.77, 7.46]**	**1.72 [1.65, 1.80]**	**1.95 [1.85, 2.08]**	**1.30 [1.28, 1.32]**	1	0.95 [0.88, 1.03]	**1.22 [1.18, 1.28]**	**1.29 [1.28, 1.30]**	**1.26 [1.25, 1.26]**	**2.74 [2.59, 2.94]**	**1.26 [1.18, 1.36]**	**1.27 [1.18, 1.36]**
IFN beta-1a 60 mcg	0.91 [0.75, 1.11]	**3.00 [3.01, 3.03]**	**5.46 [4.27, 7.28]**	**1.81 [1.76, 1.88]**	**2.05 [2.02, 2.10]**	**1.37 [1.25, 1.50]**	1.05 [0.97, 1.13]	1	**1.28 [1.25, 1.33]**	**1.37 [1.27, 1.45]**	**1.32 [1.25, 1.42]**	**2.89 [2.86, 2.94]**	**1.33 [1.32, 1.34]**	**1.33 [1.33, 1.34]**
IFN beta-1a 22 mcg	**0.71 [0.60, 0.83]**	**2.34 [2.27, 2.41]**	**4.26 [3.21, 5.83]**	**1.41 [1.41, 1.41]**	**1.60 [1.57, 1.62]**	1.07 [1.00, 1.12]	**0.82 [0.78, 0.85]**	**0.78 [0.75, 0.80]**	1	**1.05 [1.02, 1.09]**	1.02 [0.98, 1.06]	**2.25 [2.20, 2.30]**	1.03 [1.00, 1.06]	**1.04 [1.01, 1.06]**
IFN beta-1a 44 mcg	**0.67 [0.59, 0.76]**	**2.21 [2.07, 2.39]**	**4.03 [2.92, 5.77]**	**1.33 [1.28, 1.39]**	**1.51 [1.43, 1.60]**	1.01 [0.99, 1.02]	**0.78 [0.78, 0.78]**	**0.74 [0.68, 0.79]**	**0.95 [0.91, 0.99]**	1	**0.97 [0.97, 0.98]**	**2.13 [2.00, 2.27]**	0.98 [0.91, 1.05]	0.98 [0.91, 1.05]
IFN beta-1b 250 mcg	**0.67 [0.59, 0.77]**	**2.22 [2.10, 2.38]**	**4.04 [2.95, 5.74]**	**1.34 [1.30, 1.39]**	**1.52 [1.45, 1.60]**	1.01 [0.99, 1.03]	**0.78 [0.77, 0.78]**	**0.74 [0.69, 0.79]**	**0.95 [0.92, 0.98]**	1.00 [0.99, 1.01]	1	**2.14 [2.03, 2.26]**	0.98 [0.92, 1.05]	0.99 [0.93, 1.05]
Natalizumab	**0.32 [0.26, 0.38]**	**1.04 [1.03, 1.05]**	**1.89 [1.46, 2.54]**	**0.63 [0.61, 0.64]**	**0.71 [0.71, 0.71]**	**0.47 [0.44, 0.51]**	**0.36 [0.34, 0.39]**	**0.35 [0.34, 0.35]**	**0.44 [0.44, 0.45]**	**0.47 [0.44, 0.49]**	**0.45 [0.42, 0.48]**	1	**0.46 [0.46, 0.46]**	**0.46 [0.46, 0.46]**
Teriflunomide 7 mg	**0.69 [0.56, 0.83]**	**2.26 [2.27, 2.27]**	**4.12 [3.20, 5.49]**	**1.36 [1.33, 1.40]**	**1.55 [1.53, 1.57]**	1.03 [0.94, 1.12]	**0.79 [0.74, 0.85]**	**0.75 [0.75, 0.75]**	0.97 [0.94, 1.00]	1.02 [0.96, 1.08]	**1.12 [1.01, 1.26]**	**2.18 [2.16, 2.20]**	1	1.00 [1.00, 1.00]
Teriflunomide 14 mg	**0.68 [0.56, 0.83]**	**2.25 [2.26, 2.27]**	**4.10 [3.19, 5.48]**	**1.36 [1.33, 1.40]**	**1.54 [1.52, 1.56]**	1.03 [0.94, 1.12]	**0.79 [0.73, 0.85]**	**0.75 [0.75, 0.75]**	**0.96 [0.94, 0.99]**	1.01 [0.95, 1.08]	1.06 [0.97, 1.18]	**2.17 [2.16, 2.19]**	1.00 [1.00, 1.00]	1

ARR = annualized relapse rate; CrI = credible interval; IFN = interferon; mcg = microgram; mg = milligram; NMA = network meta-analysis.
Note: First column denotes treatments and first row denotes comparator. When reading from left to right, a ratio of less than 1 indicates a favour toward treatment, and a ratio of greater than 1 indicates a favour toward comparator. Bolded numbers indicate statistical significance.

Based on the results of the NMA, all treatments resulted in statistically lower ARR compared with placebo, except interferon beta-1a 60 mcg (Figure 4). Alemtuzumab 24 mg (rate ratio 0.17; 95% CrI 0.10 to 0.26), alemtuzumab 12 mg (rate ratio 0.30; 95% CrI 0.25 to 0.37), and natalizumab (rate ratio 0.32; 95% CrI 0.26 to 0.38) had the highest activity of all treatments for the reduction of ARR. This observation was supported by the full NMA results, shown in Table 23, wherein alemtuzumab (both 12 mg and 24 mg) and natalizumab were associated with statistically lower ARR compared with all other treatments. Both doses of alemtuzumab (12 mg and 24 mg) resulted in statistically lower ARR compared with natalizumab. However, the difference between natalizumab and alemtuzumab 12 mg (rate ratio 1.04; 95% CrI 1.03 to 1.05) was small.

Treatments with the next highest level of activity included fingolimod 0.5 mg and dimethyl fumarate 240 mg, whose rate ratios (95% CrI) were 0.44 (0.37 to 0.53) and 0.50 (0.42 to 0.59), respectively, compared with placebo. Both fingolimod and dimethyl fumarate had statistically lower ARR compared with glatiramer acetate, interferon beta-1a 30 mcg, interferon beta-1a 60 mcg, interferon beta-1a 22 mcg, interferon beta-1a 44 mcg, interferon beta-1b 250 mcg, teriflunomide 7 mg, and teriflunomide 14 mg (Table 23). The rate ratio (95% CrI) for fingolimod versus dimethyl fumarate was 0.88 (0.87 to 0.89), in favour of fingolimod.

Teriflunomide, glatiramer acetate, and interferons (with the exception of interferon beta-1a 30 mcg and interferon beta-1a 60 mcg) appear to have similar efficacy, with rate ratios ranging from 0.67 to 0.71 compared with placebo. Some small statistical differences between treatments were observed (Table 23). Interferon beta-1a 30 mcg and interferon beta-1a 60 mcg had the lowest activity compared with placebo.

Sensitivity analyses: Sensitivity analyses of ARR excluding older studies (before year 2000), studies of short duration (less than one year), or studies with a starting EDSS score of 0 to 3 and 1 to 3.5 did not affect the statistical significance or direction of the relative treatment differences, indicating the robustness of the results (Table A12.1).

Sensitivity analyses of ARR for treatments compared with placebo, using Poisson models adjusted for various covariates (i.e., disease duration, mean relapses, baseline EDSS, or treatment duration), revealed no marked change in the magnitude and direction of the relative treatment effect from the results of the unadjusted model for the base case, therefore indicating the robustness of the reference case results. Comparison of base case results of treatments against placebo to results using adjusted models is presented in Table A12.2.

Subgroup and meta-regression analyses (using single and multiple covariates) of ARR based on patient treatment experience (i.e., treatment-naive or others, including experienced, mixed, or unclear) did not show any changes in the magnitude and direction of the relative treatment difference for each comparator treatment (Table A12.3, Table A12.4).

Sustained Disability Progression

Sustained disability progression was analyzed as a dichotomous outcome and the summary results were expressed as risk ratio (Table A11.3). Definitions for this outcome varied among studies based on how long the reduction in EDSS needed to be sustained (three months or six months). The following analyses combined data for both definitions.

Direct pairwise comparisons:

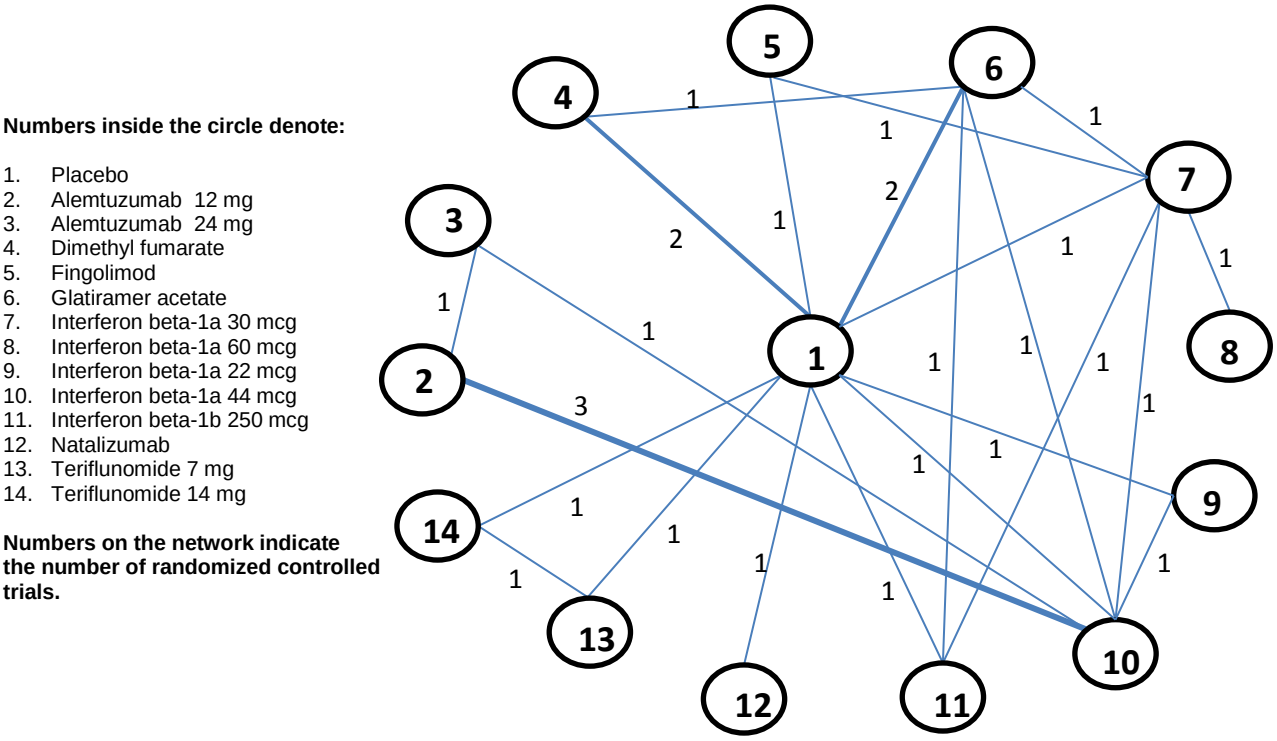
There were 10 treatments that were compared with placebo and 13 pairs of head-to-head comparisons that were obtained from 19 studies.[9,11,13-16,18,19,21-23,25-27,29,30,32,33,35]

The 10 treatments compared with placebo were dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a 30 mcg, interferon beta-1a 22 mcg, interferon beta-1a 44 mcg, interferon beta-1b 250 mcg, natalizumab, teriflunomide 7 mg, and teriflunomide 14 mg. Based on direct pairwise meta-analysis, the proportion of patients with sustained disability progression was numerically lower for all active treatments compared with placebo, with relative risks ranging from 0.59 to 0.92; however, differences were not statistically significant for glatiramer acetate, interferon beta-1b 250 mcg, interferon beta-1a 22 mcg, and teriflunomide 7 mg (Table A11.3).

Among the 13 direct pairwise head-to-head comparisons, there were statistically significant differences in favour of alemtuzumab (both 12 mg and 24 mg) compared with interferon beta-1a 44 mcg; relative risk (RR) (95% CI) of 0.59 (0.40 to 0.86) and 0.42 (0.21 to 0.84), respectively. Interferon beta-1b 250 mcg had a statistically lower risk of disability progression compared with interferon beta-1a 30 mcg (RR 0.44; 95% CI 0.25 to 0.80). There were no statistically significant differences between the other active comparisons (Table A11.3).

Network meta-analyses:
The evidence network for disability progression with the indicated number of RCTs available for each pairwise comparison is shown in Figure 5.

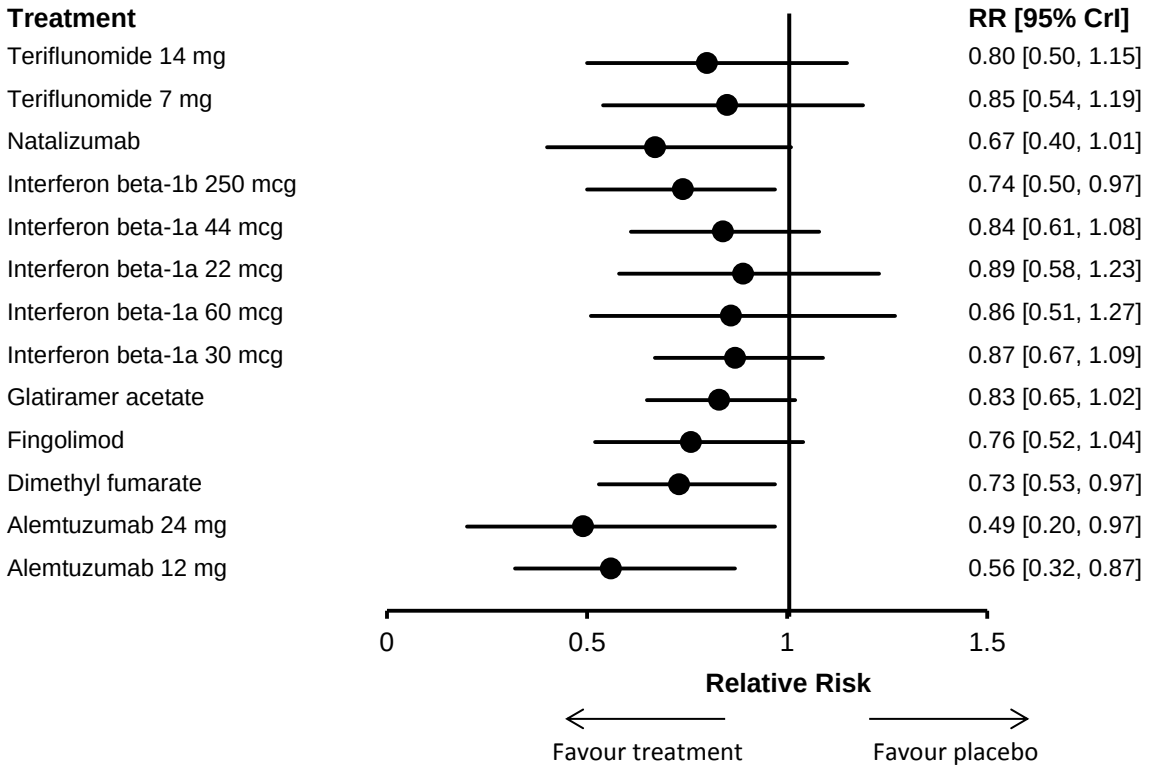
Figure 5: Evidence Network for Patients With Sustained Disability Progression



Base case: A summary of results comparing pairwise meta-analysis and random NMA for disability progression for the different comparisons is presented in Table A11.3. In most comparisons, the results of the direct pairwise estimates and NMA estimates were similar.

Figure 6 illustrates the results of the NMA for the effect of all treatments relative to a common comparator (placebo); Table 24 presents full NMA results comparing among all available treatment strategies.

Figure 6: Relative Risk of Sustained Disability Progression for Different Treatment Strategies Compared With Placebo



CrI = credible interval; mcg = microgram; mg = milligram, RR = relative risk.

Table 24: Sustained Disability Progression From NMA (Relative Risk [95% CrI])														
	Placebo	**Alemtuzumab 12 mg**	**Alemtuzumab 24 mg**	**Dimethyl fumarate**	**Fingolimod**	**Glatiramer acetate 20 mg**	**IFN beta-1a 30 mcg**	**IFN beta-1a 60 mcg**	**IFN beta-1a 22 mcg**	**IFN beta-1a 44 mcg**	**Interferon beta-1b 250 mcg**	**Natalizumab**	**Teriflunomide 7 mg**	**Teriflunomide 14 mg**
Placebo	1	**1.80 [1.16, 3.12]**	**2.03 [1.03, 5.04]**	**1.36 [1.03, 1.89]**	1.31 [0.97, 1.92]	1.21 [0.98, 1.55]	1.15 [0.92, 1.50]	1.16 [0.79, 1.95]	1.12 [0.81, 1.73]	1.20 [0.92, 1.63]	**1.35 [1.03, 1.98]**	1.49 [0.99, 2.47]	1.18 [0.84, 1.87]	1.25 [0.87, 2.00]
Alemtuzumab 12 mg	**0.56 [0.32, 0.87]**	1	1.13 [0.90, 1.62]	**0.76 [0.61, 0.89]**	**0.73 [0.62, 0.84]**	**0.67 [0.50, 0.84]**	**0.64 [0.48, 0.79]**	**0.63 [0.63, 0.68]**	**0.63 [0.56, 0.70]**	**0.67 [0.52, 0.80]**	**0.75 [0.64, 0.89]**	**0.83 [0.79, 0.86]**	**0.66 [0.60, 0.73]**	**0.69 [0.64, 0.75]**
Alemtuzumab 24 mg	**0.49 [0.20, 0.97]**	0.89 [0.62, 1.12]	1	**0.67 [0.38, 0.99]**	**0.65 [0.38, 0.93]**	**0.60 [0.31, 0.94]**	**0.57 [0.30, 0.89]**	**0.57 [0.39, 0.76]**	**0.56 [0.34, 0.78]**	**0.59 [0.32, 0.89]**	**0.66 [0.39, 1.00]**	**0.73 [0.49, 0.96]**	**0.58 [0.37, 0.81]**	**0.62 [0.40, 0.84]**
Dimethyl fumarate	**0.73 [0.53, 0.97]**	**1.32 [1.13, 1.65]**	**1.49 [1.01, 2.66]**	1	**0.96 [0.94, 1.01]**	**0.89 [0.82, 0.95]**	**0.85 [0.79, 0.89]**	0.85 [0.77, 1.03]	**0.83 [0.79, 0.92]**	**0.88 [0.86, 0.90]**	1.00 [1.00, 1.05]	1.09 [0.97, 1.31]	**0.87 [0.82, 0.99]**	0.92 [0.85, 1.06]
Fingolimod	0.76 [0.52, 1.04]	**1.37 [1.20, 1.62]**	**1.55 [1.07, 2.62]**	1.04 [0.99, 1.06]	1	0.92 [0.81, 1.01]	**0.88 [0.78, 0.95]**	0.88 [0.81, 1.02]	**0.86 [0.84, 0.90]**	**0.91 [0.85, 0.96]**	**1.03 [1.03, 1.07]**	**1.13 [1.03, 1.29]**	**0.90 [0.87, 0.97]**	0.95 [0.90, 1.04]
Glatiramer acetate	0.83 [0.65, 1.02]	**1.49 [1.18, 2.02]**	**1.68 [1.06, 3.26]**	**1.13 [1.05, 1.23]**	1.09 [0.99, 1.24]	1	**0.96 [0.94, 0.97]**	0.96 [0.80, 1.26]	0.93 [0.83, 1.12]	0.99 [0.95, 1.05]	**1.11 [1.06, 1.28]**	**1.23 [1.02, 1.60]**	0.98 [0.86, 1.21]	1.03 [0.89, 1.30]
IFN beta-1a 30 mcg	0.87 [0.67, 1.09]	**1.56 [1.26, 2.08]**	**1.76 [1.13, 3.36]**	**1.18 [1.12, 1.26]**	**1.14 [1.05, 1.28]**	**1.05 [1.03, 1.07]**	1	1.01 [0.86, 1.30]	0.98 [0.89, 1.16]	**1.04 [1.01, 1.09]**	**1.17 [1.13, 1.32]**	**1.29 [1.08, 1.65]**	1.02 [0.91, 1.25]	1.08 [0.95, 1.34]
IFN beta-1a 60 mcg	0.86 [0.51, 1.27]	**1.55 [1.47, 1.60]**	**1.75 [1.32, 2.58]**	**1.18 [0.97, 1.31]**	1.13 [0.98, 1.23]	1.04 [0.79, 1.24]	0.99 [0.77, 1.17]	1	0.97 [0.89, 1.03]	1.03 [0.84, 1.17]	**1.16 [1.02, 1.32]**	**1.28 [1.26, 1.28]**	1.02 [0.96, 1.07]	**1.08 [1.03, 1.11]**
IFN beta-1a 22 mcg	0.89 [0.58, 1.23]	**1.60 [1.42, 1.80]**	**1.80 [1.27, 2.91]**	**1.21 [1.09, 1.26]**	**1.16 [1.11, 1.19]**	1.07 [0.89, 1.20]	1.02 [0.86, 1.13]	1.03 [0.97, 1.12]	1	1.06 [0.94, 1.14]	**1.20 [1.14, 1.27]**	**1.32 [1.22, 1.43]**	**1.05 [1.03, 1.08]**	**1.11 [1.07, 1.16]**
IFN beta-1a 44 mcg	0.84 [0.61, 1.08]	**1.50 [1.25, 1.91]**	**1.69 [1.12, 3.09]**	**1.14 [1.11, 1.16]**	**1.09 [1.05, 1.18]**	1.01 [0.95, 1.06]	**0.96 [0.92, 0.99]**	0.97 [0.85, 1.20]	0.94 [0.88, 1.06]	1	**1.12 [1.12, 1.22]**	**1.24 [1.08, 1.52]**	0.99 [0.91, 1.15]	1.04 [0.94, 1.23]
IFN beta-1b 250 mcg	**0.74 [0.50, 0.97]**	**1.34 [1.12, 1.57]**	**1.51 [1.00, 2.54]**	1.00 [0.96, 1.00]	**0.97 [0.93, 0.97]**	**0.90 [0.78, 0.94]**	**0.86 [0.76, 0.89]**	**0.86 [0.76, 0.98]**	**0.84 [0.79, 0.87]**	**0.89 [0.82, 0.89]**	1	1.10 [0.96, 1.25]	**0.88 [0.81, 0.94]**	0.93 [0.84, 1.01]
Natalizumab	0.67 [0.40, 1.01]	**1.21 [1.16, 1.26]**	**1.36 [1.04, 2.04]**	0.92 [0.77, 1.03]	**0.88 [0.78, 0.97]**	**0.81 [0.63, 0.98]**	**0.78 [0.61, 0.92]**	**0.78 [0.78, 0.79]**	**0.76 [0.70, 0.82]**	**0.81 [0.66, 0.93]**	0.91 [0.80, 1.04]	1	**0.80 [0.76, 0.84]**	**0.84 [0.81, 0.88]**
Teriflunomide 7 mg	0.85 [0.54, 1.19]	**1.52 [1.38, 1.67]**	**1.72 [1.23, 2.69]**	**1.15 [1.01, 1.22]**	**1.11 [1.03, 1.15]**	**1.02 [0.83, 1.16]**	0.98 [0.80, 1.09]	0.98 [0.94, 1.04]	**0.95 [0.93, 0.97]**	1.01 [0.87, 1.10]	**1.14 [1.06, 1.23]**	**1.26 [1.18, 1.32]**	1	**1.05 [1.04, 1.07]**
Teriflunomide 14 mg	0.80 [0.50, 1.15]	**1.44 [1.33, 1.56]**	**1.63 [1.19, 2.51]**	1.09 [0.95, 1.18]	1.05 [0.96, 1.11]	0.97 [0.77, 1.12]	0.93 [0.75, 1.05]	**0.93 [0.90, 0.97]**	**0.90 [0.87, 0.93]**	0.96 [0.81, 1.06]	1.08 [0.99, 1.19]	**1.19 [1.14, 1.23]**	**0.95 [0.93, 0.96]**	1

CrI = credible interval; IFN = interferon; mg = milligram; NMA = network meta-analysis.
Note: First column denotes treatments and first row denotes comparator. When reading from left to right, a ratio of less than 1 indicates a favour toward treatment, and a ratio of greater than 1 indicates a favour toward comparator. Bolded numbers indicate statistical significance.

Based on the NMA, the proportion of patients with sustained disability progression was numerically lower for all active treatments compared with placebo, with relative risks ranging from 0.49 for alemtuzumab 24 mg to 0.89 for interferon beta-1a 22 mcg (Figure 6). However, statistical differences compared with placebo were observed only for alemtuzumab 24 mg (RR 0.49; 95% CrI 0.20 to 0.97), alemtuzumab 12 mg (RR 0.56; 95% CrI 0.32 to 0.87), dimethyl fumarate (RR 0.73; 95% CrI 0.53 to 0.97), and interferon beta-1b 250 mcg (RR 0.74; 95% CrI 0.50 to 0.97).

Full results of the NMA suggest that both doses of alemtuzumab (12 mg and 24 mg) are similar and have the highest activity among all treatments in reducing the risk of sustained disability progression. Natalizumab was associated with a lower risk of sustained disability compared with the remaining treatments, but because of wide credible intervals, natalizumab did not differ statistically from dimethyl fumarate, or interferon beta-1b 250 mcg. There were no marked differences among dimethyl fumarate, interferon beta-1b 250 mcg, fingolimod, glatiramer acetate, teriflunomide 14 mg, interferon beta-1a 44 mcg, and teriflunomide 7 mg, although some small statistical differences were noted. Interferon beta-1a 22 mcg, interferon beta-1a 30 mcg, and interferon beta-1a 60 mcg were similar, with lowest activity among all treatments.

The risk of sustained disability progression was similar among oral agents (i.e., dimethyl fumarate, fingolimod, and teriflunomide). Fingolimod was similar to dimethyl fumarate (RR 1.04; 95% CrI 0.99 to 1.06), and teriflunomide 14 mg (RR 0.95; 95% CrI 0.90 to 1.04). The risk of sustained disability was statistically lower for fingolimod compared with teriflunomide 7 mg (RR 0.90; 95% CrI 0.87 to 0.97). In addition, the risk of sustained disability was statistically lower for dimethyl fumarate compared with teriflunomide 7 mg (RR 0.87; 95% CrI 0.82 to 0.99), but not compared with teriflunomide 14 mg (RR 0.92; 95% CrI 0.85 to 1.06).

Sensitivity analyses: Sensitivity analyses of sustained disability progression excluding older studies (before year 2000), and studies with starting EDSS scores of 0 to 3 and 1 to 3.5 did not affect the significance and direction of the relative treatment difference, indicating the robustness of the results (Table A12.5). However, the effect sizes of alemtuzumab (both 12 mg and 24 mg) decreased after older studies were excluded.

Sensitivity analyses excluding short-duration studies (less than one year) were not conducted, because short-duration studies did not report data on sustained disability progression (i.e., they were already not included in the base case results).

Sensitivity analyses of sustained disability progression for treatments compared with placebo, using binomial models adjusted for various covariates (i.e., baseline EDSS, time since symptom onset, treatment duration, or mean relapses), revealed no marked change in the magnitude and direction of the relative treatment effect from the results of the unadjusted model for the reference case, therefore indicating the robustness of the reference case results. A comparison of base case results of treatments against placebo to results using adjusted models is presented in Table A12.6.

Subgroup and meta-regression analyses of sustained disability progression based on patient treatment experience (i.e., treatment-naive or others, including experienced, mixed, or unclear) did not show any changes in the magnitude and direction of the relative treatment difference for each comparator treatment (Table A12.7, Table A12.8).

Proportion of Patients Remaining Relapse-Free
Only direct pairwise meta-analyses were performed for this outcome (Table A14.1).

There were 10 treatments that were compared with placebo and 14 pairs of head-to-head comparisons from 26 studies.[9-11,13-23,25-34,34,35] The 10 treatments compared with placebo were dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a 30 mcg, interferon beta-1a 22 mcg, interferon beta-1a 44 mcg, interferon beta-1b 250 mcg, natalizumab, teriflunomide 7 mg, and teriflunomide 14 mg.

The proportion of patients remaining relapse-free was numerically higher for all active treatments compared with placebo; RRs ranged from 1.15 (interferon beta-1a 30 mcg) to 2.00 (interferon beta-1a 44 mcg). However, differences compared with placebo were not statistically significant for either interferon beta-1a 30 mcg or interferon beta-1b 250 mcg.

Among head-to-head comparisons, the following results were observed:
- The proportion of patients remaining relapse-free was higher for interferon beta-1a 44 mcg (RR 1.18; 95% CI, 1.03 to 1.34) and interferon beta-1b 250 mcg (RR 1.51; 95% CI, 1.11 to 2.06) compared with interferon beta-1a 30 mcg.
- Interferon beta-1a 44 mcg, interferon beta-1b 250 mcg, and glatiramer acetate did not differ statistically from each other.
- There was no statistically significant difference between interferon beta-1a 30 mcg and glatiramer acetate.
- The proportion of patients remaining relapse-free was higher for fingolimod compared with interferon beta-1a 30 mcg (RR 1.19; 95% CI, 1.10 to 1.28).
- Dimethyl fumarate and glatiramer acetate did not differ statistically.
- The proportion of patients remaining relapse-free was higher for both doses of alemtuzumab (12 mg and 24 mg) compared with interferon beta-1a 44 mcg (RR 1.38; 95% CI, 1.26 to 1.52 and RR 1.63; 95% CI, 1.33 to 1.99, respectively).
- There were no statistically significant differences between the different doses of alemtuzumab (12 mg versus 24 mg), teriflunomide (7 mg versus 14 mg), interferon beta-1a SC (22 mcg versus 44 mcg), and interferon beta-1a IM (30 mcg versus 60 mcg).

Mean Change in EDSS from Baseline
Only direct pairwise meta-analyses were performed for this outcome (Table A14.1).

From 13 studies[12-17,20,22,25-27,29,33] that reported mean change in EDSS scores from baseline, there were five treatments that were compared with placebo and 11 head-to-head comparisons.

Compared with placebo, all five treatments (interferon beta-1a 30 mcg, interferon beta-1a 22 mcg, interferon beta-1a 44 mcg, glatiramer acetate, and fingolimod) reported a lower mean change from baseline in EDSS score at the end of treatment. However, differences compared with placebo were not statistically significant for interferon beta-1a 22 mcg or glatiramer acetate.

Among head-to-head comparisons, the following results were observed:
- The mean changes in EDSS scores favoured interferon beta-1b 250 mcg compared with both interferon beta-1a 44 mcg (MD –0.40; 95% CI, –0.70 to –0.10) and interferon beta-1a 30 mcg (MD –0.47; 95% CI, –0.69 to –0.25); interferon beta-1a 44 mcg and interferon beta-1a 30 mcg did not differ statistically from each other.
- Neither interferon beta-1a 44 mcg nor interferon beta-1a 30 mcg differed statistically from glatiramer acetate.

- The mean changes in EDSS scores favoured both doses of alemtuzumab (12 mg and 24 mg) compared with interferon beta-1a 44 mcg. A pooled estimate was not obtained for the comparison of alemtuzumab 12 mg with interferon, because of statistical heterogeneity; CAMMS223[13] and CARE-MS II[15] showed a statistically significant difference in favour of alemtuzumab 12 mg, while CARE-MS I[14] showed no statistical difference between treatments. The mean difference (95% CI) from CAMMS223 comparing alemtuzumab 24 mg with interferon was –0.83 (–1.17 to –0.49).
- There were no statistically significant differences between doses of alemtuzumab (12 mg versus 24 mg), interferon beta-1a SC (22 mcg versus 44 mcg), or interferon beta-1a IM (30 mcg versus 60 mcg).

Mean Change in MSFC from Baseline
Only direct pairwise meta-analyses were performed for this outcome (Table A14.1).

The MSFC comprises the average of the scores on the timed 25-foot walk, the 9-hole peg test, and the Paced Auditory Serial Addition test with a 3-second interstimulus interval, with higher scores (Z-score) representing improvement.[57]

From five studies[14,15,22,33,35] reporting mean change in the MSFC, there were four pairwise comparisons (alemtuzumab 12 mg versus interferon beta-1a 44 mcg, fingolimod versus placebo, fingolimod versus interferon beta-1a 30 mcg, and interferon beta-1a 30 mcg versus glatiramer acetate). The following results were observed:
- The mean change in MSFC favoured alemtuzumab 12 mg compared with interferon beta-1a 44 mcg (MD 0.10; 95% CI, 0.05 to 0.16).
- The mean change in MSFC scores favoured fingolimod compared with placebo (MD 0.09; 95% CI, 0.02 to 0.16) and interferon beta-1a 30 mcg (MD 0.07; 95% CI, 0.01 to 0.13).
- The mean change in MSFC scores favoured glatiramer acetate compared with interferon beta-1a 30 mcg (MD 0.10; 95% CI, 0.00 to 0.20).

Proportion of Patients with Gadolinium-Enhancing Lesions
Only direct pairwise meta-analyses were performed for this outcome (Table A14.1).

From 12 studies[9,14,15,19,22,24,25,28,30-33] reporting patients with GdE lesions, there were five treatments that were compared with placebo and five head-to-head comparisons.

Compared with placebo, all five treatments (natalizumab, dimethyl fumarate, fingolimod, teriflunomide 7 mg, teriflunomide 14 mg) resulted in a statistically significantly lower proportion of patients with GdE lesions. The RRs ranged from 0.11 (natalizumab) to 0.80 (teriflunomide 7 mg).

Among head-to-head comparisons, the following results were observed:
- The proportion of patients with GdE lesions was lower for interferon beta-1b 250 mcg (RR 0.47; 95% CI, 0.29 to 0.74) and fingolimod 0.5 mg (RR 0.52; 95% CI, 0.35 to 0.75) compared with interferon beta-1a 30 mcg.
- The proportion of patients with GdE lesions was lower for interferon beta-1a 44 mcg compared with glatiramer acetate (RR 0.58; 95% CI, 0.42 to 0.80).
- The proportion of patients with GdE lesions was lower for alemtuzumab 12 mg compared with interferon beta-1a 44 mcg SC (RR 0.39; 95% CI, 0.29 to 0.53).
- There was no statistically significant difference between the two doses of teriflunomide (7 mg versus 14 mg).

Mean Number of GdE Lesions
Only direct pairwise meta-analyses were performed for this outcome (Table A14.1).

Mean number of GdE lesions was reported in 14 studies,[9,11,12,16,18,19,22,26-28,30-33] from which there were seven treatments that were compared with placebo and eight head-to-head comparisons.

Compared with placebo, natalizumab, glatiramer acetate, dimethyl fumarate, fingolimod, teriflunomide 7 mg, and teriflunomide 14 mg reported a statistically lower mean number of GdE lesions. Interferon beta-1a 30 mcg also reduced the mean numbers of GdE lesions compared with placebo, but the difference was not statistically significant. The mean differences ranged from –0.85 (interferon beta-1a 30 mcg) to –2.20 (natalizumab).

Among head-to-head comparisons, the following results were observed:
- Compared with glatiramer acetate, interferon beta-1b 250 mcg, interferon beta-1a 44 mcg, interferon beta-1a 30 mcg, and dimethyl fumarate showed no statistically significant differences.
- There were also no significant differences between interferon beta-1a 44 mcg and interferon beta-1a 30 mcg.
- The mean number of GdE lesions was lower for fingolimod compared with interferon beta-1a 30 mcg (mean difference –0.28; 95% CI, –0.50 to –0.06).
- The mean number of GdE lesions was lower for teriflunomide 14 mg compared with teriflunomide 7 mg (mean difference –0.30; 95% CI –0.49, –0.10).

Proportion of Patients Having New or Enlarging T2-Hyperintense Lesions
Only direct pairwise meta-analyses were performed for this outcome (Table A14.1).

The incidence of T2 lesions was reported in 13 studies,[9,13-16,21,22,24,25,28,30,31,33] from which there were five treatments (natalizumab, interferon beta-1a 44 mcg SC, fingolimod, teriflunomide 7 mg, and teriflunomide 14 mg) that were compared with placebo and nine head-to-head comparisons.

Compared with placebo, all five treatments resulted in a statistically significantly lower proportion of patients with new or enlarging T2 lesions. The RRs ranged from 0.45 (interferon beta-1a 44 mcg SC) to 0.79 (teriflunomide 14 mg).

Among head-to-head comparisons, the following results were observed:
- The proportion of patients having new or enlarging T2 lesions was lower for interferon beta-1a 44 mcg (RR 0.67; 95% CI, 0.58 to 0.78), interferon beta-1b 250 mcg (RR 0.60; 95% CI, 0.46 to 0.80), interferon beta-1a 60 mcg (RR 0.79; 95% CI, 0.68 to 0.93), and fingolimod (RR 0.83; 95% CI, 0.72 to 0.96) compared with interferon beta-1a 30 mcg.
- There was no significant difference between interferon beta-1a 44 mcg and glatiramer acetate.
- The proportion of patients having new or enlarging T2 lesions was lower for alemtuzumab 12 mg in the two phase 3 studies (CARE-MS I[14] and CARE-MS II[15]), but not in the phase 2 study (CAMMS223[13]), compared with interferon beta-1a 44 mcg SC (RR 0.75; 95% CI, 0.61 to 0.93).
- There was no statistically significant difference between the two doses of teriflunomide (7 mg versus 14 mg).

Mean Number of New or Enlarging T2-Hyperintense Lesions
Only direct pairwise meta-analyses were performed for this outcome (Table A14.1).

The mean number of T2 lesions was reported in 14 studies.[9,11,12,16,18,19,21,22,26-28,30,31,33] There were seven treatments that were compared with placebo and eight head-to-head comparisons. The seven treatments compared with placebo were natalizumab, interferon beta-1a 30 mcg, glatiramer acetate, dimethyl fumarate, fingolimod, and teriflunomide (7 mg and 14 mg).

Compared with placebo, there was a trend toward a lower mean number of T2 lesions for all seven treatments; mean differences ranged from –1.11 (teriflunomide 7 mg) to –12.90 (dimethyl fumarate). However, the difference compared with placebo was not statistically significant for glatiramer acetate.

Among head-to-head comparisons, the following results were observed:

- The mean number of T2 lesions was lower for interferon beta-1b 250 mcg (MD –1.30; 95% CI, –2.3 to –0.30), and dimethyl fumarate (MD –2.90; 95% CI –5.25 to –0.55) compared with glatiramer acetate.
- Neither interferon beta-1a 44 mcg nor interferon beta-1a 30 mcg differed statistically from glatiramer acetate.
- There was no significant difference between interferon beta-1a 44 mcg and interferon beta-1a 30 mcg.
- The mean number of T2 lesions was lower for fingolimod compared with interferon beta-1a 30 mcg (MD –0.90; 95% CI, –1.62 to –0.18).
- There were no statistically significant differences between doses of interferon beta-1a IM (30 mcg versus 60 mcg) and teriflunomide (7 mg versus 14 mg).

Quality of Life
Changes in health-related quality of life (HRQoL) were reported in one trial comparing interferon beta-1a 30 mcg with placebo,[86] and in one trial comparing natalizumab with placebo.[87,88]

Interferon beta-1a 30 mcg versus placebo:
The Sickness Impact Profile (SIP) — a validated patient-reported measure of overall health that consists of 136 items organized into 12 subscales — was used to evaluate the HRQoL in the MSCRG study,[89] comparing interferon beta-1a 30 mcg with placebo. There were three components: overall SIP, physical SIP, and psychosocial SIP. Scores on the SIP for each component range from 0 (no disability) to 100, in which higher scores reflect worse health.[90] Mean baseline SIP scores from MSCRG for overall, physical, and psychosocial for the interferon and placebo treatment groups were 10.2 versus 11.1, 6.1 versus 7.7, and 12.4 versus 12.3, respectively. Disability progression correlated with physical SIP only, while ARR correlated with all three components of SIP. A SIP score of 10 was chosen by the authors as the cut-off point between mild and moderate disability.

Patients with disability progression had a significant worsening in physical SIP (change from baseline: 9.19 versus 0.06, $P = 0.031$), but not in psychosocial SIP (0.22 versus –2.55, $P = 0.129$) or overall SIP (2.45 versus –0.66, $P = 0.092$) compared with those who did not have disability progression. Likewise, patients with lower ARR had better quality of life measured by mean change in overall SIP ($P = 0.0014$), physical SIP ($P = 0.0014$), and psychosocial SIP ($P = 0.05$) compared with those with higher ARR. The authors reported without showing numerical data that similar patterns were observed when data were analyzed by treatment arms (interferon or placebo).

Patients with low HRQoL at baseline (SIP scores greater than or equal to 10) and treated with interferon beta-1a experienced a decrease in overall SIP (–4.45), physical SIP (–3.78), and psychosocial SIP (–5.86) compared with baseline. However, those treated with placebo had no change in overall SIP (–0.13), an increase in physical SIP (3.57), and a decrease in psychosocial SIP (–3.93) compared with baseline. Interferon had a significant difference in physical SIP score compared with placebo ($P = 0.045$), while there were no statistically significant differences for overall SIP and psychosocial SIP. The difference in physical SIP score between interferon and placebo was 7.35, which was lower than 12.5 points, considered to be the minimal clinically important difference on the physical functioning domain.

Patients with normal HRQoL at baseline (SIP scores of less than 10) and treated with interferon beta-1a showed no significant difference in HRQoL compared with placebo.

Natalizumab versus placebo:
The Short Form 36 (SF-36) and a Subject Global Assessment Visual Analogue Scale (VAS) were used to assess HRQoL in the AFFIRM study[87,88] comparing natalizumab with placebo. The SF-36 is a multidimensional generic health measure that examines eight dimensions: physical function, role limitation (physical), bodily pain, mental health, emotional role function, social functioning, vitality, and general health perception. Scoring for each dimension ranges from 0 to 100, with higher scores representing better health.[91] A minimally clinical important difference cut-off of 5 points was used for SF-36 composite scales in this study.

HRQoL changes (as measured by Physical Component Summary, MCS, and VAS) correlated well with sustained EDSS status (improved, remained stable, or worsened), regardless of treatment with natalizumab or placebo. Natalizumab significantly increased the mean change from baseline in the PCS (0.67 versus –1.34, $P < 0.05$) and MCS (2.00 versus –0.53, $P < 0.05$) compared with placebo at week 104, as well as six out of eight individual scales including physical function (1.21 versus –5.17, $P < 0.001$), role-physical (6.81 versus –1.98, $P < 0.01$), general health (3.82 versus –0.66, $P < 0.01$), vitality (3.74 versus –2.68, $P < 0.01$), social function (4.03 versus –3.30, $P < 0.001$), and role-emotional (6.81 versus –2.73, $P < 0.001$).

The subject global assessment VAS was used to confirm SF-36 findings. Change from baseline in the VAS was also statistically higher in patients treated with natalizumab compared with placebo at week 104 (+0.2 versus –6.2, $P = 0.007$).

The percentage of patients experiencing a clinically important change on the PCS improvement was statistically greater for patients treated with natalizumab compared with placebo at week 104 (24.9% versus 16.8%; odds ratio [OR] 1.54, 95% CI, 1.06, 2.23). The percentage of patients worsened by a clinically important amount on the PCS was statistically lower in patients receiving natalizumab (18.0% versus 25.1%; OR 0.63, 95% CI, 0.45, 0.88). However, there were no statistically significant between-group differences in the percentage of patients achieving a clinically important difference on the MCS improvement or worsening.

b) ***Safety***

Results are presented in Table A14.2. The incidence of mortality and cancer was rare in all studies, and data were not reported in this section but can be found in Table A13.10 and Table A13.23, respectively. Treatment-specific adverse events that occurred at a frequency greater than 5% are summarized in Table 25. Although the incidence of cardiovascular disorders was less than 5%, it was included to reflect the special warning and precaution on the use of fingolimod.[92]

Table 25: Treatment-Specific Adverse Events	
Treatment	**Adverse Events**
Interferon beta (Betaseron, Rebif, Avonex)	• Injection site reactions • Flu-like symptoms • Liver enzyme elevation (Betaseron, Rebif)
Glatiramer acetate	• Injection site reactions • Hypersensitivity
Natalizumab	• Infusion reactions • Skin disorders (rash, dermatitis, pruritus)
Alemtuzumab	• Fatigue • Infection • Skin disorders • Thyroid disorders
Fingolimod	• Liver enzyme elevation • Gastrointestinal disorders (nausea, vomiting, diarrhea) • Cardiovascular disorders (bradycardia, atrioventricular block)
Teriflunomide	• Liver enzyme elevation • Gastrointestinal disorders (nausea, vomiting, diarrhea) • Hair thinning or decreased hair density
Dimethyl fumarate	• Flushing • Gastrointestinal disorders (nausea, vomiting, diarrhea) • Liver enzyme elevation

Table A14.2 presents the effect sizes for safety outcomes obtained from direct pairwise meta-analyses, and Table A11.2 provides an overview of the results.

Interferon beta versus placebo

Interferon beta-1b 250 mcg

One patient (0.8%) in the interferon group and ten (8%) in the placebo group discontinued treatment because of adverse events (IFNB MS[23]). Reasons for discontinuation because of adverse events in both arms included abnormal liver enzymes, injection site pain, fatigue, cardiac arrhythmia, allergic reaction, nausea, headache, and flu-like symptoms. No serious adverse events were reported. There was no notable difference in total withdrawal. Injection site reactions occurred in 69% of the interferon patients and in 6% of placebo patients. The frequency of patient-reported depressive symptoms was similar in both groups. Neutralizing antibodies were found in 11% of placebo sera and in 45% of the 250 mcg interferon sera.

Interferon beta-1a 22 mcg and 44 mcg

Six patients (3%) in the 22 mcg group, nine patients (5%) in the 44 mcg group, and two patients (1%) in the placebo group discontinued treatment because of adverse events (PRISMS[29]). Reasons for discontinuation in both arms were depression, liver enzyme elevations, injection site reactions, influenza-like symptoms, lymphopenia, anaphylactoid reaction, colon cancer, palpitation, psychological disturbance, and septicemia. There was no notable difference between interferon and placebo in total withdrawal, influenza-like illness, fatigue, depression, hypersensitivity, skin disorders, and thyroid disorders. Injection site reactions were more frequent in the 22 mcg group (61% versus 22%) and in the 44 mcg group (53% versus 20%) than the placebo group. The incidence of liver enzyme elevation was also higher in the 22 mcg group (5% versus 1%) and in the 44 mcg group (7% versus 2%) than the placebo group. At the

end of treatment, 23.8% of patients in the 22 mcg group and 12.5% of patients in the 44 mcg group had neutralizing antibodies (PRISMS[29]). The authors reported that the presence of antibodies did not affect the mean relapse count.

Interferon beta-1a 30 mcg

Seven interferon beta-1a patients (4%) and two placebo patients (1%) discontinued injections because of adverse events (MSCRG[27]). Reasons for discontinuation were not reported. There was no notable between-treatment difference in total withdrawal. Serious adverse events were similar in both groups (4%) (Kappos et al.[34]). The adverse events that were more frequently reported in the interferon beta-1a treated patients included influenza-like symptoms (50% versus 30%) and gastrointestinal disorders (47% versus 33%). There was no report of liver enzyme elevation in the interferon beta-1a group and there was no difference in depression between arms (data not shown in MSCRG[27]).

Glatiramer acetate versus placebo

There were no statistically significant differences between the glatiramer acetate and placebo groups in the incidence of serious adverse events, treatment discontinuation because of adverse events (Comi et al.,[17] CONFIRM 2012,[18] and Johnson et al.[26]). There were also no notable differences between groups in fatigue, infection, depression, and liver enzyme elevation. Total withdrawal was less frequent in glatiramer acetate (17% versus 23%). Adverse events were reported more frequently with glatiramer acetate than with placebo and included injection site reactions (43% versus 18%) and hypersensitivity (26% versus 8%).

Natalizumab versus placebo

Serious adverse events were reported in 19% of patients in the natalizumab group and 24% of patients in the placebo group (AFFIRM[9]). The most common serious adverse event was MS relapse (6% with natalizumab versus 13% with placebo; $P < 0.001$). There were no statistically significant differences between natalizumab and placebo groups in the incidence of treatment discontinuation because of adverse events. There were also no notable differences between groups in total withdrawal, fatigue, infection, depression, liver enzyme elevation, and gastrointestinal disorders. Adverse events with a higher incidence in the natalizumab compared with placebo included infusion reactions (24% versus 18%), hypersensitivity (4% versus 0%), and skin disorders (22% versus 15%), including rash, dermatitis, and pruritus. Of the 9% (57/627) of patients in the natalizumab group who had detectable antibodies, 37 patients (6%) had persistent antibodies and also had an increase in infusion reactions and a loss of efficacy of natalizumab. No cases of PML were reported in the AFFIRM study.

Fingolimod versus placebo

There were no statistically significant differences between fingolimod and placebo groups for serious adverse events, treatment discontinuation because of adverse events, and most adverse events, except liver enzyme elevation, whose incidence was higher in the fingolimod group (8% versus 2%) (FREEDOMS ,[22] Saida et al.[31]). The incidence of total withdrawal was lower in the fingolimod group (13% versus 21%), as reported in the FREEDOMS study.[22] The incidence of diarrhea was numerically higher for fingolimod compared with placebo (11.8% versus 7.4%). The incidences of bradycardia (or bradiarrhythmia or sinus bradycardia) and hypertension were also numerically higher for fingolimod compared with placebo (2.1% versus 0.7% and 6.1% versus 3.8%, respectively).

Teriflunomide 7 mg or 14 mg versus placebo

There were no statistically significant differences when comparing placebo with either the 7 mg dose or 14 mg dose of teriflunomide for serious adverse events and treatment discontinuation

because of adverse events. There were also no notable differences between groups in fatigue, infection (O'Connor et al.,[28] TEMSO[32]), and in total withdrawal (TEMSO[32]). The incidence of hypersensitivity or skin disorders was higher with teriflunomide 7 mg and 14 mg (10.3% and 11.2%, respectively) than with placebo (7.2%). Teriflunomide treatment was associated with higher incidence of liver enzyme elevation (for 7 mg: 13% versus 7%; for 14 mg: 14% versus 7%), gastrointestinal disorders (for 7 mg: 23% versus 15%; for 14 mg: 31% versus 15%), and hair loss (for 7 mg: 11% versus 4%; for 14 mg: 14% versus 4%) compared with placebo.

Dimethyl fumarate versus placebo

The incidence of total withdrawal, serious adverse events, treatment discontinuation because of adverse events, fatigue, infections, and depression were not statistically significantly different between dimethyl fumarate and placebo (CONFIRM,[18] DEFINE[19]). Adverse events with higher incidence in dimethyl fumarate than in placebo groups included flushing (34% versus 4%) and gastrointestinal disorders (26% versus 19%). Liver enzyme elevation was similar for dimethyl fumarate and placebo in CONFIRM,[18] but the incidence was higher for dimethyl fumarate in DEFINE[19] (6% versus 3%).

Interferon beta-1a 44 mcg versus interferon beta-1b 250 mcg

Safety data for comparison between interferon beta-1a and beta-1b were not reported in the Etemadifar et al. study.[20]

Interferon beta-1b 250 mcg versus interferon beta-1a 30 mcg

Five patients (5%) in the interferon beta-1b group and one patient (1%) in the interferon beta-1a group discontinued treatment because of adverse events (INCOMIN[25]). Reasons for discontinuation were not reported. Total withdrawal was less frequent in the interferon beta-1b 250 mcg group (11% versus 21%). Serious adverse events were not reported. Frequencies of many adverse events were similar between groups except for injection site reactions, which occurred more frequently in the interferon beta-1b group (37% versus 8%). Neutralizing antibodies to beta interferon happened more frequently in patients treated with interferon beta-1b than interferon beta-1a (22% versus 6%).

Interferon beta-1a 44 mcg versus interferon beta-1a 30 mcg

Frequencies of total withdrawal, serious adverse events, treatment discontinuation because of adverse events, flu-like symptoms, and depression were not different between both groups (EVIDENCE[21]). Adverse events with higher incidence in patients treated with interferon beta-1a 44 mcg were injection site reaction (83% versus 28%) and liver enzyme elevation (12% versus 5%).

Interferon beta-1b 250 mcg versus glatiramer acetate

There were no statistically significant differences between-treatment groups in the incidence of serious adverse events and treatment discontinuation because of adverse events (BECOME,[10] BEYOND[11]). There were also no notable differences between groups in fatigue, infection, depression, and gastrointestinal disorders. Total withdrawal was less frequent in patients treated with interferon beta-1b (11.7% versus 16.0%), as reported in BEYOND.[11] Influenza-like illness (40% versus 6%) and liver enzyme elevation (11% versus 4%) occurred more frequently in patients treated with interferon beta-1b than those treated with glatiramer acetate. By contrast, the incidence of injection site reactions (48% versus 58%) and hypersensitivity (5% versus 17%) was numerically lower in the interferon beta-1b group than in the glatiramer acetate group.

Interferon beta-1a 44 mcg versus glatiramer acetate

There were no statistically significant differences between the two groups in the incidence of serious adverse events and treatment discontinuation because of adverse events (REGARD[30]). There was also no notable difference between groups in depression. The incidence of total withdrawal was higher in the interferon group (21% versus 14%). The adverse events reported more commonly in the interferon group than in the glatiramer acetate group included influenza-like illness (31% versus 1%) and liver enzyme elevation (6% versus 1%). By contrast, the incidence of injection site reactions (6% versus 38%) and hypersensitivity (0% versus 5%) was lower in the interferon group than in the glatiramer acetate group. Of patients in the interferon group, 34% were positive for neutralizing antibodies at some time during the study, and neutralizing antibodies had no effect on clinical efficacy (as stated by the authors of the REGARD study,[30] with no data shown).

Interferon beta-1a 30 mcg versus glatiramer acetate

Total withdrawal was higher in the interferon group compared with the glatiramer acetate group (21% versus 14%). However, there were no statistically significant differences between groups for serious adverse events, treatment discontinuation because of adverse events, and other adverse events.

Dimethyl fumarate versus glatiramer acetate

There were no statistically significant differences between dimethyl fumarate and glatiramer acetate for serious adverse events and treatment discontinuation because of adverse events (CONFIRM[18]). There were also no notable differences between groups in total withdrawal, fatigue, infection, and liver enzyme elevation. Adverse events with higher incidence for dimethyl fumarate than for glatiramer acetate included flushing (31% versus 2%) and gastrointestinal disorders (24% versus 8%). The incidence of depression was numerically lower with dimethyl fumarate than with glatiramer acetate (4% versus 9%).

Fingolimod versus interferon beta-1a 30 mcg

There were no statistically significant differences between fingolimod and interferon beta-1a groups for serious adverse events and treatment discontinuation because of adverse events (TRANSFORMS[33]). There was also no notable difference between groups in total withdrawal. Fingolimod treatment had a numerically higher incidence of liver enzyme elevation (7% versus 2%) compared with interferon beta-1a. The incidences of diarrhea and nausea were numerically higher with fingolimod than with interferon beta-1a (7.5% versus 4.9% and 9.3% versus 6.7%, respectively). The most frequent serious cardiovascular disorders were bradycardia and atrioventricular first and second degree (occurring respectively in 0.5%, 0.2 %, and 0.2 % of patients on fingolimod versus no patient on interferon beta-1a). Influenza-like illness was 10 times more frequent with interferon beta-1a than with fingolimod treatment (36.9% versus 3.5%).

Alemtuzumab 12 mg versus interferon beta-1a 44 mcg

There was no statistically significant difference between groups in serious adverse events. Treatment discontinuation because of adverse events was less frequent in the alemtuzumab group than in the interferon beta-1a group (2% versus 8%). Total withdrawal was also less frequent in the alemtuzumab group (4% versus 17%), based on all three studies. Adverse events with higher incidence in alemtuzumab compared with interferon beta-1a were fatigue (14% versus 8%), infection (72% versus 54%), skin disorders (29% versus 7%), and thyroid disorders (18% versus 5%). Adverse events reported with higher incidence from interferon beta-1a compared with alemtuzumab were influenza-like illness (5% versus 24%), injection site

reactions (7% versus 41%), and liver enzyme elevation (4% versus 12%). The incidences of depression and gastrointestinal disorders were similar between groups.

Alemtuzumab 24 mg versus interferon beta-1a 44 mcg
There was no statistically significant difference between groups in serious adverse events. The incidence of treatment discontinuation because of adverse events in the alemtuzumab group compared with the interferon beta-1a group was lower in CAMMS223[13] (1% versus 12%), but not in CARE-MSII.[15] Total withdrawal was less frequent in the alemtuzumab group (9% versus 23%). Adverse events with higher incidence in alemtuzumab compared with interferon beta-1a were fatigue (22% versus 13%), infection (76% versus 60%), skin disorders (46% versus 8%), and thyroid disorders (19% versus 4%). Adverse events reported to be lower with alemtuzumab compared with interferon beta-1a were influenza-like illness (6% versus 25%), injection site reactions (7% versus 37%), and liver enzyme elevation (3% versus 9%). The incidences of depression and gastrointestinal disorders were similar between groups.

Alemtuzumab 12 mg versus alemtuzumab 24 mg
There were no statistically significant differences between the two doses of alemtuzumab for serious adverse events, treatment discontinuation because of adverse events, total withdrawal, or other adverse events, except gastrointestinal disorders, whose incidence was lower with the lower dose of alemtuzumab (16% versus 29%). In the CAMMS223 study,[13] alemtuzumab-binding antibodies were detected in 0.5% of patients at 12 months and in 26.3% of patients at 24 months. In the CARE-MS II study,[15] alemtuzumab-binding antibodies were found in 29% of patients before second treatment and in 81% one month after the second treatment. Authors of both studies stated that neutralizing antibodies for alemtuzumab did not affect efficacy or safety.

Teriflunomide 7 mg versus teriflunomide 14 mg
There were no statistically significant differences between the two doses of teriflunomide for serious adverse events and treatment discontinuation because of adverse events. There were also no notable differences in total withdrawal or other adverse events, except gastrointestinal disorders and hair loss, whose incidences were lower with a lower dose of teriflunomide (gastrointestinal: 23% versus 31%; hair loss: 11% versus 14%) (O'Connor et al.,[28] TEMSO[32]).

Interferon beta-1a 22 mcg versus interferon beta-1a 44 mcg
Frequency of treatment discontinuation because of adverse events, total withdrawal, and all major adverse events were similar between groups (PRISMS[29]).

Interferon beta-1a 30 mcg versus interferon beta-1a 60 mcg
Discontinuation of study drug because of adverse events occurred in 11% of patients treated with interferon beta-1a 30 mcg and in 16% patients in the 60 mcg group (Clanet et al.[16]). Reasons for discontinuation were MS symptoms, flu-like symptoms, and depression. There was no difference between groups in total withdrawal, influenza-like illness, and depression.

c) *Subgroup Analyses*

In general, the trials did not provide results stratified by subgroups of interest to allow for further meta-analysis. Four studies provided subgroup data and analyses on ARR and/or disability progression for alemtuzumab,[93] fingolimod,[94] teriflunomide,[95] and dimethyl fumarate and glatiramer.[96] The summary results are presented in Table A15.1.

Compared with placebo, alemtuzumab at 12 mg or 24 mg statistically significantly reduced ARR and disability progression in most of the analyzed subgroups, including baseline EDSS score (< 2 or ≥ 2), age (< 31 years or ≥ 31 years), gender, or number of relapses in the previous

two years before randomization (≤ 2 or > 2) compared with interferon beta-1a 44 mcg SC.[93] No tests for interaction were statistically significant, suggesting that the relative treatment effect is consistent across the above mentioned subgroups.

Compared with placebo, fingolimod 0.5 mg had statistically lower ARR across all subgroups except patients aged ≤ 40 years. Fingolimod had a numerically lower proportion of patients with disability progression in all subgroups compared with placebo, but statistical significance was reported only in males and patients with a baseline EDSS score > 3.5.

Compared with placebo, teriflunomide at 7 mg or 14 mg reduced ARR and disability progression across pre-specified subgroups including EDSS (≤ 3.5 or > 3.5), number of GdE lesions at baseline (0, or ≥ 1), age (< 38 years or ≥ 38 years), gender, or number of relapses experienced within the past two years before randomization (≤ 1, 2, 3, or ≥ 4). Between treatments, differences were not statistically significant for males, baseline EDSS score > 3.5 (for teriflunomide 14 mg), and number of prior relapses ≥ 4 (for teriflunomide 14 mg).[95] However, no tests for interaction were statistically significant, suggesting that the relative treatment effect is consistent across the above mentioned subgroups.

Compard with placebo, dimethyl fumarate reduced ARR across pre-specified subgroups. Between treatments, differences were not statistically significant for patients of ≥ 40 years of age and those who had ≥ 2 relapses in the prior year.

Compared with placebo, glatiramer acetate reduced ARR in most patient subgroups, except in patients ≥ 40 years of age, where there was no difference between glatiramer acetate and placebo. Between treatments, differences were not statistically significant for patients with EDSS > 2, the presence or absence of GdE lesions, age ≥ 40 years, female, ≥ 2 relapses in the prior year, and without prior MS treatment.

4.4.2 Combination therapy

Table A15.2 provides the summary of findings in four combination therapy studies.

In the CombiRx,[35] the combination of interferon beta-1a 30 mcg and glatiramer acetate was not statistically superior to glatiramer acetate alone in relapse rate (hazard ratio 1.10; 95% CI, 0.82, 1.46), *P* = 0.27), but was statistically superior to interferon beta-1a 30 mcg alone (ARR: 0.12 versus 0.16; *P* = 0.022). There were no statistically significant differences between combination therapy and either monotherapy in proportion of relapse-free patients, proportion of patients with sustained disability progression, or the mean change in the MSFC. Although statistical significance was not reported, there were also no apparent between-treatment differences in the proportion of patients free of enhanced T2 lesions, or in safety outcomes including death, serious adverse events, and discontinued treatment because of adverse events.

In the study by Freedman et al.,[36] ARR were not statistically significantly different between teriflunomide (either 7 mg or 14 mg) versus placebo as add-on to interferon beta (Avonex, Rebif, Betaseron). Mean numbers of GdE lesions at both teriflunomide doses were statistically lower compared with placebo. The proportions of patients with GdE lesions were numerically lower in both teriflunomide treatment groups compared with placebo, but the statistical significance of this finding was not reported. No deaths occurred during the 24-week study. Incidences of serious adverse events and discontinuation because of adverse events were low and similar among treatment groups. There was a higher incidence of increased alanine aminotransferase in teriflunomide groups (13.5% and 28.9% in 7 mg and 14 mg, respectively)

compared with placebo (12.2%). Teriflunomide groups also had a higher incidence of decrease in white blood cell count compared with placebo. However, the incidence of nasopharyngitis and urinary tract infection was similar among treatment groups. Other adverse events including fatigue and gastrointestinal disorders were also similar among treatment groups.

In GLANCE,[37] the ARR was not statistically significantly different between the combination of natalizumab plus glatiramer acetate versus glatiramer alone (0.40 versus 0.67, $P = 0.237$). In addition, the proportion of patients relapse-free was not statistically significantly different between the two treatment groups. Combination therapy resulted in a statistically significantly lower mean number of GdE lesions (0.6 versus 2.3, $P = 0.02$) and mean number of new or enlarging T2-hyperintense lesions (0.5 versus 1.3, $P = 0.029$). There were no deaths during the study. The incidence of serious adverse events was low: one in combination therapy (elective hip surgery) and two in the glatiramer alone group (hospitalization for MS relapse and anaphylactic reaction to glatiramer acetate). One patient in each group discontinued treatment because of an adverse event. The incidences of infection, depression, infusion reactions, and hypersensitivity reactions were similar between-treatment groups. However, injection site reaction occurred more frequently with combination therapy than with glatiramer acetate alone (16% versus 5%), and 14 patients out of 54 (26%) in the combination therapy had natalizumab-neutralizing antibodies.

In SENTINEL,[38] the ARR was statistically significantly lower for the combination of natalizumab plus interferon beta-1a (Avonex) compared with interferon beta-1a alone (0.34 versus 0.75, $P = 0.001$) and the proportion of patients remaining relapse-free was statistically significantly higher (54% versus 32%, $P < 0.001$) over the two-year treatment period. The proportion of patients with sustained disability progression was statistically lower for the combination therapy (23% versus 29%, $P = 0.02$). Combination therapy was also associated with a lower mean number of GdE lesions (0.1 versus 0.9; *P* value not reported) and mean number of new or enlarged T2-hyperintense lesions (0.9 versus 5.4; *P* = NR), as well as the reduction in the proportion of patients having GdE lesions and new or enlarged T2-hyperintense lesions. There were two deaths in the placebo group. The incidence of serious adverse events and discontinuation of treatment because of adverse events was similar in both groups. Of the serious adverse events, PML occurred in two patients after receiving 29 doses and 37 doses of natalizumab, respectively. Incidences of influenza-like illness, infection, and depression were similar between groups. Combination therapy was associated with a numerically higher incidence of infusion reactions (24% versus 20%), hypersensitivity reactions (1.9% versus 0.3%), and gastrointestinal disorders (26% versus 21%) compared with interferon beta-1a alone. Six patients (1%) in the combination therapy group and 12 patients (2%) in the group receiving interferon beta-1a alone were diagnosed with cancer. Seventy patients (12%) in the combination group had natalizumab-neutralizing antibodies, of which 38 patients (7%) had persistent antinatalizumab antibodies resulting in a loss of efficacy and an increase in infusion-related reactions. The incidence of new neutralizing antibodies against interferon beta-1a was 1% in the combination therapy group and < 1% in the group assigned to interferon beta-1a alone.

In SENTINEL,[87] natalizumab-treated patients reported statistically greater improvements from baseline on the PCS (1.03 versus –0.93, $P < 0.001$) but not the MCS (0.18 versus –0.96, not statistically significant), compared with interferon beta-1 a alone at week 104. In addition, natalizumab resulted in statistically greater improvements in five out of eight individual scales, including physical function (2.33 versus –3.08, $P < 0.001$), role-physical (2.08 versus –2.97, $P < 0.01$), general health (3.13 versus –1.43, $P < 0.001$), vitality (1.75 versus –1.11, $P < 0.001$), and social function (1.05 versus –4.02, $P < 0.001$). By using a minimally clinical important difference cut-off of 5 points, the percentage of patients experiencing a clinically important improvement on the PCS was significantly greater in patients treated with natalizumab compared with placebo (23.3% versus 17.4%; OR 1.47; 95% CI, 1.08, 2.03). The percentage of patients experiencing a clinically important worsening on the PCS was lower in patients receiving natalizumab (16.5% versus 21.6%; OR 0.64; 95% CI, 0.47, 0.87). There were no statistical between-treatment differences in the percentage of patients having a clinically important improvement, or worsening, on the MCS.

4.5 Pharmacoeconomic Evaluation

4.5.1 Base case analysis

a) *Monotherapy*

The results of the base case are presented in Table 26 and Figure 7.

With regard to effectiveness, natalizumab is the most effective treatment regarding QALYs (11.58), followed by dimethyl fumarate (11.44), and interferon beta-1a 30 mcg with the fewest (11.16).

Natalizumab was the most expensive treatment ($482,436), followed by fingolimod ($416,414). Glatiramer acetate was the least expensive treatment ($321,589) and therefore it was used as a reference.

The incremental cost per QALY for interferon beta-1b 250 mcg (Extavia) versus glatiramer acetate is $118,242. The incremental cost per QALY for dimethyl fumarate (Tecfidera) versus interferon beta-1b 250 mcg (Extavia) is $425,655. The incremental cost per QALY for natalizumab versus dimethyl fumarate (Tecfidera) is $872,972. Interferon beta-1b 250 mcg (Betaseron) was dominated by interferon beta-1b (Extavia); interferon beta-1a (Avonex) and interferon beta-1a 22 mcg (Rebif) were dominated by interferon beta-1b (Extavia) and glatiramer acetate, while interferon beta-1a 44mcg (Rebif) was dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate, as they produced fewer QALYs for higher cost. Fingolimod was dominated by dimethyl fumarate.

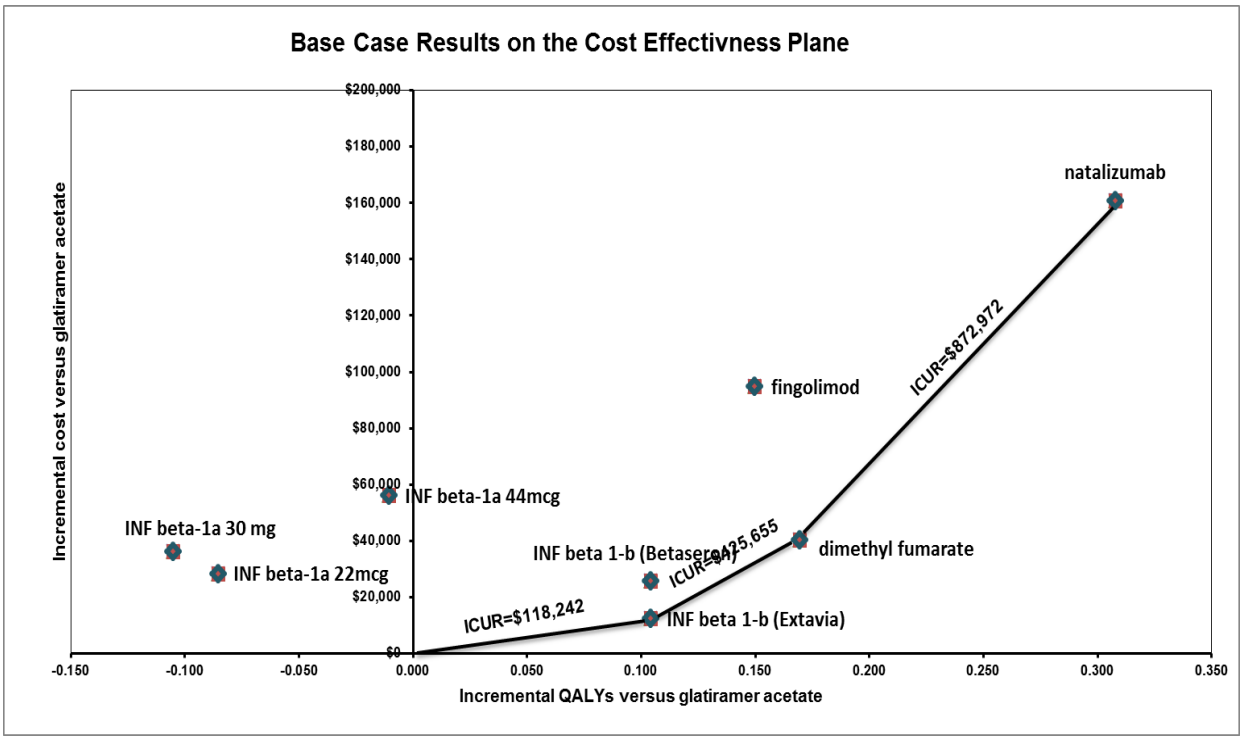
Figure 7 shows the efficiency frontier for the incremental cost per QALY outcome. The four treatments that make up the efficiency frontier are glatiramer acetate, interferon beta 1-b (Extavia), dimethyl fumarate, and natalizumab. The other treatments are dominated by the treatments comprising the frontier, and they would not be considered to be cost-effective, regardless of the value placed on gaining an incremental QALY. Therefore, the incremental cost per QALY of interferon beta 1-b (Extavia) versus glatiramer acetate is estimated to be $118,242, meaning glatiramer acetate would be considered the cost-effective treatment if a decision-maker's maximum willingness to pay for QALY is less than $118,242. For willingness to pay between $118,242 and $425,655, interferon beta-1b 250 mcg (Extavia) is the cost-effective treatment. For willingness to pay between $425,655 and $872,972, dimethyl fumarate is the cost-effective treatment. If willingness to pay is above $872,972, then natalizumab is the cost-effective treatment.

Table 26: Results of Base Case Deterministic Analysis

Treatment	Total Cost	Total QALYs	versus glatiramer acetate			Sequential ICUR
			Incremental Cost	Incremental QALYs	ICUR	
Glatiramer acetate (Copaxone)	$321,589	11.272	ref	ref	ref	ref
Interferon beta-1b (Extavia)	$333,923	11.376	$12,334	0.104	$118,242	$118,242
Dimethyl fumarate (Tecfidera)	$361,688	11.442	$40,099	0.170	$236,518	$425,655
Natalizumab (Tysabri)	$482,436	11.580	$160,847	0.308	$522,472	$872,972
Dominated treatments						
Interferon beta-1b (Betaseron)	$347,292	11.376	$25,703	0.104	$246,411	dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.187	$28,348	-0.085	dominated	dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.167	$36,069	-0.105	dominated	dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.262	$56,170	-0.010	dominated	dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	11.422	$94,825	0.150	$632,608	dominated by dimethyl fumarate

Dominated = more costly and fewer QALYs; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; mcg = microgram.

Figure 7: Base Case Results on the Cost-Effectiveness Plane



ICUR = incremental cost-utility ratio; IFN = interferon; QALY = quality-adjusted life-year; mcg = microgram; mg = milligram.

Because the model included a “no treatment” scenario, the cost-effectiveness of all treatments versus no treatment could be explored as additional information; the results are presented in Table 27. The results of this analysis show that treatment with any of the interferon therapies and glatiramer acetate dominates “no treatment”; i.e., treatment is less costly and more effective than no treatment. The ICUR of fingolimod versus no treatment is $18,234, and $121,456 versus natalizumab (Table 27).

Table 27: Results of Exploratory Deterministic Cost-Effectiveness Analysis Versus No Treatment						
Treatment	**Total Cost**	**Total QALYs**	**Versus No Treatment**			**Sequential ICUR**
			Incremental Cost	**Incremental QALYs**	**ICUR**	
Glatiramer acetate (Copaxone)	$321,589	11.272	–$86,551	0.304	Dominates no treatment	ref
Interferon beta-1b (Extavia)	$333,923	11.376	–$74,217	0.408	Dominates no treatment	$118,242
Dimethyl fumarate (Tecfidera)	$361,688	11.442	–$46,452	0.473	Dominates no treatment	$425,655
Natalizumab (Tysabri)	$482,436	11.580	$74,296	0.612	$121,456	$872,972
Dominated treatments						
No treatment	$408,140	10.968	ref	Ref	Ref	Dominated by glatiramer acetate and interferon beta 1-b (Extavia) and dimethyl fumarate
Interferon beta-1a (Avonex)	$357,658	11.167	-$50,482	0.199	Dominates	Dominated by glatiramer acetate and interferon beta 1-b (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.187	-$58,203	0.219	Dominates	Dominated by glatiramer acetate and interferon beta 1-b (Extavia)
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.262	-$30,381	0.293	Dominates	Dominated by glatiramer acetate, interferon beta 1-b (Extavia) and dimethyl fumarate
Interferon beta-1b (Betaseron)	$347,292	11.376	-$60,848	0.408	Dominates	Dominated by interferon beta 1-b (Extavia)
Fingolimod (Gilenya)	$416,414	11.422	$8,274	0.454	$18,234	Dominated by dimethyl fumarate

Dominated = more costly and fewer QALYs; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

b) *Combination therapy*

There were four clinical studies identified in the systematic review assessing the clinical effectiveness of combination therapy in RRMS; i.e., CombiRx,[35] Freedman et al.,[36] GLANCE,[37] and SENTINEL[38] (Table 19). CombiRx, Freedman et al., and GLANCE resulted with no proven improvements in measures of relapse or disability. The SENTINEL study reported that the addition of natalizumab to an ongoing regimen of interferon beta-1a 30 mcg provided additional clinical benefit regarding relapse and disease progression. However, the lack of a natalizumab-only arm in the SENTINEL study precluded a definite conclusion that the observed effects of the combination therapy were the result of additive effects of two active treatments; potentially, a switch to natalizumab may have produced similar benefits to the add-on strategy. Therefore, based on the available data, there is not enough clinical evidence to support inclusion of combination therapy in the health economic model. The cost-effectiveness of combination therapy in RRMS remains unknown.

4.5.2 Exploratory analysis including emerging treatments

The current treatments that are approved and available in Canada were included in the primary analysis. The emerging treatments in RRMS (alemtuzumab and teriflunomide) were included in an exploratory analysis. Because the cost of these treatments is unknown, international prices were used as a guide, where available. The price of teriflunomide was available for the US market, and therefore the ratio between the US price and the US price of fingolimod was applied to estimate the Canadian cost of teriflunomide. Because the price of alemtuzumab was not publicly available from international sources at the time the analyses were conducted, it was assumed that alemtuzumab would be priced in line with the highest-cost treatment (natalizumab). Additional analysis was conducted using different pricing for these two emerging treatments.

Table 28: Results of Exploratory Deterministic Cost-Effectiveness Analysis Including Emerging Treatments

Treatment	Total Cost	Total QALYs	versus glatiramer acetate			Sequential ICUR
			Incremental Cost	Incremental QALYs	ICUR	
Glatiramer acetate (Copaxone)	$321,589	11.272	ref	ref	ref	
Interferon beta-1b (Extavia)	$333,923	11.376	$12,334	0.104	$118,242	$118,242
Alemtuzumab 24 mg [a]	$490,468	11.906	$168,879	0.634	$266,553	$295,783
Dominated Treatments						
Interferon beta-1b (Betaseron)	$347,292	11.376	$25,703	0.104	$246,411	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.187	$28,348	–0.085	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.167	$36,069	–0.105	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 28: Results of Exploratory Deterministic Cost-Effectiveness Analysis Including Emerging Treatments						
Treatment	**Total Cost**	**Total QALYs**	**versus glatiramer acetate**			**Sequential ICUR**
Dimethyl fumarate (Tecfidera)	$361,688	11.442	$40,099	0.170	$236,518	Extendedly dominated by interferon beta-1b 250 mcg (Extavia) and alemtuzumab 24 mg
Teriflunomide oral 7 mg[b]	$375,361	11.244	$53,772	–0.028	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Teriflunomide oral 14 mg[b]	$375,782	11.299	$54,193	0.027	$2,037,065	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.262	$56,170	–0.010	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Fingolimod (Gilenya)	$416,414	11.422	$94,825	0.150	$632,608	Extendedly dominated by interferon beta-1b 250 mcg (Extavia) and alemtuzumab 24 mg
Natalizumab (Tysabri)	$482,436	11.580	$160,847	0.308	$522,472	Extendedly dominated by interferon beta-1b 250 mcg (Extavia) and alemtuzumab 24 mg
Alemtuzumab 12 mg[a]	$490,896	11.759	$169,307	0.487	$347,578	Dominated by alemtuzumab 24 mg

Dominated = more costly and fewer QALYs; ICUR = incremental cost-utility ratio; mcg = microgram; mg = milligram; QALY = quality-adjusted life-year.
[a]The price of alemtuzumab is unavailable in Canada, and it was assumed to be the same as for natalizumab ($40,271)
[b]The price of teriflunomide was based on the ratio between the price of fingolimod and the price of teriflunomide in the US[73] ($24,184).
Note: A wide range of prices was tested in the sensitivity analysis.

The results show that, under the aforementioned drug price assumptions, teriflunomide 7 mg is dominated by interferon beta-1b (Extavia) and glatiramer acetate; teriflunomide 14 mg is dominated by interferon beta-1b (Extavia); alemtuzumab 12 mg is dominated by alemtuzumab 24 mg; and the ICUR of alemtuzumab 24 mg versus interferon beta-1b (Extavia) is $295,783. Therefore, if the willingness to pay is $295,783 or higher, then alemtuzumab 24 mg is a cost-effective treatment.

4.5.3 Deterministic sensitivity analysis

a) Parameter Uncertainty

Sensitivity analysis around background costs

The background cost per EDSS states were derived from two Canadian studies and involved some extrapolation. To assess the uncertainty regarding the background costs, a sensitivity analysis was conducted by increasing and decreasing the cost by 100%. The results are presented in Table 29 and Table 45, showing that increasing the background costs results in lower ICURs.

Table 29: Results of the Univariate Sensitivity Analysis Regarding Background Cost

Scenario	Result
Base case	If λ < $118,242, glatiramer acetate is a cost-effective treatment. If $118,242 < λ < $425,655, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $425,655 < λ < $872,972, dimethyl fumarate is a cost-effective treatment. If λ > $872,972, natalizumab is a cost-effective treatment.
Increase background cost by 100%	If λ < $41,675, glatiramer acetate is a cost-effective treatment. I If $41,675 < λ < $207,064, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment If $207,064 < λ < $827,812, dimethyl fumarate is a cost-effective treatment. If λ > $827,812, natalizumab is a cost-effective treatment.
Decrease background cost by 100%	If λ < $156,526, glatiramer acetate is a cost-effective treatment. If $156,526 < λ < $227,517, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $227,517 < λ < $895,552, dimethyl fumarate is a cost-effective treatment. If λ > $895,552, natalizumab is a cost-effective treatment.

mcg = microgram.

In all scenarios, interferon beta-1a 30 mcg, interferon beta-1a 44 mcg, interferon beta-1a 22 mcg, interferon beta-1b 250 mcg (Betaseron), and fingolimod are dominated therapies.

Sensitivity analysis regarding natural history of disease progression

To explore the impact of using one data source for the natural history of disease, sensitivity analysis was conducted by varying the rate of disability progression. Results showed that if the rate of disability progression is slower than reported in the London Ontario study, then the ICURs would be higher than those in the base case. Results are presented in Table 30.

Table 30: Results of the Univariate Sensitivity Analysis Regarding the Natural History of Disability Progression	
Scenario	**Result**
Base case	If λ < $118,242, glatiramer acetate is a cost-effective treatment. If $118,242 < λ < $425,655, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $425,655 < λ < $872,972, dimethyl fumarate is a cost-effective treatment. If λ > $872,972, natalizumab is a cost-effective treatment.
Increase natural history of disability progression by 50%	If λ < $67,609, glatiramer acetate is a cost-effective treatment; I If $67,609 < λ < $375,641, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $376,641 <λ < $596,368, dimethyl fumarate is a cost-effective treatment. If λ > $827,812, natalizumab is a cost-effective treatment.
Decrease natural history of disability progression by 50%	If λ < $396,532, glatiramer acetate is a cost-effective treatment. If $396,532 < λ < $474,856, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment; If $474,856 < λ < $1,410,447, dimethyl fumarate is a cost-effective treatment. If λ > $1,410,447 natalizumab is a cost-effective treatment.

mcg = microgram.

Sensitivity analysis around cost per relapse

To address the uncertainty regarding the cost of relapse univariate, a sensitivity analysis was conducted. The results show that this parameter does not have a significant impact on the results (Table 31).

In all scenarios, interferon beta-1a 30 mcg and interferon beta-1a 22 mcg are dominated by glatiramer acetate and interferon beta-1b 250 mcg (Extavia). Interferon beta-1b 250 mcg (Betaseron) is dominated by interferon beta-1b 250 mcg (Extavia). Interferon beta-1a 44 mcg is dominated by glatiramer acetate, interferon beta-1b 250 mcg (Extavia) and dimethyl fumarate. Fingolimod is dominated by dimethyl fumarate.

Table 31: Results of the Univariate Sensitivity Analysis Regarding Cost of Relapse	
Scenario	**Result**
Base case[62] Cost per mild or moderate relapse =$6,402 Cost per severe relapse = $15,364	If λ < $118,242, glatiramer acetate is a cost-effective treatment. If $118,242 < λ < $425,655, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $425,655 < λ < $872,972, dimethyl fumarate is a cost-effective treatment. If λ > $872,972, natalizumab is a cost-effective treatment.
Grima et al.[74] Cost per relapse = $1,405	If λ < $109,519, glatiramer acetate is a cost-effective treatment. If $109,519 < λ < $503,474, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $503,474 < λ < $913,177, dimethyl fumarate is a cost-effective treatment. If λ > $913,177, natalizumab is a cost-effective treatment.
Karampampa et al.[75] Cost per relapse = $6,402	If λ < $115,694 glatiramer acetate is a cost-effective treatment. If $115,694 < λ < $448,383, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $448,383 < λ < $884,714, dimethyl fumarate is a cost-effective treatment. If λ>$884,714, natalizumab is cost-effective treatment.
Increase cost of relapse for 100% Cost per mild or moderate relapse = $12,804 Cost per severe relapse = $30,728	If λ < $128,702, glatiramer acetate is a cost-effective treatment. If $128,702 < λ < $332,343, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment; If $332,343 < λ < $824,762, dimethyl fumarate is a cost-effective treatment. If λ > $824,762, natalizumab is a cost-effective treatment.

mcg = microgram.

Utilities

There were several studies reporting utilities associated with RRMS. Although the utilities from Prosser et al.[62] were used, the impact of using other sources was assessed.

When considering the different data sources for utility values, while there were numerical changes to the QALYs gained, these were no significant changes to the cost-effectiveness results (Table 32).

Table 32: Univariate Sensitivity Analysis — Health Utilities	
Source for Utilities	**Result**
Prosser et al.[62] (Base case)	If λ < $118,242, glatiramer acetate is cost-effective treatment. If $118,242 < λ < $425,655, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $425,655 < λ < $872,972, dimethyl fumarate is a cost-effective treatment. If λ > $872,972, natalizumab is a cost-effective treatment.
Kobelt et al.[77]	If λ < $139,729, glatiramer acetate is cost-effective treatment. If $139,729 < λ < $436,994, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $436,994 < λ < $942,812, dimethyl fumarate is a cost-effective treatment. If λ > $942,812, natalizumab is a cost-effective treatment.
ScHARR[78]	If λ < $105,735, glatiramer acetate is cost-effective treatment. If $105,735 < λ < $416,432, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $416,432 < λ < $802,304, dimethyl fumarate is a cost-effective treatment. If λ > $802,304, natalizumab is a cost-effective treatment.
Earnshaw et al.[79]	If λ < $131,124, glatiramer acetate is a cost-effective treatment. If $131,124 < λ < $432,653, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $432,653 < λ < $911,411, dimethyl fumarate is a cost-effective treatment. If λ > $911,411, natalizumab is a cost-effective treatment.
Karampampa et al.[75]	If λ < $101,765, glatiramer acetate is a cost-effective treatment. If $101,765 < λ < $413,253, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $413,253 < λ < $784,639, dimethyl fumarate is a cost-effective treatment. If λ > $784,639, natalizumab is a cost-effective treatment.

In all scenarios, interferon beta-1a 30 mcg and interferon beta-1a 22 mcg are dominated by glatiramer acetate and interferon beta-1b 250 mcg (Extavia). Interferon beta-1b 250 mcg (Betaseron) is dominated by interferon beta-1b 250 mcg (Extavia). Interferon beta-1a 44 mcg is dominated by glatiramer acetate, interferon beta-1b 250 mcg (Extavia), and dimethyl fumarate. Fingolimod is dominated by dimethyl fumarate.

Disutility of relapse

Several studies reported disutilities associated with relapse; however, only Prosser et al.[62] made a distinction between mild or moderate and severe relapse. It was assumed that the reported disutility in the alternative sources was for mild or moderate relapse. Therefore, to estimate the utility decrement associated with severe relapse by using the alternative data sources, the ratio between disutility associated with mild or moderate relapse and severe relapse used in the Prosser et al. study[62] was applied to the disutility reported by the alternative sources to estimate the disutility associated with severe relapse.

Table 33: Disutilities Associated With Relapse Based on Alternative Data Sources				
Disutility Values	**Prosser et al.[62] (base case)**	**Parkin et al[97]**	**ScHARR[78]**	**Earnshaw[79]**
Mild or moderate relapse	–0.091	–0.0136	–0.078	–0.094
Severe relapse	–0.302	–0.451[a]	–0.259[a]	–0.312[a]

[a] Estimated value

Results were not sensitive to the disutility associated with relapse (Table 34).

Table 34: Results of the Univariate Sensitivity Regarding Disutility of Relapse	
Source for Utilities	**Result**
Prosser et al.[62] (Base case)	If λ < $118,242, glatiramer acetate is a cost-effective treatment. If $118,242 < λ < $425,655, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $425,655 < λ < $872,972, dimethyl fumarate is a cost-effective treatment. If λ > $872,972, natalizumab is a cost-effective treatment.
Parkin et al.[97]	If λ < $118,855, glatiramer acetate is a cost-effective treatment. If $118,855 < λ < $411,514, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $411,514 < λ < $858,226, dimethyl fumarate is a cost-effective treatment. If λ > $858,226, natalizumab is a cost-effective treatment.
ScHARR[78]	If λ < $116,245, glatiramer acetate is a cost-effective treatment. If $116,245 < λ < $480,638, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $480,630 < λ < $925,974, dimethyl fumarate is a cost-effective treatment. If λ > $925,974, natalizumab is a cost-effective treatment.
Earnshaw et al.[79]	If λ < $118,715, glatiramer acetate is a cost-effective treatment. If $118,715 < λ < $414,652, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $414,652 < λ < $861,530, dimethyl fumarate is a cost-effective treatment. If λ > $861,530, natalizumab is a cost-effective treatment.

mcg = microgram.

In all scenarios, interferon beta-1a 30 mcg and interferon beta-1a 22 mcg are dominated by glatiramer acetate and interferon beta-1b 250 mcg (Extavia). Interferon beta-1b 250 mcg (Betaseron) is dominated by interferon beta-1b 250 mcg (Extavia). Interferon beta-1a 44 mcg is dominated by glatiramer acetate, interferon beta-1b 250 mcg (Extavia) and dimethyl fumarate. Fingolimod is dominated by dimethyl fumarate.

Discontinuation rate

There is evidence to suggest that there are no significant differences in adherence between the disease-modifying agents.[65] There is some difference in opinion regarding the rates of treatment discontinuation, ranging from annual rates of 10% (based on expert opinion, and other health economic evaluations) to 25% reported by Wong et al.[65] In the base case, a constant annual rate of 15% was assumed across all treatments for the first two years, based on the discontinuation rate in the clinical trials included in the systematic review. After two years, the discontinuation rate was assumed to be zero, assuming that all patients who discontinue treatment would have done so by the end of the second year. Sensitivity analysis was also conducted, varying the constant discontinuation rate.Results show that ICURs are not very

sensitive to the discontinuation rate. In addition, exploratory analysis was conducted assuming a lower discontinuation rate with the oral treatments — fingolimod and dimethyl acetate — (10%) versus injectable treatments (25%), which resulted with an increased ICUR for natalizumab but did not change which treatments would comprise the cost-effectiveness frontier (Table 35, Table 49).

Table 35: Results of the Univariate Sensitivity Analysis Regarding Annual Discontinuation Rate

Scenario	Result
15% for the first 2 years (base case)	If λ < $118,242, glatiramer acetate is a cost-effective treatment. If $118,242 < λ < $425,655, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $425,655 < λ < $872,972, dimethyl fumarate is a cost-effective treatment. If λ > $872,972, natalizumab is a cost-effective treatment.
0% annual discontinuation rate	If λ < $122,032, glatiramer acetate is a cost-effective treatment. If $122,032 < λ < $426,213, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $426,213 < λ < $880,388, dimethyl fumarate is a cost-effective treatment. If λ > $880,388, natalizumab is a cost-effective treatment.
25% annual discontinuation rate for the first 2 years	If λ < $15,584, glatiramer acetate is a cost-effective treatment. If $115,584 < λ < $425,339, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $425,339 < λ < $867,743, dimethyl fumarate is a cost-effective treatment. If λ > $867,743, natalizumab is a cost-effective treatment.
10% annual discontinuation rate of oral treatments, 25% of injectable treatments for the first 2 years	If λ < $115,584, glatiramer acetate is a cost-effective treatment. If $115,584 < λ < $416,037, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $416,037 < λ < $1,449,326, dimethyl fumarate is a cost-effective treatment. If λ > $1,449,326, natalizumab is a cost-effective treatment.

mcg = microgram.

In all scenarios, interferon beta-1a 30 mcg and interferon beta-1a 22 mcg are dominated by glatiramer acetate and interferon beta-1b 250 mcg (Extavia). Interferon beta-1b 250 mcg (Betaseron) is dominated by interferon beta-1b 250 mcg (Extavia). Interferon beta-1a 44 mcg is dominated by glatiramer acetate, interferon beta-1b 250 mcg (Extavia), and dimethyl fumarate. Fingolimod is dominated by dimethyl fumarate.

Percent of PML associated with natalizumab

The risk of PML associated with natalizumab has been included in the model. Based on a recently published article by Hunt and Giovannoni,[70] there is a risk of 0.15% for patients on natalizumab for developing PML, which is associated with a mortality rate of 18.5%. To measure the impact of PML, a threshold analysis was conducted, showing the ICURs of natalizumab versus glatiramer acetate if the rate of PML was in the range of 0% to 1% and mortality associated with PML in the range of 0% to 30% (Table 36).

Table 36: Results of Threshold Analysis Regarding PML Associated With Natalizumab				
PML rate	**Mortality rate**	**Total Cost**	**Total QALYs**	**Versus Glatiramer Acetate**
				ICUR
0.00%	18.5%	$482,692	11.585	$514,201
0.15% (base case)	18.5%	$482,436	11.580	$522,472
0.20%	18.5%	$482,348	11.578	$525,377
1.00%	18.5%	$480,983	11.549	$575,626
0.15%	0%	$482,692	11.585	$514,201
0.15%	10%	$482,550	11.582	$518,755
0.15%	18.50% (base case)	$482,436	11.580	$522,472
0.15%	30%	$482,293	11.577	$527,229

ICUR = incremental cost-utility ratio; PML = progressive multifocal leukoencephalopathy; QALY = quality-adjusted life-year.

The results of the analysis show that, because of the low rate of PML associated with natalizumab, the scenario assuming no PML associated with natalizumab has similar results to the base case.

Threshold analysis regarding the price of emerging treatments
Because there is uncertainty regarding the price of emerging treatments, threshold analysis was conducted exploring what the treatment costs need to be in order for treatments to be considered cost-effective under different willingness-to-pay thresholds. The results are presented in Table 37.

Table 37: Sensitivity Analysis Regarding Cost of Emerging Treatments			
Treatment	**Estimated Annual cost**	**λ = $50,000 (ICUR versus glatiramer acetate)**	**λ = $100,000 (ICUR versus glatiramer acetate)**
Alemtuzumab 12 mg	$40,281[a]	$21,900	$25,000
Alemtuzumab 24 mg	$40,281[a]	$23,550	$26,950
Teriflunomide 14 mg	$24,184[b]	$16,420	$16,650

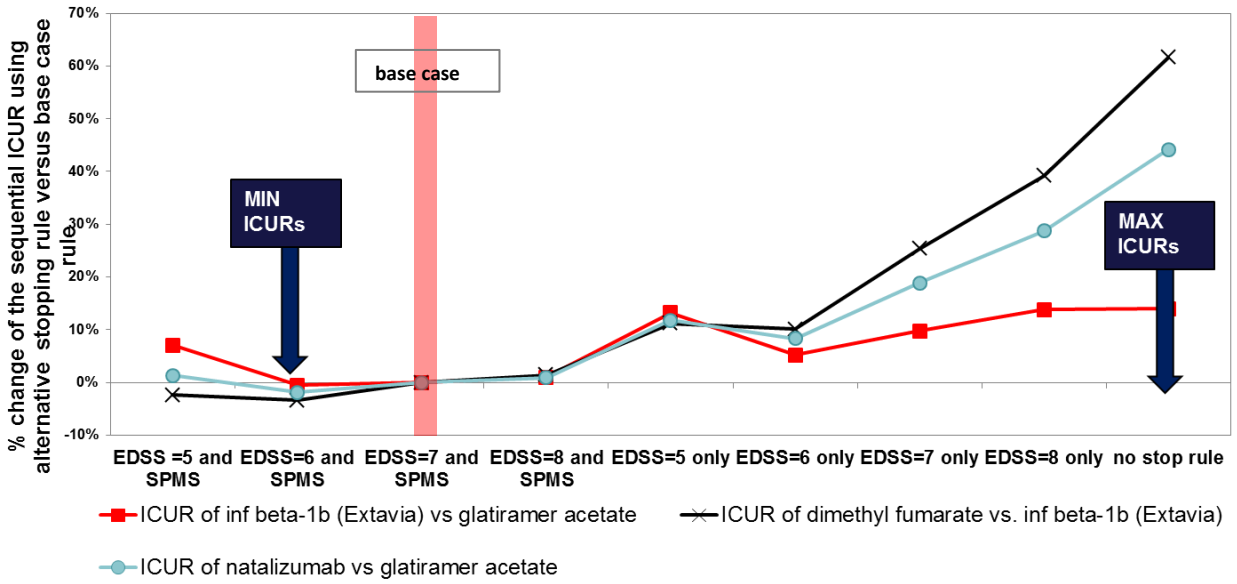
ICUR = incremental cost-utility ratio; mg = milligram.
[a] Assumption, based on the price of natalizumab.
[b] Assumption, based on the US price.

b) Structural uncertainty

Stopping rule
For the base case scenario, it was assumed that, once patients progress to EDSS = 7.0 or SPMS, they will discontinue treatment. Due to the differences in stopping rules across the Canadian provincial plans, a sensitivity analysis was conducted varying the EDSS score that would lead to treatment discontinuation, as well as treatment discontinuation with the progression to SPMS. Results are presented in Figure 8 and in Table 53.

The analysis showed that a stopping rule at EDSS = 6 or progression to SPMS would lead to lower ICURs. The ICURs were very close to those when considering a stopping rule at EDSS = 7. However, earlier treatment discontinuation at EDSS = 5, as well as late discontinuation at EDSS > 7, increased the ICURs. Because the model assumes no treatment benefit for patients who have progressed to SPMS, a stopping rule without considering SPMS progression would result in much higher ICURs.

Figure 8: Sensitivity Analysis Regarding Stopping Rule

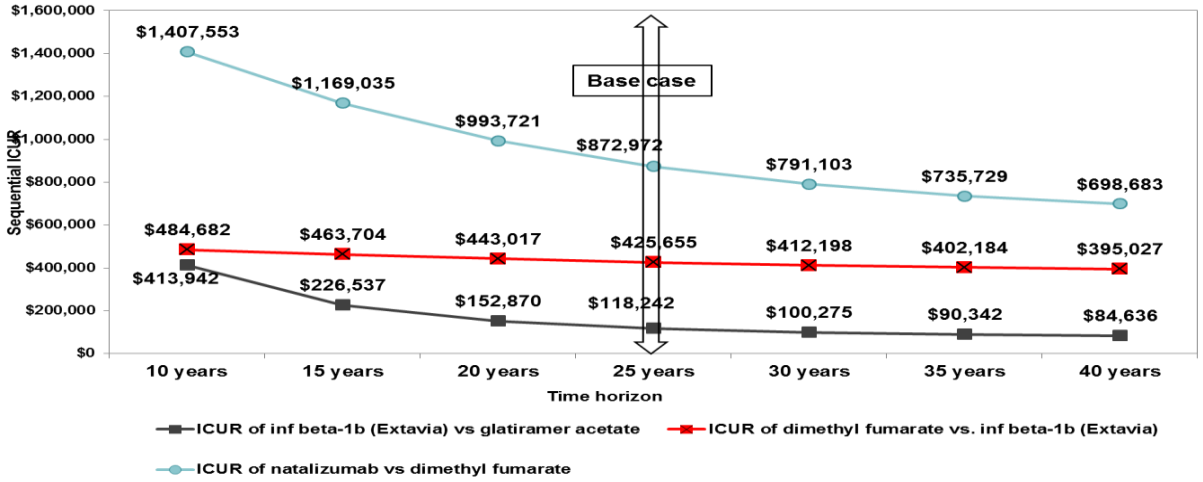


EDSS = Expanded Disability Status Scale; QALY = quality-adjusted life-year; SPMS = secondary-progressive multiple sclerosis.
Note: The dominated treatments are not included.

Time horizon of 10 years, 30 years, and 40 years

The base case scenario was based on a time horizon of 25 years. Sensitivity analysis was conducted by varying the time horizon within the range of 10 years to 40 years (lifetime). Figure 9 shows the impact of the time horizon of the economic model on the sequential ICURs. (Figure 9).

Figure 9: Sensitivity Analysis Regarding Time Horizon



ICUR = incremental cost-utility ratio; mg = milligram; QALY = quality-adjusted life-year.
Note: The dominated treatments are not included in the graph.

Improvements in EDSS scores

The base case model includes improvements on the EDSS scale, based on findings from the study by Tremlett et al.,[63] which concluded that disability improvements in MS over one or two years are not unusual. A scenario analysis was conducted to measure the impact of not allowing improvements in EDSS in the economic model. The analyses resulted in slightly lower, but not significantly lower, ICURs. Results are presented in Table 38, and in more detail in Table 51.

Table 38: Results of the Univariate Sensitivity Analysis Regarding Improvements on EDSS Scale

Source for Utilities	Result
Improvements on EDSS scale (base case)	If λ < $118,242, glatiramer acetate is a cost-effective treatment. If $118,242 < λ < $425,655, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $425,655 < λ < $872,972, dimethyl fumarate is a cost-effective treatment. If λ > $872,972, natalizumab is a cost-effective treatment.
No improvements on EDSS scale	If λ < $104,221, glatiramer acetate is a cost-effective treatment. If $104,221 < λ < $438,617, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $438,617 < λ < $829,108, dimethyl fumarate is a cost-effective treatment. If λ > $829,108, natalizumab is a cost-effective treatment.

EDSS = Expanded Disability Status Scale; mcg = microgram.

In all scenarios, interferon beta-1a 30 mcg and interferon beta-1a 22 mcg are dominated by glatiramer acetate and interferon beta-1b 250 mcg (Extavia). Interferon beta-1b 250 mcg (Betaseron) is dominated by interferon beta-1b 250 mcg (Extavia). Interferon beta-1a 44 mcg is dominated by glatiramer acetate, interferon beta-1b 250 mcg (Extavia), and dimethyl fumarate. Fingolimod is dominated by dimethyl fumarate.

Relapse rate being modelled as a constant rather than time-dependent variable

There is available evidence suggesting that the frequency of relapse is affected by a patient's age and disease duration;[68] i.e., is a time-dependent variable.[5] To assess the impact, a sensitivity analysis was conducted by applying a constant relapse rate, as per alternative sources.[62,64,69] Table 39 summarizes the reported relapse rates for untreated patients in the identified studies. Table 40 presents the results of the sensitivity analysis showing that increasing the relapse rates decreases the ICURs.

Table 39: Relapse Rate Based on Natural History of Disease

Source	Relapse Rate	
	EDSS 0-2	**EDSS 3-5**
ScHARR[64]	0.835	1.423
Prosser et al.(2004)[62]	1.395	1.395
Patzold and Pocklington (1982) (constant, time since onset 5 years)[69]	1.110	1.110

EDSS = Expanded Disability Status Scale.

Table 40: Results of the Univariate Sensitivity Analysis Regarding Relapse Rates	
Source for utilities	**Result**
Time-dependent variable (base case)	If λ < $118,242, glatiramer acetate is cost-effective treatment. If $118,242 < λ < $425,655, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $425,655 < λ < $872,972, dimethyl fumarate is a cost-effective treatment. If λ > $872,972, natalizumab is cost-effective treatment.
ScHARR[64] **Relapse rate = 0.835 (EDSS = 0-2)** **Relapse rate = 1.423 (EDSS = 3-5)**	If λ < $124,172, glatiramer acetate is cost-effective treatment. If $124,172 < λ < $354,333, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $354,333 < λ < $803,519, dimethyl fumarate is a cost-effective treatmen. If λ > $803,519, natalizumab is a cost-effective treatment.
Prosser et al. (2004)[62] **Relapse rate = 1.395**	If λ < $140,432 glatiramer acetate is cost-effective treatment. If $140,432 < λ < $241,362 interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $241,362 < λ < $665,950, dimethyl fumarate is a cost-effective treatment. If λ > $665,950, natalizumab is a cost-effective treatment.
Patzold and Pocklington (1982)[69] **Relapse rate = 1.1**	If λ < $132,012, glatiramer acetate is cost-effective treatment. If $132,012 < λ < $297,194, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $297,194 < λ < $737,176, dimethyl fumarate is a cost-effective treatment. If λ > $737,176, natalizumab is a cost-effective treatment.

EDSS = Expanded Disability Status Scale; mcg = microgram.

In all scenarios, interferon beta-1a 30 mcg and interferon beta-1a 22 mcg are dominated by glatiramer acetate and interferon beta-1b 250 mcg (Extavia). Interferon beta-1b 250 mcg (Betaseron) is dominated by interferon beta-1b 250 mcg (Extavia). Interferon beta-1a 44 mcg is dominated by glatiramer acetate, interferon beta-1b 250 mcg (Extavia) and dimethyl fumarate. Fingolimod is dominated by dimethyl fumarate.

Heterogeneity

Starting EDSS score:

The base case scenario included distribution around a starting EDSS score with mean 2 and standard error of 0.8, to reflect the average patient group based on the baseline characteristics of the clinical trials included in the systematic review.

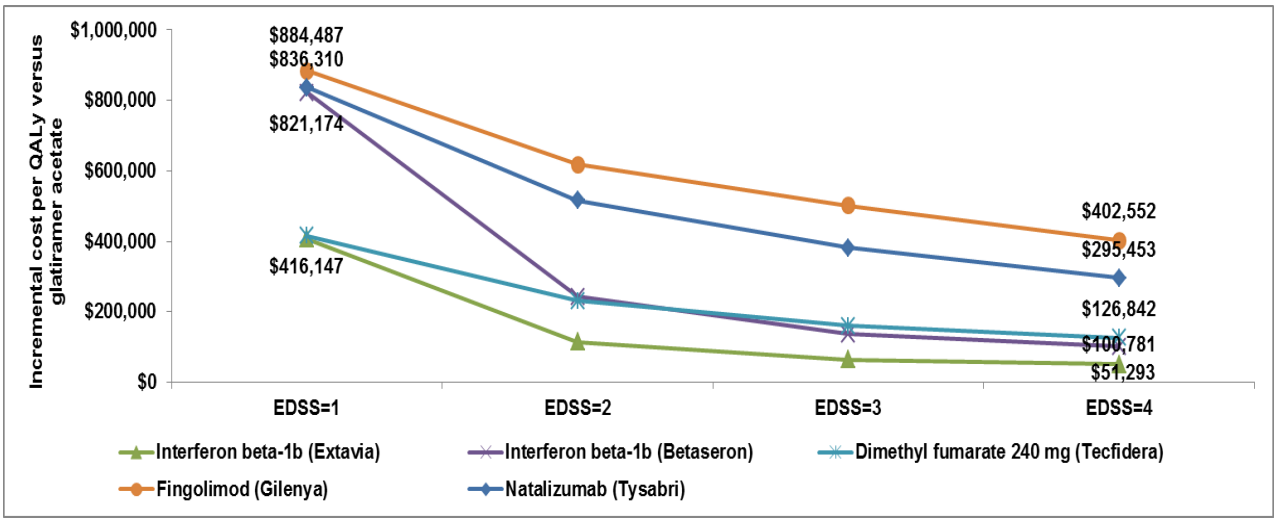
To measure the impact of the starting EDSS score, this parameter was varied in the economic model. Because there was no subgroup analysis available per EDSS score, the treatment efficacy was assumed to be the same, regardless of choice of baseline EDSS score. Results are graphically presented in Figure 10. A detailed table with the results is available in the in Table 54.

The results showed that early treatment with the more expensive treatments leads to significantly higher ICURs. The decrease in ICURs with increased EDSS score is especially prominent in the case of interferon beta-1b 250 mcg (Betaseron), because of the very small gain in QALY (0.04) for patients with EDSS = 1.0.

Starting age

The model allowed variation in the patient's starting age. The results are presented in Table 41 and do not appear to be overly sensitive to this parameter, although they showed lower ICURs when treating younger patients. Details of the results are presented in Table 55.

Figure 10: Impact of Starting EDSS Score on ICUR versus Glatiramer Acetate



EDSS = Expanded Disability Status Scale; ICUR = incremental cost-utility ratio; mg = milligram; QALY = quality-adjusted life-year.

Table 41: Results of the Univariate Sensitivity Analysis Regarding Starting Age	
Source for Utilities	**Result**
Starting age = 36 years (base case)	If λ < $118,242, glatiramer acetate is cost-effective treatment. If $118,242 < λ < $425,655, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $425,655 < λ < $872,972, dimethyl fumarate is a cost-effective treatment. If λ > $872,972, natalizumab is a cost-effective treatment.
Starting age = 20 years	If λ < $116,736, glatiramer acetate is costa cost-effective treatment. If $116,736 < λ < $424,763, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $424,763 < λ < $867,355, dimethyl fumarate is a cost-effective treatment. If λ > $867,355, natalizumab is a cost-effective treatment.
Starting age = 50 years	If λ < $124,133, glatiramer acetate is cost-effective treatment. If $124,133 < λ < $428,976, interferon beta-1b 250 mcg (Extavia) is a cost-effective treatment. If $428,976 < λ < $894,322, dimethyl fumarate is a cost-effective treatment. If λ > $894,322, natalizumab is cost-effective treatment.

mcg = microgram.

In all scenarios, interferon beta-1a 30 mcg and interferon beta-1a 22 mcg are dominated by glatiramer acetate and interferon beta-1b 250 mcg (Extavia). Interferon beta-1b 250 mcg (Betaseron) is dominated by interferon beta-1b 250 mcg (Extavia). Interferon beta-1a 44 mcg is dominated by glatiramer acetate, interferon beta-1b 250 mcg (Extavia) and dimethyl fumarate. Fingolimod is dominated by dimethyl fumarate.

4.5.4 Probabilistic sensitivity analysis

The expected cost and QALYs did not significantly vary from the deterministic results, and therefore the ICURs produced by the probabilistic sensitivity analysis also did not vary. Results are presented in Table 42 below. The cost-effectiveness frontier also comprised glatiramer acetate, interferon beta 1-b 250 mg (Extavia), and natalizumab. However, the 95% credible intervals for incremental QALYs versus glatiramer acetate crossed zero for all treatments, which highlights the uncertainty regarding the gain in QALYs.

A cost-effectiveness acceptability curve (CEAC), derived from the joint distribution of costs and effects, was also constructed, and it illustrates the probability of ICURs falling below range of willingness to pay.

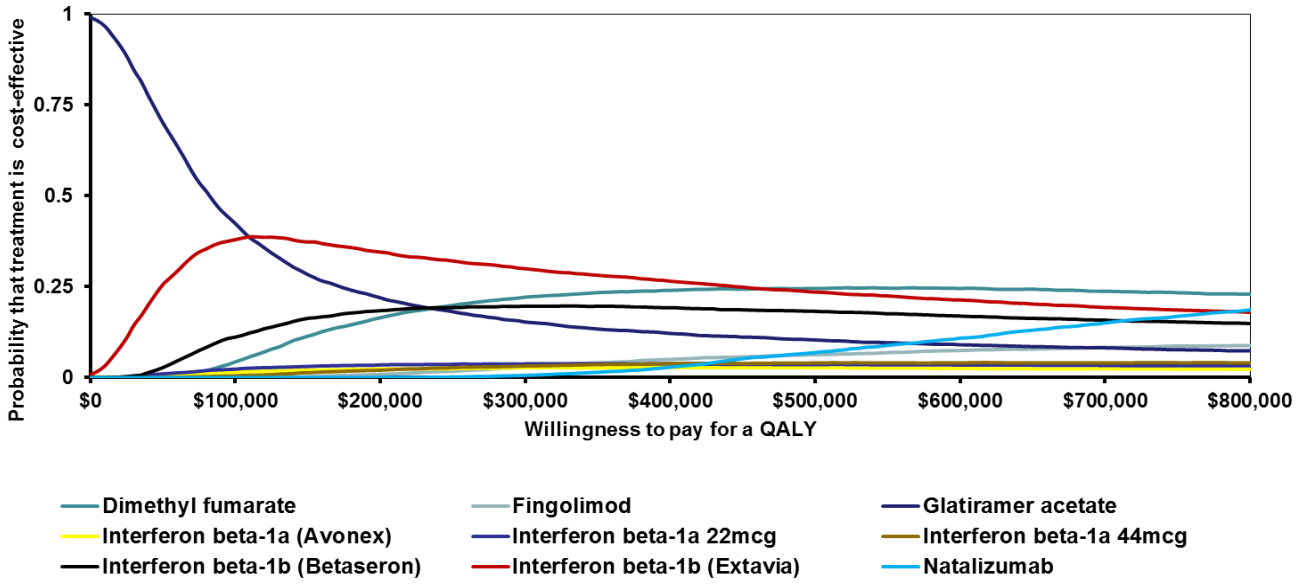
- Where the decision-maker is willing to pay a maximum of $50,000 per QALY (λ = $50,000), glatiramer acetate was the cost-effective treatment in 70% of replications, followed by interferon beta-1b (Extavia) in 26% and beta-1b (Betaseron) in 3%.
- Where the decision-maker is willing to pay a maximum of $100,000 per QALY (λ = $100,000), glatiramer acetate was the cost-effective treatment in 42% of replications, followed by interferon beta-1b (Extavia) in 38% and beta-1b (Betaseron) in 11%.

Table 42: Results of Probabilistic Sensitivity Analysis						
Treatment	**Total Cost**	**Total QALYs**	**Versus Glatiramer Acetate**			**Sequential ICUR**
			Incremental Cost	**Incremental QALYs**	**ICUR**	
Glatiramer acetate (Copaxone)	$327,756 ($312,066, $345,615)	11.29 (10.81, 11.78)	ref	ref	ref	ref
Interferon beta-1b (Extavia)	$341,304 ($325,665, $360,207)	11.41 (10.94, 11.88)	$13,548 ($2,945, $25,092)	0.11 (–0.33, 0.52)	$117,928	$147,568
Dimethyl fumarate (Tecfidera)	$371,624 ($358,949, $387,199)	11.48 (11.02, 11.95)	$43,868 ($34,373, $54,589)	0.18 (–0.25, 0.57)	$239,636	$444,720
Natalizumab (Tysabri)	$503,274 ($486,460, $524,445)	11.62 (11.18, 12.07)	$175,518 ($159,423, $195,837)	0.33 (–0.1, 0.71)	$532,441	$898,098
Dominated therapies						
Interferon beta-1b 250 mcg (Betaseron)	$355,925 ($340,524, $374,448)	11.4 (10.94, 11.87)	$28,169 ($18,148, $39,917)	0.11 (–0.32, 0.52)	$249,915	dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$358,627 ($343,038, $377,159)	11.2 (10.72, 11.71)	$30,871 ($20,097, $42,175)	–0.09 (–0.53, 0.36)	dominated	dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 30 mcg (Avonex)	$367,009 ($348,557, $388,343)	11.18 (10.71, 11.68)	$39,253 ($27,133, $51,526)	–0.11 (–0.55, 0.32)	dominated	dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$389,206 ($373,922, $407,682)	11.28 (10.8, 11.8)	$61,450 ($51,720, $73,678)	–0.01 (–0.44, 0.44)	dominated	dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$431,256 ($417,459, $448,866)	11.45 (11, 11.93)	$103,500 ($92,195, $117,801)	0.16 (–0.28, 0.58)	$641,378	dominated by dimethyl fumarate

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; mcg = microgram.; extendedly dominated = the combination of two other alternatives dominated the treatment.

Dominated = more costly and fewer QALYs

Figure 11: Cost-Effectiveness Acceptability Curve



QALY = quality-adjusted life-year; mcg = microgram.

4.5.5 Value of information analysis

Dominance measure
Based on the dominance measure screening method, the parameters that resulted in a positive dominance measure are utility values for health state 3 and health state 4, MS-related costs for health state 3 and health state 4, as well as the RR of disability progression of glatiramer acetate, interferon beta-1b 250 mcg (Extavia), and dimethyl fumarate. The rest of the input parameters resulted in a zero dominance measure, meaning that that their impact to the model uncertainty is likely to be negligible.

Expected value of partial perfect information
The estimated EVPPI is noticeably high for the RR of disability progression of interferon beta-1b 250 mcg (Extavia/Betaseron), and dimethyl fumarate, meaning that most of the uncertainty in the model is related to the relative effectiveness of disease progression for these treatments (Table 43). Assuming a prevalence rate of 240 per 100,000 persons — i.e., 84,000 patients in Canada — the EVPPI per total RRMS population would be $1.7M for the RR of disease progression of dimethyl fumarate (Tecfidera) and $78M for the RR of disease progression of interferon beta-1b 250 mcg (Extavia/Betaseron).

Table 43: Results of the Expected Value of Information Analysis for Parameters with Significantly High EVPPI		
Parameter	**EVPPI Per Patient**	**EVPPI Per Population (In Millions)**
RR of disease progression dimethyl fumarate	$21	$1.7
RR of disease progression of interferon beta-1b 250 mcg (Extavia/Betaseron)	$1,130	$95

EVPPI= expected value of partial perfect information; mcg = microgram, RR= relative risk.

Thus, the most important input parameters in the model appear to be the RR of disease progression of dimethyl fumarate and interferon beta-1b 250 mcg. It would be expected to be worth $1.7M and $95M to reduce all uncertainty around the RR of disease progression of dimethyl fumarate and interferon beta-1b 250 mcg, respectively.

5 DISCUSSION

5.1 Summary of Evidence

The systematic review included 30 individual RCTs that reported the efficacy and safety of disease-modifying agents in patients with RRMS. There were 27 studies[9-35] that provided comparisons of monotherapies and four[35-38] that provided comparisons between combination therapy and monotherapy. Evaluated interventions included alemtuzumab, natalizumab, interferon beta-1b, interferon beta-1a subcutaneous, interferon beta-1a intramuscular, glatiramer acetate, dimethyl fumarate, fingolimod, and teriflunomide. One monotherapy trial[15] was restricted to treatment-experienced patients, and a number of studies[10,11,13,14,23,25-30] were restricted to treatment-naïve patients. However, the majority of monotherapy trials either did not specify whether patients had previously received disease-modifying treatments, or they included a mixed patient population (treatment-naive and treatment-experienced). None of the monotherapy trials specifically enrolled patients who had failed or were intolerant to previous treatments.

Of the four combination therapy trials, one (CombiRx) included treatment-naïve patients. The other three combination trials enrolled patients who had been previously treated with monotherapy; however, the extent to which patients could be considered to have failed previous treatment was unclear.

Data available for efficacy and safety outcomes were analyzed by direct pairwise meta-analyses. NMAs were conducted for two efficacy outcomes (ARR and sustained disability progression) to estimate comparative efficacies between all interventions.

5.2 Interpretation of the Results

5.2.1 Comparisons among treatment strategies

Comparisons were made for diverse treatment strategies that differed in chemical structure, mechanism of action, mode of administration, dosage, and treatment-related adverse events. The different modes of administration included intravenous infusion (alemtuzumab, natalizumab), subcutaneous (interferon beta-1b, interferon beta-1a, glatiramer acetate),

intramuscular (interferon beta-1a), and oral (fingolimod, dimethyl fumarate, teriflunomide). Adverse events were treatment-specific, as expected because of the diversity of chemical structure and mechanism of action. Such diversity precluded the conduct of NMA on safety outcomes, which makes between-treatment comparisons of benefit and risk more challenging.

a) Monotherapy

For ARR, results from the NMA suggest that, compared with all other treatments, natalizumab and alemtuzumab result in statistically lower ARR, reducing the ARR by approximately 70% compared with no treatment (placebo). Two oral agents (fingolimod and dimethyl fumarate) appear to have similar activity to each other, reducing the ARR by approximately 50% compared with no treatment (placebo). Subcutaneous interferons, glatiramer acetate, and teriflunomide appear to have similar activity to each other, reducing the ARR by approximately 30% compared with no treatment (placebo). Intramuscular interferons appear to have the lowest activity of all agents.

Results from the NMA for ARR are generally consistent with the results from the available head-to-head trials that report greater efficacy for alemtuzumab compared with interferon beta-1a, greater efficacy of fingolimod and dimethyl fumarate compared with older agents (intramuscular interferon beta 1a and glatiramer acetate, respectively), and similar efficacy between glatiramer acetate and interferons.

Estimates of relative treatment effect from the NMA for disability (regarding the proportion of patients achieving sustained disability progression) show less precision than for ARR. Natalizumab and alemtuzumab again appear to have the greatest activity compared with all other agents; however, credible intervals are wide and demonstrate considerable overlap between agents, resulting in uncertainty in the relative efficacy of the remaining treatments. In addition, there is less consistency between direct and indirect estimates than was observed for ARR. Lesser between-treatment differences in disability compared with ARR may be an indication that relapse frequency is not directly related to disability progression. Alternatively, the disparity between the ARR and disability results may be related to the short duration of trials and the insensitivity of the measure of disability. Because RRMS is a slow-progressing disease, an accurate assessment of disability would require follow-up for longer than the two to three years used in many of the included studies. In addition, EDSS is an ordinal scale that focuses on mobility, and therefore does not capture all key components of disability in MS.

There were insufficient data to conduct an NMA for the remainder of the protocol-defined outcomes. However, findings from head-to-head trials report that MRI findings were more favourable for alemtuzumab compared with interferon beta-1a 44 mcg, and more favourable for all three of fingolimod, interferon beta-1b 250 mcg, and interferon beta-1a 44 mcg compared with interferon beta-1a 30 mcg. Compared with glatiramer, dimethyl fumarate resulted in a statistically lower mean number of T2 lesions, but the mean number of GdE lesions was not statistically different between these two treatments. However, it should be noted that only one trial contributed evidence for this comparison, the study was not powered for the active comparison, and MRI findings were not the planned primary outcome.

Evidence on HRQoL was limited to two treatments (interferon beta-1a 30 mcg and natalizumab) compared with placebo. For the comparison between interferon beta-1a 30 mcg and placebo in the MSCRG study, the difference in physical SIP score between interferon and placebo was 7.35, which was lower than the 12.5 points considered to represent a minimal clinically important difference in the physical domain. For the comparison between natalizumab and

placebo in the AFFIRM study, a change of 5.0 points for PCS and MCS scales was considered to be a clinically meaningful difference. However, the differences between natalizumab and placebo in the proportion of patients achieving a clinically important change on the PCS improvement (8%) and PCS worsening (7%) were small. Thus, both treatments appear to have a small improvement in HRQoL on the physical domain, but not on the mental or psychosocial domain.

Adverse events of note were treatment-specific. Of the two treatments that appear to have the greatest activity (based on the NMA), alemtuzumab was associated with a high incidence of thyroid disorders compared with interferon beta-1a (17% versus 4%), while there is concern regarding the association between natalizumab and the risk of PML. Post-marketing data have estimated the risk of developing PML to be 1 in 500 patients treated with natalizumab.[48] The risk of developing PML was increased with increasing treatment duration, history of previous exposure to immunosuppressive therapy, and presence of anti-JC Virus antibodies.[48] Other adverse events that were associated with alemtuzumab included fatigue, infection, and skin disorders, and those associated with natalizumab included infusion reactions, hypersensitivity, and skin disorders.

Patient input provided specifically for this Therapeutic Review suggests persons with MS prefer oral agents to injectable agents. Their preference stems from a variety of reasons — including anxiety associated with needles, issues with rotation of sites, cannot use a needle because of coordination issues, side effects (injection site reactions, lipoatrophy, and bruising on the skin), and inconvenience with refrigeration/travel. The findings in this review suggest that the three oral agents had similar activity in sustained disability progression, while results were more favourable for fingolimod and dimethyl fumarate compared with teriflunomide regarding ARR. These oral drugs also showed improved MRI outcomes compared with placebo. Common adverse events among the three oral agents were gastrointestinal disorders (nausea, vomiting, and diarrhea) and liver enzyme elevation. An adverse event specifically associated with fingolimod was cardiovascular disorder, typically bradycardia and atrioventricular block, while for dimethyl fumarate it was flushing (warmth and redness), and for teriflunomide it was alopecia (hair loss). Adverse events that were commonly observed with interferons were injection site reactions and influenza-like symptoms, whereas injection site reactions and hypersensitivity were commonly reported for glatiramer acetate. Liver enzyme elevation was reported more frequently for interferon beta-1a 44 mcg compared with interferon beta-1a 30 mcg and glatiramer acetate.

Few statistically significant between-treatment differences in adverse events, and no statistically significant between-treatment differences in serious adverse events, were identified. This is unsurprising given that clinical trials are frequently underpowered to identify infrequent or rare adverse events and that the identification of important safety issues may not occur until the post-market period. It should be noted that older agents such as the interferons and glatiramer have the benefit of a longer post-market period. Further, given the differences in the adverse event profiles of the available treatments, it is desirable that patient specific factors be considered in treatment selection, as suggested by patient-group input.

b) Combination therapy

Three of four combination studies assessed the efficacy and safety of adding a second disease-modifying agent to ongoing treatment. However, it was not clear that patients would be considered to have failed prior treatment. Two studies (GLANCE[37] and Freedman et al.[36]) did not report improvements in measures of relapse or disability with the addition of a second agent,

likely because of their small size and short duration; both studies did report more favourable MRI findings with add-on therapy. The SENTINEL study[38] reported that the addition of natalizumab to an ongoing regimen of interferon beta-1a 30 mcg IM for at least 12 months provided additional clinical benefit in lower relapse rate, reduced risk of disease progression, and favourable MRI findings. However, the lack of a natalizumab-only arm in the SENTINEL study precluded a definite conclusion that the observed effects of the combination therapy were the result of the additive effects of two active treatments; potentially, a switch to natalizumab may have produced similar benefits to the add-on strategy. Two patients treated with natalizumab in SENTINEL developed PML, and the development of neutralizing antibodies to natalizumab with reduced efficacy was noted.

The fourth combination trial (CombiRx[35]) was designed to compare both glatiramer acetate and interferon beta-1a monotherapy with the combination of the two agents as initial treatment (enrolled patients were treatment-naive). As an initial treatment, the combination did not appear to be superior to either agent alone for a number of outcomes, although the ARR was 25% lower for patients treated with the combination compared with interferon beta-1a alone.

5.2.2 Pharmacoeconomic Considerations

a) Monotherapy

The results of the base case show that treatment with any of the interferon therapies, glatiramer acetate, or dimethyl fumarate dominates no treatment; i.e., treatment is less costly and more effective than no treatment. The ICUR of fingolimod versus no treatment is $18,234, and the ICUR of natalizumab versus no treatment is $121,456.

In the base case analysis, glatiramer acetate was likely to be the cost-effective treatment choice, assuming decision-maker willingness-to-pay threshold is lower than $118,242 per QALY. For willingness to pay between $118,242 and $425,655, interferon beta-1b 250 mcg (Extavia) is the cost-effective treatment. If willingness to pay is between $425,625 and $872,972, dimethyl fumarate is a cost-effective treatment. If willingness to pay is higher than $872,972, then natalizumab is the cost-effective treatment. Interferon beta-1a 30 mcg and interferon beta-1a 22 mcg are dominated by glatiramer acetate and interferon beta-1b 250 mcg (Extavia). Interferon beta-1b 250 mcg (Betaseron) is dominated by interferon beta-1b 250 mcg (Extavia). Interferon beta-1a 44 mcg is dominated by glatiramer acetate, interferon beta-1b 250 mcg (Extavia) and dimethyl fumarate. Fingolimod is dominated by dimethyl fumarate.

Probabilistic sensitivity analysis showed that there is some degree of uncertainty regarding these results, especially related to the treatment efficacy. Cost-effectiveness acceptability curves were constructed, and at a willingness to pay of $50,000, glatiramer acetate was the cost-effective treatment in 70% of replications, followed by interferon beta-1b (Extavia) in 26% of replications and beta-1b (Betaseron) in 3% of replications.

Extensive sensitivity analyses were conducted around the model input parameters and the structural uncertainty was tested. Although ICURs did vary, none of these analyses, with an exception of cost per treatment, changed the conclusions of the analysis.
The emerging treatments in RRMS for which regulatory approval has not been granted (alemtuzumab and teriflunomide) were included in an exploratory analysis. Because the cost of these treatments is unknown, international prices were used as a guide, where available. The price of teriflunomide was available for the US market, and therefore the ratio between the US price and the US price of fingolimod was applied to estimate a Canadian cost for teriflunomide.

The price of alemtuzumab was not publicly available from international sources at the time of the review, and therefore it was assumed that alemtuzumab would be priced in line with the highest-cost treatment (natalizumab). Under these assumptions, teriflunomide 7 mg and teriflunomide 14 mg are dominated by interferon beta-1b (Extavia); alemtuzumab 12 mg is dominated by alemtuzumab 24 mg; and the ICUR of alemtuzumab 24 mg versus interferon beta-1b (Extavia) is $295,793. With inclusion of the emerging treatments, natalizumab, dimethyl fumarate and fingolimod are extendedly dominated by interferon beta-1b (Extavia) and alemtuzumab 24mg. Therefore, if the willingness to pay is $295,793 or higher, then alemtuzumab 24 mg is the cost-effective treatment.

Due to the differences in treatment-stopping rules across the Canadian provincial plans, a sensitivity analysis was conducted varying the EDSS score that would lead to treatment discontinuation. The base case scenario assumed a stopping rule at EDSS = 7 or progression to SPMS. The sensitivity analysis showed earlier treatment discontinuation (at EDSS = 5), as well as late discontinuation (at EDSS > 7), increased the ICURs; i.e., the optimal stopping rule for the ICUR is at EDSS = 6 to 7. As the model assumes no treatment benefit for patients who progressed to SPMS, a stopping rule without considering SPMS progression resulted in much higher ICURs.

PML has been identified by physicians and decision-makers as an important concern, and consequently the risk of PML associated with natalizumab was included in the model. The results of the analysis show that, because of the low rate of PML associated with natalizumab, the scenario assuming no PML associated with natalizumab has similar results to the base case when there is a risk of 0.15% for patients on natalizumab developing PML.[70]

To measure the impact of the starting EDSS score, this parameter was varied in the economic model. As there was no subgroup analysis available per EDSS score, the treatment efficacy was assumed to be the same, regardless of choice of baseline EDSS score. The results showed that early treatment with the more expensive treatments leads to significantly higher ICURs.

b) Combination therapy

As there is not enough clinical evidence to support the inclusion of combination therapy in the health economics model, the cost-effectiveness of combination therapy in RRMS remains unknown.

5.3 Strengths and Limitations of the Systematic Review

5.3.1 Strengths

This systematic review was conducted according to a pre-specified protocol, using standard approaches for collecting evidence, performing data extraction, quality assessment, and analysis. This review included currently available and emerging treatment agents of different classes for RRMS. The evidence was analyzed and presented using both direct pairwise meta-analyses and an NMA. The robustness of the NMA was supported by the similarity between the results of the indirect comparison and those of the pairwise comparison. Selected meta-regression and subgroup analyses were conducted to explore heterogeneity, and demonstrated the robustness of the findings in the reference case analysis. A comprehensive economic evaluation was conducted using available cost data and the results of the NMAs.

5.3.2 Limitations

a) Clinical limitations

In addition to the aforementioned strengths, key limitations of the review are related to the availability of data and the suitability of available data for pooling. As previously noted, we identified no trials specifically designed to assess comparative efficacy and safety of disease-modifying treatments in patients who had failed, or were intolerant to, previous treatments. In addition, a number of outcomes of particular interest to patients were not widely captured in the included trials. These include fatigue, difficulty walking, memory or attention problems, and impact on work life. Fatigue was captured as an adverse event in a number of trials, rather than assessed with a valid sleep scale. Difficulty walking and memory or attention problems may be captured as components of the MSFC (as the timed 25-foot walk test and the paced auditory serial-addition test, respectively). However, only five trials included the MSFC as an outcome, and only a global score for the MSFC was reported; the trials did not report the components separately. Patient-group input suggests that there is considerable inter-patient variability in MS symptoms and thus patients desire to have numerous treatment options available.

Another data limitation was the general lack of data stratified by subgroups of interest. Only four trials (CAMMS223,[13] CONFIRM,[18] FREEDOMS,[22] and TEMSO[32]) reported subgroup analyses of clinical efficacy outcomes including ARR and sustained disability progression. All four studies reported consistent effects across subgroups (defined by age, gender, EDSS score, prior relapse, and GdE lesions), with no evidence of effect modification.

NMAs could not be conducted on MRI and safety outcomes. The evidence networks of MRI outcomes were relatively unstable because of a sparse connection between treatments, and the MRI populations in many studies were subsets of patients with unclear selection criteria for MRI scans. For safety outcomes including death, serious adverse events, and treatment discontinuation because of adverse events, the low frequency of events precluded NMA.

NMA involves the pooling of trials. To avoid the introduction of bias, it is important that clinical and methodological variation across studies is minimized. If variability does exist, the assessment of its effects on NMA results is required. We observed between-trial variability in both study characteristics (treatment duration, year of publication) and baseline patient characteristics (EDSS score, prior relapses, time since symptom onset, treatment history). The included studies were conducted over a 20-year time period, over which the diagnosis and treatment of MS evolved. The resultant between-trial differences in-patient characteristics may be important predictors of treatment effect. To address this heterogeneity, we performed meta-regression and subgroup analyses using patient characteristics as covariates. However, the small number of studies in relation to the number of treatment strategies may not allow for adequate control of confounding.

For a fixed-effects model to be applicable, an assumption that all the studies included in the analysis are functionally identical must be met, therefore enabling the computation of the common effects size for the identified population but restricting extrapolation to other populations. The results of the systematic review indicated variation in the characteristics of included patient populations: RRMS versus SPMS and treatment-naïve versus other. Typically, when the subjects or interventions in studies differ in ways that would affect the results, a common effects size cannot be assumed. Therefore, in these cases, the random-effects model is more easily justified than the fixed-effects model.

For analyses of ARR, there were some limitations in the reporting of data required for pooling in meta-analyses and NMA. Specifically, not all studies reported the total relapses and/or total observed person-years; several studies reported only mean ARR values as an outcome. As described in the NMA methodology, imputations were required to circumvent this issue in order to derive a best estimate of the total relapses and person-years to conduct the NMA using a Poisson distribution model. Incorporation of a mean value to impute the model inputs raises uncertainty as to the accuracy and reliability of the resulting model inputs, as it overlooks the issue of skewness of mean values in the presence of outliers. In order to address this heterogeneity, sensitivity analyses (results not shown) using only studies that reported total relapses and total observed person-years were performed; results were consistent with those obtained for the base case.

The definition of sustained disability progression differed between the trials, with the main difference being that, in some trials, the reduction in EDSS needed to be maintained for six months, whereas in other trials, a reduction sustained for three months was sufficient. For that reason, the proportion of patients experiencing disability progression was expected to vary across trials. We combined data for this outcome across all trials despite the difference in definition, based on the expectation that the relative differences between treatments would be unaffected. However, this is a potential source of heterogeneity. To examine the effect of this potential source of heterogeneity, a meta-regression analysis (results not shown) using three- and six-month time intervals for measuring sustained disease progression was conducted, which failed to detect any significant changes in the results. Nevertheless, given the between-trial differences in the definition of sustained disability and the wide credible intervals observed in the NMA, small between-treatment differences observed in the NMA should be interpreted with caution.

Finally, the subgroup analyses to examine the effect of prior treatment experience as a potential source of heterogeneity was complicated by a lack of clarity within the published reports. Several trials had clearly stated inclusion or exclusion criteria that established patients as either treatment-naive or treatment-experienced. In many trials, the included patients were a mixture of treatment-naive and treatment-experienced, which could be determined from the baseline characteristics reported. However, in numerous trials, prior history was unclear; in several instances, assumptions were made regarding treatment history based on a mixture of inclusion and exclusion criteria, the year(s) the study was conducted, and clinical expert input, although it remained unclear in many trials. Thus, our subgroup analyses by prior-treatment history were based on categorization as treatment-naive or “other.” The results of the subgroup analyses did show minor changes to the treatment effects on both ARR and sustained disease progression outcomes; however, we may not have precisely captured the effects of treatment history because of the data limitations. In line with our findings, the subgroup analyses from three studies comparing active agents (fingolimod, teriflunomide, dimethyl fumate, and glatiramer acetate) with placebo showed slight changes in ARR and sustained disability progression between patients who did and did not receive previous MS treatment. However, there were no statistically significant between-group differences for those two outcomes when categorizing based on treatment history.

b) Economic limitations

As with all economic models, a simplification of reality was necessary, and numbers of assumptions were made in this economic evaluation. It was assumed that the adverse events, except PML, were transient in nature and not associated with significant health costs or implications to quality (did not affect the ICUR), and were not included in the economic

evaluation. Fixed discontinuation rate across all treatments for the first two years was assumed, followed by no discontinuation thereafter. Neutralizing antibodies were not included in the analysis because of lack of data, and confirmation from clinical experts that results are still controversial.

The pricing of the emerging treatments that are not marketed in Canada yet (alemtuzumab and teriflunomide) was not available at the time the analyses were conducted, and therefore it was assumed to be in line with international pricing. Where international pricing was not available, the price was assumed to be in line with the highest-priced drug.

Ideally, the model would use transitional probabilities derived directly from one of the large Canadian database studies, such as the London, Ontario study on natural history[47] or the British Columbia study.[46] However, none of these data were directly available or easily accessible, and therefore the transitional probabilities were based on published literature estimates. The data on natural history of disease were based on the published ScHARR report to NICE, which in turn was based on data from the London, Ontario longitudinal study.[78]

With respect to the efficacy data inputs (sustained disability progression and relapse rate) used in the model, the CADTH systematic review combined data from trials with differences in study populations, primarily as a means of allowing comparison across as many treatments as possible. The observed variability in both study characteristics (treatment duration, year of publication) and baseline patient characteristics (EDSS score, prior relapses, time since symptom onset, treatment history) may be important predictors of treatment effect. To address this heterogeneity, meta-regression and subgroup analyses using patient characteristics as covariates were performed; however, the small number of studies in relation to the number of treatment strategies may not allow for adequate control of confounding.

There is also limited clinical evidence relating to the sequential use of treatments after failure of first-line treatment or switching across treatments. The CADTH systematic review identified no trials specifically designed to assess the comparative efficacy and safety of disease-modifying treatments in patients who had failed, or were intolerant to, previous treatments. Therefore, the economic model does not assess separately the comparative cost-effectiveness between individual disease-modifying agents in RRMS in treatment-naive and experienced patients.

Finally, based on the available data, there is not enough clinical evidence to support the inclusion of combination therapy in the health economics model. Three out of four clinical studies identified in the systematic review resulted with no proven improvements in measures of relapse or disability. The forth one, the SENTINEL study,[38] reported that the addition of natalizumab to interferon beta-1a 30 mcg provided improvements in relapse and disease progression; however, the lack of the natalizumab-only arm precluded a definite conclusion that the observed effects of the combination therapy were the result of additive effects of two active treatments. Therefore, the cost-effectiveness of combination therapy in RRMS remains unknown.

6 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Results from the systematic review and NMA suggest that all active treatments produce statistically significant reductions in the ARR compared with no treatment, and that there are clear between-treatment differences. Specifically, compared with no treatment, reductions in the ARR are approximately 70% for natalizumab or alemtuzumab, 50% for fingolimod or dimethyl fumarate, and 30% for subcutaneous interferons, glatiramer acetate, or teriflunomide. Between-treatment differences were less apparent in the risk of sustained disability progression. Given the wide credible intervals observed in the NMA, small between-treatment differences observed in the NMA should be interpreted with caution.

Adverse events were treatment-specific and may be an important consideration in treatment selection. Given that the included studies were limited in their ability to identify infrequent or rare adverse events, decision-makers may consider that older agents such as the interferons and glatiramer have the benefit of a longer post-market period.

Patient-group input suggests that patient experience is variable, and that having options that match a person's life and situation are important considerations in treatment selection.

Results from the base case economic analysis suggest that, when compared with no treatment, treatment with any of the interferon therapies, glatiramer acetate, or dimethyl fumarate dominates no treatment (less costly and more effective). The ICUR of fingolimod versus no treatment is $18,234, and the ICUR of natalizumab versus no treatment is $121,456. Regarding comparative cost-effectiveness across active treatments, based on the base case, glatiramer is the most cost-effective treatment unless willingness to pay exceeds $118,242 per QALY, at which point interferon beta-1b 250 mcg (Extavia) is the cost-effective treatment unless willingness to pay exceeds $425,655, at which point dimethyl fumarate is the cost-effective treatment unless willingness to pay exceeds $872,972, at which point natalizumab is the cost-effective treatment. Base case results were little affected by varying model assumptions in sensitivity analyses.

The review was limited in its ability to assess the clinical and cost-effectiveness of sequential treatment, given that none of the reviewed trials specifically included patients with inadequate response or intolerance to previous treatments. The review was likewise limited by the paucity of data related to quality of life and many of the outcomes of importance to patients.

The development of novel treatments for MS is an area of active research, given the unmet need of patients for acceptable, safe, and effective treatments. New oral agents for the treatment of RRMS have recently been approved by Health Canada and additional agents are expected to enter the Canadian market shortly. Further research is needed that addresses outcomes of importance to patients and that establishes the value for money of existing and emerging treatments for MS.

7 REFERENCES

1. Zintzaras E, Doxani C, Mprotsis T, Schmid CH, Hadjigeorgiou GM. Network analysis of randomized controlled trials in multiple sclerosis. Clin Ther. 2012 Apr;34(4):857-69.

2. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology. 2008 Jul 8;71(2):129-35.

3. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol. 2010 May;9(5):520-32.

4. Ramagopalan SV, Sadovnick AD. Epidemiology of multiple sclerosis. Neurol Clin. 2011 May;29(2):207-17.

5. Richards RG, Sampson FC, Beard SM, Tappenden P. A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models. Health Technol Assess (Winch Eng) [Internet]. 2002 [cited 2013 Feb 28];6(10):1-73. Available from: http://www.hta.ac.uk/execsumm/summ610.htm

6. Trojano M, Paolicelli D, Tortorella C, Iaffaldano P, Lucchese G, Di Renzo V, et al. Natural history of multiple sclerosis: have available therapies impacted long-term prognosis? Neurol Clin. 2011 May;29(2):309-21.

7. Olek MJ. Treatment of relapsing-remitting multiple sclerosis in adults. 2013 [cited 2013 Feb 28]. In: UpToDate [Internet]. Waltham (MA): UpToDate. Available from: www.uptodate.com Subscription required.

8. O'Connor P, Devonshire V, Canadian Network of MS Clinics. The use of disease-modifying agents in multiple sclerosis--by the Canadian Network of MS Clinics. Can J Neurol Sci [Internet]. 2008 May [cited 2013 Feb 28];35(2):127-9. Available from: http://cjns.metapress.com/content/ex21864q62217889/fulltext.pdf

9. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):899-910.

10. Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K, et al. Efficacy of treatment of MS with IFN β-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology. 2009 Mar 11;72(23):1976-83.

11. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009 Oct;8(10):889-97.

12. Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler. 2012 Apr;18(4):418-24.

13. The CAMMS223 Trial Investigators, Compston DAS, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. Alemtuzumab vs. interferon β-1a in early multiple sclerosis. N Engl J Med. 2008;359(17):1786-801.

14. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012 Oct 31.

15. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012 Oct 31.

16. Clanet M, Radue EW, Kappos L, Hartung HP, Hohlfeld R, Sandberg-Wollheim M, et al. A randomized, double-blind, dose-comparison study of weekly interferon β-1a in relapsing MS. Neurology. 2002 Nov 26;59(10):1507-17.

17. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol. 2001 Mar;49(3):290-7.

18. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1087-97.

19. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1098-107.

20. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand. 2006 May;113(5):283-7.

21. Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, et al. Randomized, comparative study of interferon β-1a treatment regimens in MS: The EVIDENCE Trial. Neurology. 2002 Nov 26;59(10):1496-506.

22. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010 Feb 4;362(5):387-401.

23. The IFNB Multiple Sclerosis Study Group. Interferon beta-1β is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology. 1993 Apr;43(4):655-61.

24. De Stefano N, Curtin F, Stubinski B, Blevins G, Drulovic J, Issard D, et al. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. Mult Scler. 2010 Jul;16(7):888-92.

25. Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet. 2002 Apr 27;359(9316):1453-60.

26. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. Neurology. 1995 Jul;45(7):1268-76.

27. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol. 1996;39(3):285-94.

28. O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GP, Confavreux C, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology. 2006 Mar 28;66(6):894-900.

29. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet. 1998 Nov 7;352(9139):1498-504.

30. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008 Oct;7(10):903-14.

31. Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, et al. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. Mult Scler. 2012;18(9):1269-77.

32. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011 Oct 6;365(14):1293-303.

33. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010 Feb 4;362(5):402-15.

34. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet. 2011 Nov 19;378(9805):1779-87.

35. Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al. Randomized study combining interferon & glatiramer acetate in multiple sclerosis. Ann Neurol. 2013 Feb 19.

36. Freedman MS, Wolinsky JS, Wamil B, Confavreux C, Comi G, Kappos L, et al. Teriflunomide added to interferon-β in relapsing multiple sclerosis: a randomized phase II trial. Neurology. 2012 Jun 5;78(23):1877-85.

37. Goodman AD, Rossman H, Bar-Or A, Miller A, Miller DH, Schmierer K, et al. GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study. Neurology [Internet]. 2009 Mar 3 [cited 2012 Nov 16];72(9):806-12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821836/pdf/6342.pdf

38. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue E-W, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):911-23.

39. Olek MJ. Treatment of progressive multiple sclerosis in adults. 2012 [cited 2013 Feb 27]. In: UpToDate [Internet]. Waltham (MA): UpToDate. Available from: www.uptodate.com Subscription required.

40. CBC News. Global MS prevalance data [Internet]. Toronto: Canadian Broadcasting Corporation (CBC); 2010 Apr 12. [cited 2012 Nov 13]. Available from: http://www.cbc.ca/news/health/story/2010/04/12/f-multiple-sclerosis-ms-prevalence-map.html

41. Olek MJ. Epidemiology and clinical features of multiple sclerosis in adults. 2012 [cited 2013 Feb 27]. In: UpToDate [Internet]. Waltham (MA): UpToDate. Available from: www.uptodate.com Subscription required.

42. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001 Jul;50(1):121-7.

43. Polman CH, Wolinsky JS, Reingold SC. Multiple sclerosis diagnostic criteria: three years later. Mult Scler. 2005 Feb;11(1):5-12.

44. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005 Dec;58(6):840-6.

45. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol [Internet]. 2011 Feb [cited 2013 Apr 4];69(2):292-302. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3084507

46. Tremlett H, Paty D, Devonshire V. Disability progression in multiple sclerosis is slower than previously reported. Neurology. 2006 Jan 24;66(2):172-7.

47. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain. 1989 Feb;112 (Pt 1):133-46.

48. Yadav V, Bourdette D. New disease-modifying therapies and new challenges for MS. Curr Neurol Neurosci Rep. 2012 Oct;12(5):489-91.

49. Tysabri (natalizumab) concentrate for solution for intravenous infusion 300mg/15mL [product monograph]. Mississauga (ON): Biogen Idec Canada Inc.; 2013 Jan 3.

50. Gilenya - fingolimod (as fingolimod hydrochloride) oral capsules, 0.5 mg fingolimod (as fingolimod hydrochloride) [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada; 2012 Dec 19.

51. Copaxone (glatiramer acetate injection) 20 mg/1mL, pre-filled syringes for subcutaneous injection [product monograph]. Petach Tikva (Israel): Teva Pharmaceutical Industries Ltd.; 2011 Jun 7.

52. Avonex (interferon beta -1a) liquid for injection [product monograph]. Mississauga (ON): Biogen Idec Canada Inc.; 2012 Feb 24.

53. Rebif (interferon beta-1a) 8.8 µg/0.2 mL, 22 µg/0.5 mL and 44 µg/0.5 mL solution for injection in pre-filled syringes; multidose 22 µg × 3 (66 µg/1.5 mL), multidose 44 µg × 3 (132 µg/1.5 mL) solution for injection in pre-filled cartridges; Rebif RebiDose, 8.8 µg/0.2 mL, 22 µg/0.5 mL and 44 µg/0.5 mL solution for injection in pre-filled pens; immunomodulator [product monograph]. Mississauga (ON): EMD Serono; 2012 Sep 28.

54. Betaseron (interferon beta-1b) - lyophilized powder for subcutaneous injection 0.3 mg/vial [product monograph]. Toronto: Bayer Inc.; 2012 Nov 28.

55. Extavia (interferon beta-1b) lyophilized powder for subcutaneous injection, 0.3 vial [product monograph on the Internet]. Dorval (QC): Novartis Pharmaceuticals Canada Inc; 2010 Dec 21. [cited 2013 Apr 10]. Available from: http://www.novartis.ca/asknovartispharma/resources.htm?letter=E

56. Tecfidera™ (dimethyl fumarate enteric-coated capsules) 120mg and 240mg [product monograph]. Mississauga: Biogen Idec Canada Inc; 2012 Apr 6.

57. Fischer JS, Jak AJ, Kniker JE, Rudick RA, Cutter G. Multiple Sclerosis Functional Composite (MSFC): Administration and scoring manual. Revised.National Multiple Sclerosis Society; 2001 Oct.

58. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0. [Oxford, United Kingdom]: The Cochrane Collaboration; 2011 Mar. [cited 2013 Jul 22]. Available from: http://www.cochrane-handbook.org

59. Wiebe N, Vandermeer B, Platt RW, Klassen TP, Moher D, Barrowman NJ. A systematic review identifies a lack of standardization in methods for handling missing variance data. J Clin Epidemiol. 2006 Apr;59(4):342-53.

60. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60.

61. Weinshenker BG. The natural history of multiple sclerosis: update 1998. Semin Neurol. 1998;18(3):301-7.

62. Prosser LA, Kuntz KM, Bar-Or A, Weinstein MC. Cost-effectiveness of interferon beta-1a, interferon beta-1b, and glatiramer acetate in newly diagnosed non-primary progressive multiple sclerosis. Value Health. 2004;7(5):554-68.

63. Tremlett H, Zhu F, Petkau J, Oger J, Zhao Y, BC MS Clinic Neurologists. Natural, innate improvements in multiple sclerosis disability. Mult Scler. 2012 Oct;18(10):1412-21.

64. Tappenden P, McCabe C, Chilcott J, Simpson E, Nixon R, Madan J, et al. Cost-effectiveness of disease-modifying therapies in the management of multiple sclerosis for the medicare population. Value Health. 2009;12(5):657-65.

65. Wong J, Gomes T, Mamdani M, Manno M, O'Connor PW. Adherence to multiple sclerosis disease-modifying therapies in Ontario is low. Can J Neurol Sci. 2011 May;38(3):429-33.

66. Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. Oxford, United Kingdom: Oxford University Press; 2006. (Handbooks in health economic evaluation).

67. Tappenden P, Chilcott J, O'Hagan T, McCabe C, Cooper N, Abrams K, et al. Cost effectiveness of beta interferons and glatiramer acetate in the management of multiple sclerosis [Internet]. Sheffield (UK): School of Health and Related Research (ScHARR); 2001 Jul. [cited 2013 May 13]. Available from: http://www.nice.org.uk/nicemedia/pdf/msscharrreport.pdf

68. O'Connor P, Canadian Multiple Sclerosis Working Group. Key issues in the diagnosis and treatment of multiple sclerosis. An overview. Neurology. 2002 Sep 24;59(6 Suppl 3):S1-33.

69. Patzold U, Pocklington PR. Course of multiple sclerosis. First results of a prospective study carried out of 102 MS patients from 1976-1980. Acta Neurol Scand. 1982 Apr;65(4):248-66.

70. Hunt D, Giovannoni G. Natalizumab-associated progressive multifocal leucoencephalopathy: a practical approach to risk profiling and monitoring. Pract Neurol. 2012 Feb;12(1):25-35.

71. Table 2a complete life table, Canada, 2000 to 2002: males [Internet]. Catalogue No. 84-537-XIE. In: Life tables, Canada, provinces and territories. 2000 to 2002. Ottawa: Statistics Canada; 2006 [cited 2013 May 14]. Available from: http://www.statcan.gc.ca/pub/84-537-x/t/pdf/4198612-eng.pdf.

72. Table 2b complete life table, Canada, 2000 to 2002: females [Internet]. Catalogue No. 84-537-XIE. In: Life tables, Canada, provinces and territories. 2000 to 2002. Ottawa: Statistics Canada; 2006 [cited 2013 May 14]. Available from: http://www.statcan.gc.ca/pub/84-537-x/t/pdf/4198611-eng.pdf.

73. McBride R. Biogen prices Tecfidera below oral MS rival Gilenya [Internet]. Washington (DC): FierceMarkets; 2013 Mar 29. [cited 2013 Apr 22]. Available from: http://www.fiercepharma.com/story/biogen-prices-tecfidera-below-oral-ms-rival-gilenya/2013-03-29

74. Grima DT, Torrance GW, Francis G, Rice G, Rosner AJ, Lafortune L. Cost and health related quality of life consequences of multiple sclerosis. Mult Scler. 2000;6(2):91-8.

75. Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. Treatment experience, burden, and unmet needs (TRIBUNE) in multiple sclerosis: the costs and utilities of MS patients in Canada. J Popul Ther Clin Pharmacol. 2012;19(1):e11-e25.

76. Patwardhan MB, Matchar DB, Samsa GP, McCrory DC, Williams RG, Li TT. Cost of multiple sclerosis by level of disability: a review of literature. Mult Scler. 2005;11(2):232-9.

77. Kobelt G, Berg J, Atherly D, Hadjimichael O. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. Neurology. 2006;66(11):1696-702.

78. MS appraisal: addendum to ScHARR final report on economic modelling [Internet]. London: National Institute for Health and Clinical Excellence; 2002 Feb 27. [cited 2013 Mar 25]. Available from: http://www.nice.org.uk/nicemedia/live/11441/32297/32297.pdf

79. Earnshaw SR, Graham J, Oleen-Burkey M, Castelli-Haley J, Johnson K. Cost effectiveness of glatiramer acetate and natalizumab in relapsing-remitting multiple sclerosis. Appl Health Econ Health Policy. 2009;7(2):91-108.

80. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 3rd ed. Ottawa: The Agency; 2006 Mar. [cited 2013 Sep 13]. Available from: http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf

81. Coyle D, Buxton MJ, O'Brien BJ. Measures of importance for economic analysis based on decision modeling. J Clin Epidemiol. 2003;56(10):989-97.

82. Claxton K. Bayesian approaches to the value of information: implications for the regulation of new pharmaceuticals. Health Econ. 1999 May;8(3):269-74.

83. Milev S. Assessing parameter importance in decision models application to health economic evaluations [dissertation on the Internet]. Ottawa: University of Ottawa; 2013. 156 p. [cited 2013 Jul 11]. Available from: http://www.ruor.uottawa.ca/en/bitstream/handle/10393/23810/Milev_Sandra_2013_thesis.pdf

84. Sadatsafavi M, Bansback N, Zafari Z, Najafzadeh M, Marra C. Need for speed: an efficient algorithm for calculation of single-parameter expected value of partial perfect information. Value Health. 2013 Mar;16(2):438-48.

85. Kappos L, Gold R, Miller DH, MacManus DG, Havrdova E, Limmroth V, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet. 2008 Oct 25;372(9648):1463-72.

86. Bradley J, Blume S, Bal MM, Honeybourne D, Elborn JS. Health related quality of life (HRQoL) and health utility in patients with cystic fibrosis (CF) and chronic Pseudomonas aeruginosa (PA) infection in the UK [abstract]. Journal of Cystic Fibrosis. 2011;10:S88.

87. Rudick RA, Miller D, Hass S, Hutchinson M, Calabresi PA, Confavreux C, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. Ann Neurol. 2007 Oct;62(4):335-46.

88. Phillips JT, Giovannoni G, Lublin FD, O'Connor PW, Polman CH, Willoughby E, et al. Sustained improvement in Expanded Disability Status Scale as a new efficacy measure of neurological change in multiple sclerosis: treatment effects with natalizumab in patients with relapsing multiple sclerosis. Mult Scler. 2011 Aug;17(8):970-9.

89. Miller DM, Weinstock-Guttman B, Bourdette D, You X, Foulds P, Rudick RA. Change in quality of life in patients with relapsing-remitting multiple sclerosis over 2 years in relation to other clinical parameters: results from a trial of intramuscular interferon beta-1a. Mult Scler. 2011 Jun;17(6):734-42.

90. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care. 1981 Aug;19(8):787-805.

91. Ware JE. SF-36 health survey update. Spine. 2000 Dec 15;25(24):3130-9.

92. Direct healthcare professional communication, refined guidance on when first dose monitoring procedures should be repeated for Gilenya (fingolimod) [Internet]. Surrey (UK): Novartis; 2012 Dec. [cited 2013 Apr 17]. Available from: http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con228789.pdf

93. Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. Lancet Neurol. 2011 Apr;10(4):338-48.

94. Devonshire V, Havrdova E, Radue EW, O'Connor P, Zhang-Auberson L, Agoropoulou C, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol. 2012 May;11(5):420-8.

95. Miller AE, O'Connor P, Wolinsky JS, Confavreux C, Kappos L, Olsson TP, et al. Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis. Mult Scler. 2012;18(11):1625-32.

96. Hutchinson M, Fox RJ, Miller DH, Phillips JT, Kita M, Havrdova E, et al. Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the CONFIRM study. J Neurol. 2013 Jun 8.

97. Parkin D, Jacoby A, McNamee P, Miller P, Thomas S, Bates D. Treatment of multiple sclerosis with interferon beta: an appraisal of cost-effectiveness and quality of life. J Neurol Neurosurg Psychiatry [Internet]. 2000 Feb [cited 2013 Mar 15];68(2):144-9.

Available from:
http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1736797&blobtype=pdf

98. Ravnborg M, Blinkenberg M, Sellebjerg F, Ballegaard M, Larsen SH, Sorensen PS. Responsiveness of the Multiple Sclerosis Impairment Scale in comparison with the Expanded Disability Status Scale. Mult Scler. 2005 Feb;11(1):81-4.

99. Patzold T, Schwengelbeck M, Ossege LM, Malin JP, Sindern E. Changes of the MS functional composite and EDSS during and after treatment of relapses with methylprednisolone in patients with multiple sclerosis. Acta Neurol Scand. 2002 Mar;105(3):164-8.

100. Ozakbas S, Cagiran I, Ormeci B, Idiman E. Correlations between multiple sclerosis functional composite, expanded disability status scale and health-related quality of life during and after treatment of relapses in patients with multiple sclerosis. J Neurol Sci. 2004 Mar 15;218(1-2):3-7.

101. Cohen YC, Hassin-Baer S, Olmer L, Barishev R, Goldhammer Y, Freedman L, et al. MS-CANE: a computer-aided instrument for neurological evaluation of patients with multiple sclerosis: enhanced reliability of expanded disability status scale (EDSS) assessment. Mult Scler. 2000 Oct;6(5):355-61.

102. Schumacker GA, Beebe G, Kibler RF, Kurland LT, Kurtzke JF, McDowell F, et al. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. Ann N Y Acad Sci. 1965 Mar 31;122:552-68.

103. Goldman MD, Motl RW, Rudick RA. Possible clinical outcome measures for clinical trials in patients with multiple sclerosis. Ther Adv Neurol Disord [Internet]. 2010 Jul [cited 2013 Mar 14];3(4):229-39. Available from:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3002657

104. Pryse-Phillips W. Twenty questions about multiple sclerosis clinical trials methodologies. Neurol Sci. 2001 Apr;22(2):187-93.

105. Scalfari A, Neuhaus A, Daumer M, Deluca GC, Muraro PA, Ebers GC. Early relapses, onset of progression, and late outcome in multiple sclerosis. JAMA Neurol. 2013 Feb 1;70(2):214-22.

106. Bennetto L, Burrow J, Sakai H, Cobby J, Robertson NP, Scolding N. The relationship between relapse, impairment and disability in multiple sclerosis. Mult Scler. 2011 Oct;17(10):1218-24.

107. Wang YC, Sandrock A, Richert JR, Meyerson L, Miao X. Short-term relapse quantitation as a fully surrogate endpoint for long-term sustained progression of disability in RRMS patients treated with natalizumab. Neurol Res Int [Internet]. 2011 [cited 2013 Mar 13];2011:195831. Available from:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253472/pdf/NRI2011-195831.pdf

108. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y, UBC Neurologists. Impact of multiple sclerosis relapses on progression diminishes with time. Neurology [Internet]. 2009 Nov 17 [cited 2013 Feb 27];73(20):1616-23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2881858/pdf/7121.pdf

109. Bejaoui K, Rolak LA. What is the risk of permanent disability from a multiple sclerosis relapse? Neurology. 2010 Mar 16;74(11):900-2.

110. Binquet C, Quantin C, Le Teuff G., Pagliano JF, Abrahamowicz M, Moreau T. The prognostic value of initial relapses on the evolution of disability in patients with relapsing-remitting multiple sclerosis. Neuroepidemiology. 2006;27(1):45-54.

111. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med. 2000 Nov 16;343(20):1430-8.

112. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health. 2007 Jan;10(1):54-60.

113. Miller DH. In assessing multiple sclerosis disease activity patient report measures are a waste of time: cut to the MRI scan!--Yes. Mult Scler [Internet]. 2012 Mar [cited 2013 Mar 15];18(3):264-5. Available from: http://msj.sagepub.com/content/18/3/264.full.pdf+html

114. Barkhof F, Filippi M. MRI--the perfect surrogate marker for multiple sclerosis? Nat Rev Neurol. 2009 Apr;5(4):182-3.

115. Horakova D, Dwyer MG, Havrdova E, Cox JL, Dolezal O, Bergsland N, et al. Gray matter atrophy and disability progression in patients with early relapsing-remitting multiple sclerosis: a 5-year longitudinal study. J Neurol Sci. 2009 Jul 15;282(1-2):112-9.

116. Roosendaal SD, Bendfeldt K, Vrenken H, Polman CH, Borgwardt S, Radue EW, et al. Grey matter volume in a large cohort of MS patients: relation to MRI parameters and disability. Mult Scler. 2011 Sep;17(9):1098-106.

117. Rudick RA, Lee JC, Nakamura K, Fisher E. Gray matter atrophy correlates with MS disability progression measured with MSFC but not EDSS. J Neurol Sci [Internet]. 2009 Jul 15 [cited 2013 Mar 14];282(1-2):106-11. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2726444/pdf/nihms126632.pdf

118. Mowry EM, Beheshtian A, Waubant E, Goodin DS, Cree BA, Qualley P, et al. Quality of life in multiple sclerosis is associated with lesion burden and brain volume measures. Neurology [Internet]. 2009 May 19 [cited 2013 Mar 14];72(20):1760-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2683738

119. Mainero C, De Stefano N., Iannucci G, Sormani MP, Guidi L, Federico A, et al. Correlates of MS disability assessed in vivo using aggregates of MR quantities. Neurology. 2001 May 22;56(10):1331-4.

120. Cohen M, Lebrun C, Aufauvre D, Chanalet S, Filleau-Bertogliatti C, Camu W, et al. [Longitudinal study of health related quality of life in multiple sclerosis: correlation with MRI parameters]. Rev Neurol (Paris). 2010 Nov;166(11):894-900.

121. van Walderveen MA, Barkhof F, Hommes OR, Polman CH, Tobi H, Frequin ST, et al. Correlating MRI and clinical disease activity in multiple sclerosis: relevance of hypointense lesions on short-TR/short-TE (T1-weighted) spin-echo images. Neurology. 1995 Sep;45(9):1684-90.

122. Rovaris M, Agosta F, Sormani MP, Inglese M, Martinelli V, Comi G, et al. Conventional and magnetization transfer MRI predictors of clinical multiple sclerosis evolution: a medium-term follow-up study. Brain. 2003 Oct;126(Pt 10):2323-32.

123. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med. 2002 Jan 17;346(3):158-64.

124. Kappos L, Moeri D, Radue EW, Schoetzau A, Schweikert K, Barkhof F, et al. Predictive value of gadolinium-enhanced magnetic resonance imaging for relapse rate and changes in disability or impairment in multiple sclerosis: a meta-analysis. Gadolinium MRI Meta-analysis Group. Lancet. 1999 Mar 20;353(9157):964-9.

125. Sormani MP, Li DK, Bruzzi P, Stubinski B, Cornelisse P, Rocak S, et al. Combined MRI lesions and relapses as a surrogate for disability in multiple sclerosis. Neurology. 2011 Nov 1;77(18):1684-90.

126. Caramanos Z, Francis SJ, Narayanan S, Lapierre Y, Arnold DL. Large, nonplateauing relationship between clinical disability and cerebral white matter lesion load in patients with multiple sclerosis. Arch Neurol. 2012 Jan;69(1):89-95.

127. Goodin DS, Traboulsee A, Knappertz V, Reder AT, Li D, Langdon D, et al. Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon -1b trial in multiple sclerosis. J Neurol Neurosurg Psychiatry [Internet]. 2012 Mar [cited 2013 Mar 14];83(3):282-7. Available from: http://jnnp.bmj.com/content/83/3/282.full.pdf+html

128. Coles A, Fox E, Vladic A, Gazda S, Brinar V, Selmaj K, et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. Supplementary appendix. Lancet Neurol. 2013;10:338-48.

APPENDIX 1: PATIENT INPUT INFORMATION

1. Brief Description of Patient Group(s) Supplying Input

The Multiple Sclerosis Society of Canada is a national voluntary organization which supports both multiple sclerosis (MS) research and services for people with MS and their families. Its mission is to enable people affected by MS to enhance their quality of life, and to be a leader in fighting MS by supporting research into its cause, treatment, and cure. The Society is governed by a national board of volunteer directors; has an estimated 13,500 volunteers who carry out its service programs, fundraising events, public awareness campaigns, and government relations activities; and has a membership of 20,500.

In 2012, the Society received educational grants from the following companies: Bayer, Biogen Idec, EMD Serono, Novartis, Pfizer, Genzyme — a Sanofi Company, Allergan, and Teva Neuroscience. The contributions totalled less than 2% of the Society's overall revenue and are subject to strict policies that prevent any control or influence by the donor on the Society's decision-making. No conflicts of interest were declared in preparation of this submission.

2. Condition and Current Therapy-Related Information

The information in this submission was gathered through publicly available information about the impact of MS, and from an online survey (n = 1,345) conducted by the Multiple Sclerosis Society in February 2013 and designed to gather patient input for CADTH's Therapeutic Review on disease-modifying therapies (DMTs). The Canada-wide survey respondents included patients (91%) and caregivers (9%). Respondents reported the following types of MS: relapsing-remitting (70%), possible MS (clinically isolated syndrome), secondary-progressive, primary-progressive, and do not know. The survey was not population-based and cannot be interpreted as reflecting the views of all people with MS or caregivers in Canada.

MS is an unpredictable, often disabling disease of the central nervous system. In the 2013 survey, respondents indicated that the following common symptoms of MS had major impacts on their lives: fatigue (77%), difficulty in walking (52%), memory or attention problems (39%), bladder problems (38%), numbness or tingling (37%), and pain (36%). In addition, 94% of respondents said MS had negatively affected their lives somewhat (48%) to a lot (46%). Further, 81% of respondents said their work lives had been affected somewhat (26%) to a lot (55%). Other aspects of day-to-day life that had been affected a lot were recreational activities (48%), sleep (34%), and mobility (33%).

Some respondents commented about improvements in their MS condition since being treated for chronic cerebrospinal venous insufficiency, and others commented that these improvements were not always sustained. Some respondents commented that they use only alternative therapies (e.g., diet, exercise, vitamins, acupuncture) to manage their disease.

The care and assistance that many people with MS receive from their spouses, other family, and friends are key factors in their ability to maintain their quality of life, independence in the community, and as normal a life as possible. Caregivers assist in many tasks, both medical and non-medical — for example, giving injections, which can be difficult to self-administer because MS can result in numbness and a lack of coordination. In the survey, 53% of caregivers indicated that they assist with the administration of medication some or all of the time. When

asked if providing such assistance impacted their own daily routines, 41% reported that it did all the time and 32% said that it did sometimes.

Sixty-two per cent of caregivers reported that there are negative side effects of the current DMT on the person they care for at least sometimes. Some caregivers commented on the impact on their ability to work and earn an income due to the need to care for their loved one and perform other household duties, as well as how the side effects of the therapy (extreme fatigue, flu-like symptoms, full body aches) limit their loved one's ability to go to work and to contribute to childcare and household duties.

Seven therapies that reduce the frequency and severity of MS relapses were approved in Canada at the time of the survey, some of which have some data suggesting a slowing effect on the accumulation of disability over time. None of these treatments are a cure and none prevent persistent symptoms such as fatigue or numbness. A number of drugs are available to help relieve MS symptoms such as spasticity, fatigue, and pain. No DMT has been approved to treat primary-progressive MS. The lack of current therapies for progressive forms of MS was mentioned by numerous respondents as a concern.

In the survey, 63% of respondents reported that they were currently using a DMT — Copaxone (23%); Rebif (17%); Avonex (9%); Tysabri (6%); Betaseron (5%); Gilenya (3%); and Extavia (0.2%). Of the symptoms respondents stated as the most important symptoms to be controlled by a DMT, 87% reported progression of disability and 70% reported number and/or severity of relapses. In response to the question about how the treatment was helping, respondents said it reduced the frequency and severity of relapses (53%), appeared to slow the progression of disability (41%), allowed them to have a better quality of life (26%), and made them feel better generally (25%). One participant summarized by presuming the DMT did all of the above and would rather be taking it than finding out what might happen without it.

However, side effects from DMTs were frequent complaints for survey participants, with injection site reactions ranking first, followed by fatigue, sore muscles and joints, and headache. Other side effects that were not pre-defined survey answers but were mentioned included lipoatrophy, thyroid problems, liver toxicity, poor sleep, nausea, low white blood cell count, and skin bruising. Many were uncertain whether these effects were caused by their drugs or merely symptoms of MS. Most respondents (67%) said that side effects did not impact taking their therapy on a regular basis, though among those who did alter their therapy, the most frequently cited reasons were fatigue and injection site reactions.

The dislike of using a needle was second only to the high cost of MS therapies as factors preventing respondents from taking their current DMT at times. Other factors were anxiety regarding the use of needles, difficulty in using needles, rotation of sites, travel-related inconvenience, and concerns with insurance coverage. Some participants commented on their belief that the therapy has made an important difference in their lives, while others commented that for them, current DMTs did not work and they did not see any benefit in taking them.

3. Related Information About the Drugs Being Reviewed

The vast majority of respondents had no experience with the new therapies (teriflunomide, dimethyl fumarate, or alemtuzumab). Many reported looking forward to having a drug that did not require injection because of pain, injection site reactions, inconvenience of infusions, and their belief that quality of life would be significantly improved. Other preferences for a new DMT included lower and/or limited side effects, greater affordability, convenience, and improvements

in everyday function. Regarding their expectations of new therapies, some participants commented on having a therapy that is not injection-based and that is more affordable, and having a new oral drug with minimal side effects.

Forty-five respondents reported experience with new therapies and some comments about them included that the therapies have had a positive impact on their lives. Other remarks included how new drugs better manage side effects: fewer and milder relapses, preference for a daily pill instead of a needle, and ease of using a pill because of its portability and no need for special equipment.

People with MS cope with an unpredictable disease. The potential choice of more MS drugs that have greater efficacy and easier mode of administration is desirable, and respondents indicated that having options that match a person's life and situation are important considerations.

APPENDIX 2: VALIDITY OF OUTCOMES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

1. Objective

To describe the scoring and validity of the Expanded Disability Status Scale (EDSS) as a measure of disability, and to determine the utility of common trial outcomes (relapse and magnetic resonance imaging [MRI] findings) in predicting disability and/or quality of life.

2. Findings

EDSS

The EDSS is an ordinal scale used to measure disability in Multiple Sclerosis (MS). It relies on the identification of eight functional systems (plus "other"). These are pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. Each functional system is graded separately (normal = 0). The scale is a composite of different types of effects on the body and mental functioning. The distribution of MS patients is typically biphasic, accumulating around 2 to 3 points, and 6 to 7 points, indicating that patients do not stay equally long at each step of the scale. There are many criticisms of the EDSS, including the fact that it has only modest intra-rater reliability, low reproducibility, poor assessment of upper limb and cognitive function, and it lacks linearity.[98-101] Flaws identified include that it is an arbitrary scale with limited and discrete levels of disability, that it relies heavily on evaluation of motor function, and that it requires a subjective evaluation of disability using a parametric scale. Despite its flaws, many other studies have been performed, comparing it to other assessment tools. For example, a Danish study performed in an MS clinic compared the reliability of the MS Impairment Scale to the EDSS, finding a better rate of responsiveness for the MS Impairment Scale, and also had a higher reliability of change coefficient (0.69 versus 0.41).[98] However, despite the inherent criticisms of the Scale, at present it represents a readily available tool to assess neurological disability in the MS population.

0	Normal neurological exam (all grade 0 in functional systems [FS]; Cerebral grade 1 acceptable)
1	No disability, minimal signs in one FS (i.e., grade 1, excluding Cerebral grade 1)
1.5	No disability, minimal signs in more than one FS (more than one grade 1, excluding Cerebral grade 1)
2.0	Minimal disability in one FS (one FS grade 2; other 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others O or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relative severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 metres
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistances; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 metres
5.0	Ambulatory without aid or rest for about 200 metres; disability severe enough to impair full daily activities (e.g. to work full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)
5.5	Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0)
6.0	Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk about 100 metres with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)

6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 metres without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
7.0	Unable to walk beyond about 5 metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone.)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+.)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair; but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems.)
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions. (Usual FS equivalents are combinations, generally 4+ in several systems.)
9.0	Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+.)
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+.)
10.0	Death due to MS

In summary, the EDSS is an ordinal scale used to measure disability in MS. It relies on identification of eight functional systems (plus "other"). These are pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. Each functional system is graded separately (normal = 0). The scale is a composite of different types of effects on the body and mental functioning. Patient scores tend to accumulate around the 2 to 3 point range and at 6 to 7 points, and the scale has modest intra-rater reliability, low reproducibility, poor assessment of upper limb and cognitive function, and it lacks linearity.

Relapse

MS relapse is defined as new or worsening symptoms that last 24 hours in duration and occur in the absence of fever or infection.[102] In clinical trials, relapses can be identified by patient notification or by history and exam changes observed during scheduled study visits.[103] Relapse results have been reported in clinical trials as mean annual number of exacerbations, mean relapse rates over "x" years, the rate of the proportion of patients who are relapse-free, time to first relapse, relapse severity, and relapse duration, with no clear justification for the use of one end point over others.[104]

Relapse and disability progression

A cohort study of 730 relapsing-remitting MS (RRMS) patients, with a 28-year follow-up (1972 to 2000), examined the relationship between early relapses, progression, and accumulation of severe disability.[105] The study was conducted in Canada at the London Multiple Sclerosis Clinic. None of the patients received DMTs. In this cohort, 158 patients were identified as having a "high frequency" of relapses (three or more within the first two years). The authors found that:

- Of these patients with a high frequency of relapses, 65.2% converted to SPMS, and this conversion was described as "rapid," with a median duration of five years.
- However, the remaining 35% did not convert to SPMS, despite these early frequent relapses. The authors noted a large variation in outcomes for patients with early frequent relapses, and suggested a disassociation between early relapse frequency and onset of SPMS.

A smaller cohort study (N = 141) attempted to explain the challenges in linking relapse frequency with long-term disability in relapse-onset MS.[106] Patients were examined for local clinical signs of disability, and were asked about relapse history. The authors concluded that:

- Afferent pathways appear to be more susceptible to relapses than motor pathways. This might explain why the EDSS, a scale that is highly motor-dependent, does not reveal a clear link between relapse and disability,

An analysis of data from the AFFIRM study (natalizumab) sought to determine whether there was a relationship between MS relapses and disability progression. The authors used a Cox proportional hazard model and found that, based on findings from AFFIRM, a patient with one or more relapses during the first year of the study was 2.26 times more likely to develop sustained progression of disability (based on the EDSS) compared to a patient with one less relapse during the first year. They concluded that the short-term (one year in this case) relapse rate is a valid surrogate marker for disability progression at two years.[107]

A cohort of 2,477 patients with definite relapsing-onset MS were followed-up for 20 years after the first onset of disease in order to study the relationship between relapses and long-term disability.[108] Results showed that:

- Relapses during the first five years of disease onset have an impact on short-term disease progression. However, the impact of later relapses (more than 5 to 10 years post-onset) lessened over time. The long-term impact was minimal, either for early or later relapses.
- Those findings were similar whether considering disease progression as time to requiring a cane to walk (EDSS 6) or the onset of secondary progression.
- A higher relapse rate was associated with a shorter time to a fixed disability milestone (EDSS 6).
- Further, once secondary progression was reached, relapses had no discernible influence on further disease progression.
- Patients with longer disease history appear to have fewer numbers of relapses.

A database analysis of 1,078 MS patients' records was conducted to determine how often patients with RRMS develop severe (EDSS ≥ 6.0), sustained (greater than six months) disability due to an acute relapse.[109] Results from the study showed that:

- Severity of a particular relapse does not have a reliable impact on progression of the EDSS.

A retrospective analysis of 288 MS patients' records was conducted to evaluate the prognostic value of MS attacks during the first two years of the disease and the first inter-attack interval on the first occurrence of moderate disability.[110] Moderate disability was defined as unlimited walking distance without rest, but unable to run; or a significant, not ambulation-related disability. When considering MS attacks as time-dependent covariate, results adjusted for gender and age showed that:

- The number of MS relapses during the first two years may be associated with the disability course; the risk of advancing toward moderate disability increased by 21% (95% CI, 1.00 to 1.39; $P = 0.055$) with every additional relapse;
- However, the inter-attack interval was not associated with the progression of disability (HR = 1.0, 95% CI, 0.99 to 1.01; $P = 0.71$).

A database analysis of 1,844 MS patients was conducted to evaluate the influence of the patterns of onset of MS and relapses of the disease on the time course of irreversible disability.[111] The trial concluded that relapses do not significantly influence the progression of irreversible disability.

Relapse and utility

A survey was conducted in the UK to evaluate the disutility associated with acute MS relapses using a multi-attribute utility system (EQ-5D).[112] The survey included 12,968 patients and had

2,048 responders with analyzable data. The results showed that recent relapses, in the last three months, were significantly correlated with the utility score derived from the EQ-5D.

In summary, MS relapse is commonly used in clinical trials as a primary outcome. However, the link between relapses and disability is not entirely clear. The impact of early relapses on early disability appears to be more established than the link between relapses and long-term disability. One possible explanation for inconsistent findings linking relapse with disability is the weaknesses with the EDSS instrument itself.

MRI findings

Before reviewing findings from various clinical trials, it is important to distinguish the different types of information provided by each of the various types of MRI data reported in clinical trials. For example, gadolinium-enhancing (GdE) lesions on T1-weighted MRI identify new inflammatory lesions, as the GdE indicates acute breakdown of the blood-brain barrier with inflammation. The GdE is not permanent, and lasts for approximately four weeks. Conversely, a new T2 lesion indicates a more permanent footprint of new disease activity. Thus, new T2-weighted lesions will appear on scans performed at longer intervals (e.g., one year), while GdE lesions indicate active inflammation at the time of the scan.[113,114]

Brain volume is another MRI parameter that is reported in clinical trials of MS. While it seems to be well-established that brain volume diminishes with time in MS, the relationship between specific reductions in brain volume and clinical disability is less well-defined. A further complication when trying to assess changes in brain volume in a clinical trial is that these changes are likely to occur over a much longer time frame than the lesions that have traditionally been assessed with MRI.[115] A large cross-sectional study attempted to address some of the questions surrounding the relation between brain atrophy and disability by comparing grey and white matter volumes across patients with CIS (N = 95), RRMS (N = 657), SPMS (N = 125), and primary-progressive MS (N = 50).[116] The authors found that:

- Grey matter atrophy was greater in SPMS than in RRMS, and RRMS atrophy was greater than in CIS. Primary-progressive MS was comparable to RRMS.
- However, white matter volume in SPMS was comparable to that of RRMS.
- Grey matter volume was the strongest independent predictor of physical disability and cognitive impairment, and was associated with both T2 and T1 lesion volume.

Another study of brain volume observed a cohort of CIS, RRMS, SPMS, and healthy controls over a mean period of 6.6 years to assess the relationship between brain volume and disability using the EDSS and the MSFC.[117] This was a small study (N = 70), but the authors noted progression in the MSFC was more closely correlated with atrophy rates than progression on the EDSS.

A limited literature search looking for studies evaluating the association of MRI surrogates with relapse rate, disability, and quality of life provided two cross-sectional studies, two short-term cohorts — one medium- and long-term cohort each — and two meta-analyses.

The instant correlation of MRI examination, with quality of life and/or EDSS, was evaluated in four studies.[118-121] The correlation varied according to MRI surrogates and the clinical outcome. Mowry et al.[118] showed that inter-patient variations of 25 mL of T2-weighted lesions and 15 mL of T1-weighted lesions were significantly correlated with an inter-patient variation of 0.97-point in the emotional well-being scale. Using the thinking/fatigue scale, 1.73-point inter-patient variation cut-off, provided a significant correlation with 22 mL of T2-weighted lesions, but it was not significant for 19 mL T1-weighted lesions variation.[118] The trial did not provide support for

the used cut-off points for MRI or clinical outcomes.[118] Cohen et al.[120] also evaluated the correlation of MRI surrogates with quality of life and found that the presence of one or more GdE lesions, number of T1-weighted, and T2-weighted lesions were correlated with quality of life scores. Two trials evaluated the correlation of T1, T2, and number of active lesions with EDSS scores;[119,121] weak but significant correlation was found in one trial for T2-weighted lesions; $r = 0.3$, $P < 0.05$.[121]

Four studies evaluated the predictive value of fixed-time point MRI readings for the future change of EDSS.[121-124] T1-weighted lesions did not significantly predict the progression of EDSS score.[121,122] On the other hand, T2-weighted lesions significantly predicted the change of EDSS evaluation; the predictive value was weak when assessed in short-[121] and medium-term[122] follow-up ($r = 0.38$, $P < 0.05$ and odds ratio = 1.05, $P = 0.03$, respectively), and it showed medium value when assessed in long-term follow-up ($r = 0.48$ to 0.60, $0.001 < P < 0.01$). One meta-analysis evaluated the predictive value of the initial GdE lesions count and showed that baseline count could not significantly predict the worsening of EDSS after one and two years' follow-up.[124] The same meta-analysis provided results indicating that the mean number of GdE lesions on monthly scans (months 0 to 6) was positively associated with relapse rate in year one ($P = 0.023$), but not at year two ($P = 0.128$). A recent study that examined data from PRISMS (interferon beta-1a) attempted to further characterize the relationship between relapses and MRI as surrogates for disability. The authors evaluated the extent to which relapses and active T2 lesions fulfilled Prentice criteria for assessment of surrogate markers. When combined, relapses and MRI data in the first year accounted for 100% of the effect seen on disability (EDSS) progression, while separately, MRI accounted for 63% and relapses accounted for 61% of disability progression seen in PRISMS.[125]

Correlation of changes on MRI readings with the change of EDSS score was evaluated in three trials.[121-123] Significant correlation was found for change of volume of T1-weighted lesions in one trial;[121] ($r = 0.74$, $P < 0.002$) and for T2-weighted lesions volume change in another trial;[123] $r = 0.58$, $P < 0.001$; 0.41, $P = 0.002$; 0.35, $P = 0.02$, for the follow-up periods 0 to 5, 5 to10, and 10 to 14 years, respectively. It was noted from the last trial that the correlation decreased with longer follow-up periods. Median changes in EDSS scores for the same follow-up periods were 1.5, 0.5, and 0, respectively, providing an indication that volume of T2-weighted lesions continue to change with longer periods of the disease but the clinical changes become less and less apparent.

A 2012 retrospective analysis, carried out at a single centre, sought to further characterize the relationship between MRI data and EDSS scores, using cerebral white matter lesion load.[126] In this study that included 110 patients, the authors found that:

- There was a relatively flat relationship between EDSS and cerebral white matter lesion load on MRI in patients with low EDSS scores (2 or less).
- A proposed explanation for these findings was that MS patients may be able to compensate for the damage found on MRI until a threshold is reached.
- An alternative explanation proposed by the authors is that this relatively flat relationship at low EDSS scores might indicate the poor responsiveness of EDSS at low scores. This has been a criticism of the EDSS scale in the past.

Goodin et al. examined long-term (16-year) follow-up data from the first clinical trial of interferon beta-1b.[127] This trial concluded 20 years ago, and thus this study likely represents one of the longest, if not the longest, published follow-up from an MS trial, with nearly 6,000 patient-years of follow-up. In 2005, 12 years after the end of the original study, 260 of 373 patients who remained from the original trial consented to participate in this long-term follow-up. Disability

was assessed using the EDSS, while cognitive function was assessed using five different tests: PASAT, the Symbol Digit Modality Test, California Verbal Learning Test II, the Controlled Oral Word Association Task, and the DeliseKaplan Executive Function System test. The authors noted that the original baseline characteristics for this cohort seemed to reflect that of the entire study population. One difference was that the long-term follow-up cohort had a higher proportion of patients who took interferon beta-1b 250 mcg compared with the patients not in the long-term follow-up cohort (37% versus 25% of patients). The authors found that:

- With the exception of third ventricular width, a change in MRI findings over the course of the original randomized controlled trial did not correlate with either late cognitive or late physical disability.
- The most significant predictor of both physical and cognitive outcome after 16 years was baseline EDSS.

In summary, over the short term, MRI surrogates showed good correlation with quality of life and EDSS evaluation and could provide weak to medium prediction value of future EDSS. However, limited evidence was found to support the correlation of specific changes seen on MRI with those scored for the EDSS.

The relationship between MRI data and long-term disability, including cognition, is less well-defined. There are few studies that attempt to link MRI data with long-term disability outcomes. The study with the longest-term follow-up of RCT data found that most of the commonly used MRI outcomes did not correlate with long-term disability, either physical or cognitive. One of the complications with assessing long-term follow-up data is that the management and assessment of MS has changed over the past 20 years. While at one time a patient with MS was likely to be placed on either an interferon or glatiramer, in the last few years the number of Health Canada-approved options has grown to include natalizumab, fingolimod, and dimethyl fumarate. In addition, MRI technology has improved, additional emphasis has been placed on disability outcomes such as cognition, and for reasons not entirely clear, even the relapse rate in MS has been steadily declining over the past 20 years.

APPENDIX 3: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase Ovid MEDLINE Ovid MEDLINE In-Process & Other Non-Indexed Citations Ovid MEDLINE Daily **Note:** Subject headings have been customized for each database.
Date of Search:	November 9, 2012
Alerts:	Monthly search updates began November 10, 2012 and ran until October 2013.
Study Types:	health technology assessments; systematic reviews; meta-analyses; randomized controlled trials; safety studies
Limits:	English Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.ot	Original title
.nm	Name of substance word
.rn	CAS registry number

MEDLINE STRATEGY	
Line #	**Strategy**
1	Multiple Sclerosis, Relapsing-Remitting/ or multiple sclerosis/
2	(relapsing remitting adj2 multiple sclerosis).ti,ab,sh,hw,ot.
3	(remitting relapsing adj2 multiple sclerosis).ti,ab,sh,hw,ot.
4	((relapsing remitting adj2 ms) or (remitting relapsing adj2 ms)).ti,ab,sh,hw,ot.
5	((exacerbat* or disseminated or insular or secondary progressive or primary progressive or progressive relapsing) adj2 (sclerosis or ms)).ti,ab,sh,hw,ot.
6	(rrms or encephalomyelitis disseminat*).ti,ab,sh,hw,ot.
7	or/1-6
8	(163451-81-8 or 162359-55-9 or 248281-84-7 or 624-49-7).rn,nm.
9	(Teriflunomide or A 1726 or A 77 1726 or A 771726 or HMR 1726 or HMR1726 or aubagio).ti,ab,rn,nm,sh,hw,ot.
10	(fingolimod or FTY-720 or FTY270 or Gilenya or Gilenia).ti,ab,rn,nm,sh,hw,ot.
11	(dimethyl fumarate or FAG 201 or FAG201 or "BRN 0774590" or BRN0774590 or HSDB 7725 or Methyl fumarate or NSC 167432 or NSC 25942 or TL 353 or Fumaderm or dimethylfumarate or bg 12 or "BG 00012" or BG00012).ti,ab,rn,nm,sh,hw,ot.
12	or/8-11
13	Interferon-beta/
14	(152923-56-3 or 637334-45-3 or 220581-49-7 or 145155-23-3 or 189261-10-7 or 147245-92-9 or 216503-57-0).rn,nm.
15	(interferon-beta-1 or interferon-1a or interferon-1b or interferon beta or beta Interferon or fibroblast Interferon or Fiblaferon or Interferon beta 1).ti,ab,rn,nm,sh,hw,ot.
16	(avonex or rebif or betaferon or betaseron or BAY 86-5046 or BAY86-5046 or copaxone or extavia or glatiramer acetate).ti,ab,rn,nm,sh,hw,ot.
17	(natalizumab or tysabri or antegren).ti,ab,rn,nm,sh,hw,ot.
18	(alemtuzumab or campath or LDP-03 or lemtrada or mabcampath).ti,ab,rn,nm,sh,hw,ot.
19	or/13-18
20	7 and (12 or 19)
21	meta-analysis.pt.
22	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
23	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
24	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
25	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
26	(data synthes* or data extraction* or data abstraction*).ti,ab.
27	(handsearch* or hand search*).ti,ab.
28	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
29	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview*).ti,ab.
30	(meta regression* or metaregression*).ti,ab.
31	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
32	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
33	(cochrane or (health adj2 technology assessment) or evidence report).jw.

MEDLINE STRATEGY	
Line #	**Strategy**
34	(meta-analysis or systematic review).md.
35	(comparative adj3 (efficacy or effectiveness)).ti,ab.
36	(outcomes research or relative effectiveness).ti,ab.
37	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
38	or/21-37
39	Randomized Controlled Trial.pt.
40	Randomized Controlled Trials as Topic/
41	"Randomized Controlled Trial (topic)"/
42	Randomized Controlled Trial/
43	Randomization/
44	Random Allocation/
45	Double-Blind Method/
46	Double Blind Procedure/
47	Double-Blind Studies/
48	Single-Blind Method/
49	Single Blind Procedure/
50	Single-Blind Studies/
51	Placebos/
52	Placebo/
53	(random* or sham or placebo*).ti,ab,hw.
54	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
55	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
56	or/39-55
57	exp *drug toxicity/
58	exp *drug hypersensitivity/
59	*abnormalities, drug-induced/
60	exp *postoperative complications/
61	exp *intraoperative complications/
62	exp *adverse drug reaction/
63	exp *drug safety/
64	exp *side effect/
65	exp *postoperative complication/
66	exp *peroperative complication/
67	"side effects (drug)"/
68	"side effects (treatment)"/
69	(safe or safety).ti.
70	side effect*.ti.
71	(adverse or undesirable or harm* or toxic or injurious or risk or risks or reaction* or toxic or toxicit* or toxologic* or complication* or noxious or tolerability or poison* or teratogen* or intoxication or warning*).ti.
72	((drug or chemically) adj induced).ti.
73	or/57-72
74	38 or 56 or 73
75	20 and 74
76	exp animals/

MEDLINE STRATEGY	
Line #	**Strategy**
77	exp animal experimentation/ or exp animal experiment/
78	exp models animal/
79	nonhuman/
80	exp vertebrate/ or exp vertebrates/
81	animal.po.
82	or/76-81
83	exp humans/
84	exp human experimentation/ or exp human experiment/
85	human.po.
86	or/83-85
87	82 not 86
88	75 not 87
89	limit 88 to english language

EMBASE STRATEGY	
Line #	**Strategy**
1	Multiple Sclerosis/
2	(relapsing remitting adj2 multiple sclerosis).ti,ab.
3	(remitting relapsing adj2 multiple sclerosis).ti,ab.
4	((relapsing remitting adj2 ms) or (remitting relapsing adj2 ms)).ti,ab.
5	((exacerbat* or disseminated or insular or secondary progressive or primary progressive or progressive relapsing) adj2 (sclerosis or ms)).ti,ab.
6	(rrms or encephalomyelitis disseminat*).ti,ab.
7	or/1-6
8	*teriflunomide/ or *fingolimod/ or *laquinimod/ or *fumaric acid dimethyl ester/
9	(Teriflunomide or A 1726 or A 77 1726 or A 771726 or HMR 1726 or HMR1726 or aubagio).ti,ab.
10	(fingolimod or FTY-720 or FTY270 or Gilenya or Gilenia).ti,ab.
11	(dimethyl fumarate or FAG 201 or FAG201 or "BRN 0774590" or BRN0774590 or HSDB 7725 or Methyl fumarate or NSC 167432 or NSC 25942 or TL 353 or Fumaderm or dimethylfumarate or bg 12 or "BG 00012" or BG00012).ti,ab.
12	or/8-11
13	*beta interferon/ or *natalizumab/ or *glatiramer/ or *ocrelizumab/
14	(interferon-beta-1 or interferon-1a or interferon-1b or interferon beta or beta Interferon or fibroblast Interferon or Fiblaferon or Interferon beta 1).ti,ab.
15	(avonex or rebif or betaferon or betaseron or BAY 86-5046 or BAY86-5046 or copaxone or extavia or glatiramer acetate).ti,ab.
16	(natalizumab or tysabri or antegren).ti,ab.
17	(alemtuzumab or campath or LDP-03 or lemtrada or mabcampath).ti,ab.
18	or/13-17
19	7 and (12 or 18)
20	meta-analysis.pt.
21	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
22	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
23	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or

EMBASE STRATEGY	
Line #	**Strategy**
	overview*))).ti,ab.
24	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
25	(data synthes* or data extraction* or data abstraction*).ti,ab.
26	(handsearch* or hand search*).ti,ab.
27	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
28	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview*).ti,ab.
29	(meta regression* or metaregression*).ti,ab.
30	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
31	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
32	(cochrane or (health adj2 technology assessment) or evidence report).jw.
33	(meta-analysis or systematic review).md.
34	(comparative adj3 (efficacy or effectiveness)).ti,ab.
35	(outcomes research or relative effectiveness).ti,ab.
36	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
37	or/20-36
38	Randomized Controlled Trial.pt.
39	Randomized Controlled Trials as Topic/
40	"Randomized Controlled Trial (topic)"/
41	Randomized Controlled Trial/
42	Randomization/
43	Random Allocation/
44	Double-Blind Method/
45	Double Blind Procedure/
46	Double-Blind Studies/
47	Single-Blind Method/
48	Single Blind Procedure/
49	Single-Blind Studies/
50	Placebos/
51	Placebo/
52	(random* or sham or placebo*).ti,ab,hw.
53	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
54	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
55	or/38-54
56	exp *drug toxicity/
57	exp *drug hypersensitivity/
58	*abnormalities, drug-induced/
59	exp *postoperative complications/
60	exp *intraoperative complications/
61	exp *adverse drug reaction/
62	exp *drug safety/
63	exp *side effect/
64	exp *postoperative complication/
65	exp *peroperative complication/

EMBASE STRATEGY	
Line #	**Strategy**
66	"side effects (drug)"/
67	"side effects (treatment)"/
68	(safe or safety).ti.
69	side effect*.ti.
70	(adverse or undesirable or harm* or toxic or injurious or risk or risks or reaction* or toxic or toxicit* or toxologic* or complication* or noxious or tolerability or poison* or teratogen* or intoxication or warning*).ti.
71	((drug or chemically) adj induced).ti.
72	or/56-71
73	37 or 55 or 72
74	19 and 73
75	exp animals/
76	exp animal experimentation/ or exp animal experiment/
77	exp models animal/
78	nonhuman/
79	exp vertebrate/ or exp vertebrates/
80	animal.po.
81	or/75-80
82	exp humans/
83	exp human experimentation/ or exp human experiment/
84	human.po.
85	or/82-84
86	81 not 85
87	74 not 86
88	conference abstract.pt.
89	87 not 88
90	limit 89 to english language

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
The Cochrane Library (Issue 10, 2012)	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for The Cochrane Library databases.

Grey Literature

Date of Search:	November 2012
Keywords:	Relapsing-remitting multiple sclerosis and interferon-beta-1a/1b, natalizumab, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, and alemtuzumab.
Limits:	None

The following sections of the CADTH grey literature checklist, *Grey matters: a practical tool for evidence-based searching* (http://www.cadth.ca/resources/grey-matters) were searched:

- Health Technology Assessment Agencies
- Advisories/Warnings/Safety
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Drug Class Reviews
- Internet Search.

APPENDIX 4: COST TABLE

Table 44: Cost Table of RRMS Treatments					
Drug/Comparator	**Strength**	**Dosage Form**	**Unit Cost ($)**	**Recommended Treatment Regimen**	**Annual Drug Cost ($)**
Alemtuzumab	12 mg 24 mg	Vial	N/A	12 mg for 5 consecutive days at first month, 3 consecutive days at month 12 24 mg for 5 consecutive days at first month, 3 consecutive days at month 12	$40,281[a]
Dimethyl fumarate (Tecfidera)	240 mg	Cap	N/A	240 mg twice daily	$23, 019[b]
Fingolimod (Gilenya)	0.5 mg	Cap	85.1648	once daily	$31,170
Glatiramer acetate (Copaxone)	20 mg/mL	Pre-filled syringe	44.4960	20 mg daily	$16,286
Interferon beta-1a (Avonex)	30 mcg/0.5 mL	Pre-filled syringe	393.9400	30 mcg IM per week	$20,597
Interferon beta-1a (Rebif)	22 mcg (6 MIU)	Pre-filled syringe	128.8433	22 mcg given 3 times per week	$20,210
Interferon beta-1a (Rebif)	44 mcg (12 MIU)	Pre-filled syringe	156.8533	44 mcg given 3 times per week	$24,604
Interferon beta-1b (Betaseron)	0.3 mg	Injection	110.0000	250 mcg SC every other day	$20,130
Interferon beta-1b (Extavia)	0.3 mg	Powder for injection	99.3593	250 mcg SC every other day	$18,183
Natalizumab (Tysabri)	300 mg/15 mL	Vial	3081.5800	300 mg IV infusion every four weeks	$40,281
Teriflunomide	7 mg 14 mg	Tab	N/A	7 mg oral daily 14 mg oral daily	$24,184[c]

Source: Ontario Exceptional Access Program (EAP) (June 2013)
IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N/A = not available; SC = subcutaneous.
[a]The price of alemtuzumab is unavailable, and it was assumed to be the same as for natalizumab.
[b]The price of dimethyl fumarate was provided by the manufacturer.
[c]The assumed price of teriflunomide was based on the ratio between the price of fingolimod and the price of teriflunomide in the US.[73]

APPENDIX 5: SENSITIVITY ANALYSES

Table 45: Univariate Sensitivity Analysis Regarding Background Cost				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus Glatiramer Acetate**	**Sequential ICUR**
Increase background cost by 100%				
Glatiramer acetate (Copaxone)	$494,269	11.272	ref	ref
Interferon beta-1b (Extavia)	$498,616	11.376	$41,675	$41,675
Dimethyl fumarate 240 mg (Tecfidera)	$525,492	11.442	$184,164	$207,064
Natalizumab (Tysabri)	$639,994	11.580	$473,350	$827,812
Dominated treatments				
Interferon beta-1b (Betaseron)	$511,985	11.376	$169,844	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$527,959	11.187	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$533,823	11.167	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$551,090	11.262	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$583,010	11.422	$592,018	Dominated by dimethyl fumarate
Decrease background cost by 100%				
Glatiramer acetate (Copaxone)	$235,249	11.272	ref	ref
Interferon beta-1b (Extavia)	$251,576	11.376	$156,526	$156,526
Dimethyl fumarate 240 mg (Tecfidera)	$279,786	11.442	$262,696	$227,517
Natalizumab (Tysabri)	$403,658	11.580	$547,033	$895,552
Dominated treatments				
Interferon beta-1b (Betaseron)	$264,945	11.190	$284,694	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg(Rebif)	$260,926	11.395	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 45: Univariate Sensitivity Analysis Regarding Background Cost				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a (Avonex)	$269,576	11.168	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 22mcg (Rebif)	$291,094	11.271	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$333,116	11.466	$652,903	Dominated by dimethyl fumarate

ICUR = incremental cost-utility ratio; mcg = microgram; mg = milligram; QALY = quality-adjusted life-year

Table 46: Univariate Sensitivity Analysis Regarding Cost of Relapse				
Cost per relapse = $1,405 Grima et al.[74]				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Glatiramer acetate (Copaxone)	$288,507	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$299,930	11.376	$109,519	$109,519
Dimethyl fumarate (Tecfidera)	$332,772	11.442	$261,092	$503,474
Natalizumab (Tysabri)	$459,081	11.580	$554,068	$913,177
Dominated treatments				
Interferon beta-1b (Betaseron)	$313,300	11.376	$237,687	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$316,087	11.187	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$319,267	11.167	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$344,575	11.262	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$389,409	11.422	$673,157	Dominated by dimethyl fumarate
Cost per relapse = $6,402 Karampampa et al.[75]				
Glatiramer acetate (Copaxone)	$311,927	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$323,995	11.376	$115,694	$115,694
Dimethyl fumarate (Tecfidera)	$353,243	11.442	$243,695	$448,383
Natalizumab (Tysabri)	$475,615	11.580	$531,700	$884,714
Dominated treatments				
Interferon beta-1b (Betaseron)	$337,364	11.395	$243,863	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$340,051	11.190	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 46: Univariate Sensitivity Analysis Regarding Cost of Relapse				
Cost per relapse = $1,405 **Grima et al.[74]**				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Interferon beta-1a (Avonex)	$346,446	11.168	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$368,068	11.271	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$408,527	11.422	$644,451	Dominated by dimethyl fumarate
Increase cost of relapse by 100% **Cost of moderate relapse = $12,804** **Cost of severe relapse = $30,730**				
Glatiramer acetate (Copaxone)	$361,258	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$374,683	11.376	$128,702	$128,702
Dimethyl fumarate (Tecfidera)	$396,362	11.442	$207,052	$332,343
Natalizumab (Tysabri)	$510,441	11.580	$484,584	$824,762
Dominated treatments				
Interferon beta-1b (Betaseron)	$388,052	11.376	$256,871	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$390,526	11.187	dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$403,693	11.167	dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$417,550	11.262	dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$448,795	11.422	$583,987	Dominated by dimethyl fumarate

ICUR = incremental cost-utility ratio; mcg = microgram; mg = milligram; QALY = quality-adjusted life-year

Table 47: Univariate Sensitivity Analysis Regarding Health Utilities				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Prosser et al.[62] (base case)				
Glatiramer acetate (Copaxone)	$321,589	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	11.376	$118,242	$118,242
Dimethyl fumarate (Tecfidera)	$361,688	11.442	$236,518	$425,655
Natalizumab (Tysabri)	$482,436	11.580	$522,472	$872,972
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	11.376	$246,411	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.187	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.167	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.262	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	11.422	$632,608	Dominated by dimethyl fumarate
Kobelt et al.[77]				
Glatiramer acetate (Copaxone)	$321,589	9.298	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	9.386	$139,729	$139,729
Dimethyl fumarate(Tecfidera)	$361,688	9.450	$264,147	$436,994
Natalizumab (Tysabri)	$482,436	9.578	$574,702	$942,812
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	9.386	$291,189	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	9.224	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 47: Univariate Sensitivity Analysis Regarding Health Utilities				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Interferon beta-1a (Avonex)	$357,658	9.200	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	9.289	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	9.436	$689,437	Dominated by dimethyl fumarate
ScHARR[78]				
Glatiramer acetate (Copaxone)	$321,589	7.638	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	7.755	$105,735	$105,735
Dimethyl fumarate(Tecfidera)	$361,688	7.822	$218,736	$416,432
Natalizumab (Tysabri)	$482,436	7.972	$481,831	$802,304
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	7.755	$220,347	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	7.545	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	7.528	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	7.627	Dominated	Dominated by interferon beta-1b 250 mcg (extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	7.798	$595,664	Dominated by dimethyl fumarate
Earnshaw et al.[79]				
Glatiramer acetate (Copaxone)	$321,589	9.221	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	9.315	$131,124	$131,124

Table 47: Univariate Sensitivity Analysis Regarding Health Utilities				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Dimethyl fumarate(Tecfidera)	$361,688	9.379	$253,412	$432,653
Natalizumab (Tysabri)	$482,436	9.512	$553,268	$911,411
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	9.315	$273,255	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	9.143	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	9.121	Dominated	Dominated by interferon beta-1b 250 mcg (extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	9.212	Dominated	Dominated by interferon beta-1b 250 mcg (extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	9.363	$667,951	Dominated by dimethyl fumarate
Karampampa et al.[75]				
Glatiramer acetate (Copaxone)	$321,589	8.046	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	8.167	$101,765	$101,765
Dimethyl fumarate(Tecfidera)	$361,688	8.234	$212,856	$413,253
Natalizumab (Tysabri)	$482,436	8.388	$469,933	$784,639
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	8.167	$212,073	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	7.950	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	7.934	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 47: Univariate Sensitivity Analysis Regarding Health Utilities				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Interferon beta-1a 44 mcg (Rebif)	$377,759	8.034	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	8.209	$583,000	Dominated by dimethyl fumarate

ICUR = incremental cost-utility ratio; mcg = microgram; mg = milligram; QALY = quality-adjusted life-year

Table 48: Univariate Sensitivity Analysis Regarding Disutilities Associated with Relapse				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Versus Glatiramer Acetate**	**Sequential ICUR**
Prosser et al.[62] (base case)				
Glatiramer acetate (Copaxone)	$321,589	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	11.376	$118,242	$118,242
Dimethyl fumarate (Tecfidera)	$361,688	11.442	$236,518	$425,655
Natalizumab (Tysabri)	$482,436	11.580	$522,472	$872,972
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	11.376	$246,411	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.187	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.167	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.262	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	11.422	$632,608	Dominated by dimethyl fumarate
Parkin[97]				
Glatiramer acetate (Copaxone)	$321,589	11.259	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	11.363	$118,855	$118,855
Dimethyl fumarate(Tecfidera)	$361,688	11.431	$234,168	$411,524
Natalizumab (Tysabri)	$482,436	11.571	$515,641	$858,226
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	11.363	$247,688	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.174	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 48: Univariate Sensitivity Analysis Regarding Disutilities Associated with Relapse				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Versus Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a (Avonex)	$357,658	11.152	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.249	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	11.412	$621,842	Dominated by dimethyl fumarate
ScHARR[78]				
Glatiramer acetate (Copaxone)	$321,589	11.314	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	11.420	$116,245	$116,245
Dimethyl fumarate(Tecfidera)	$361,688	11.478	$244,702	$480,638
Natalizumab (Tysabri)	$482,436	11.608	$546,596	$925,974
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	11.420	$242,249	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.230	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.217	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.304	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	11.455	$671,330	Dominated by dimethyl fumarate
Earnshaw et al.[79]				
Glatiramer acetate (Copaxone)	$321,589	11.262	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	11.366	$118,715	$118,715
Dimethyl fumarate(Tecfidera)	$361,688	11.433	$234,698	$414,652
Natalizumab (Tysabri)	$482,436	11.573	$517,177	$861,533

Table 48: Univariate Sensitivity Analysis Regarding Disutilities Associated with Relapse				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Versus Glatiramer Acetate**	**Sequential ICUR**
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	11.366	$247,397	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.177	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.155	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.252	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Interferon beta-1b (Betaseron)	$347,292	11.366	$247,397	Dominated by interferon beta-1b 250 mcg (Extavia)

ICUR = incremental cost-utility ratio; mcg = microgram; mg = milligram; QALY = quality-adjusted life-year.

Table 49: Univariate Sensitivity Analysis Regarding Discontinuation Rate				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Versus Glatiramer Acetate**	**Sequential ICUR**
15% discontinuation rate (base case)				
Glatiramer acetate (Copaxone)	$321,589	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	11.376	$118,242	$118,242
Dimethyl fumarate (Tecfidera)	$361,688	11.442	$236,518	$425,655
Natalizumab (Tysabri)	$482,436	11.580	$522,472	$872,972
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	11.376	$246,411	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.187	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.167	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.262	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	11.422	$632,608	Dominated by dimethyl fumarate
25% discontinuation rate				
Glatiramer acetate (Copaxone)	$310,638	11.254	Ref	Ref
Interferon beta-1b (Extavia)	$321,035	11.344	$115,584	$115,584
Dimethyl fumarate (Tecfidera)	$371,695	11.466	$288,388	$416,037
Natalizumab (Tysabri)	$447,439	11.518	$518,223	$1,449,326
Dominated treatments				
Interferon beta-1b (Betaseron)	$332,432	11.344	$242,297	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$334,929	11.181	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 49: Univariate Sensitivity Analysis Regarding Discontinuation Rate				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Versus Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a (Avonex)	$341,479	11.164	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$358,583	11.245	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$466,167	11.499	$638,153	Dominated by dimethyl fumarate
0% discontinuation rate				
Glatiramer acetate (Copaxone)	$310,638	11.254	Ref	Ref
Interferon beta-1b (Extavia)	$321,035	11.344	$115,584	$115,584
Dimethyl fumarate (Tecfidera)	$344,695	11.400	$233,947	$425,339
Natalizumab (Tysabri)	$447,439	11.518	$518,223	$867,743
Dominated treatments				
Interferon beta-1b (Betaseron)	$332,432	11.344	$242,297	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$334,929	11.181	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$341,479	11.164	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$358,583	11.245	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$391,423	11.383	$628,720	Dominated by dimethyl fumarate
10% for oral treatments, 25% for injectable treatments				
Glatiramer acetate (Copaxone)	$310,638	11.254	Ref	Ref
Interferon beta-1b (Extavia)	$321,035	11.344	$115,584	$115,584

Table 49: Univariate Sensitivity Analysis Regarding Discontinuation Rate				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Versus Glatiramer Acetate**	**Sequential ICUR**
Dimethyl fumarate (Tecfidera)	$371,695	11.466	$288,388	$416,037
Natalizumab (Tysabri)	$447,439	11.518	$518,223	$1,449,326
Dominated treatments				
Interferon beta-1b (Betaseron)	$332,432	11.344	$242,297	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$334,929	11.181	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$341,479	11.164	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$358,583	11.245	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$431,125	11.445	$632,229	Dominated by dimethyl fumarate

ICUR = incremental cost-utility ratio; mcg = microgram; mg = milligram; QALY = quality-adjusted life-year

Table 50: Univariate Sensitivity Analysis Regarding Time Horizon				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
25-year time horizon (base case)				
Glatiramer acetate (Copaxone)	$321,589	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	11.376	$118,242	$118,242
Dimethyl fumarate (Tecfidera)	$361,688	11.442	$236,518	$425,655
Natalizumab (Tysabri)	$482,436	11.580	$522,472	$872,972
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	11.376	$246,411	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.187	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.167	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.262	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	11.422	$632,608	Dominated by dimethyl fumarate
10-year time horizon				
Glatiramer acetate (Copaxone)	$167,085	6.755	Ref	Ref
Interferon beta-1b (Extavia)	$176,574	6.778	$413,942	$413,942
Dimethyl fumarate 240 mg (Tecfidera)	$195,912	6.818	$458,870	$484,682
Natalizumab (Tysabri)	$278,951	6.877	$918,311	$1,407,553
Dominated treatments				
Interferon beta-1b (Betaseron)	$185,932	6.778	$822,202	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$187,116	6.729	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 50: Univariate Sensitivity Analysis Regarding Time Horizon				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a (Avonex)	$192,888	6.702	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$207,260	6.752	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$234,313	6.822	$1,005,305	Dominated by dimethyl fumarate
15-year time horizon				
Glatiramer acetate (Copaxone)	$229,549	8.826	Ref	Ref
Interferon beta-1b (Extavia)	$240,577	8.875	$226,537	$226,537
Dimethyl fumarate 240 mg (Tecfidera)	$264,091	8.925	$347,537	$463,704
Natalizumab (Tysabri)	$365,678	9.012	$730,737	$1,169,035
Dominated treatments				
Interferon beta-1b (Betaseron)	$251,932	8.875	$459,774	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$253,761	8.780	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$260,552	8.753	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$277,812	8.820	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate

Table 50: Univariate Sensitivity Analysis Regarding Time Horizon				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Fingolimod (Gilenya)	$310,627	8.923	$836,586	Dominated by dimethyl fumarate
20-year time horizon				
Glatiramer acetate (Copaxone)	$281,159	10.278	Ref	Ref
Interferon beta-1b (Extavia)	$292,953	10.355	$152,870	$152,870
Dimethyl fumarate 240 mg (Tecfidera)	$319,053	10.414	$278,492	$443,017
Natalizumab (Tysabri)	$432,244	10.528	$604,401	$993,721
Dominated treatments				
Interferon beta-1b (Betaseron)	$305,539	10.355	$315,986	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$307,954	10.211	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$315,310	10.188	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$334,291	10.270	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$370,615	10.403	$715,143	Dominated by dimethyl fumarate
30-year time horizon				
Glatiramer acetate (Copaxone)	$351,257	11.937	Ref	Ref
Interferon beta-1b (Extavia)	$364,090	12.065	$100,275	$100,275
Dimethyl fumarate 240 mg (Tecfidera)	$392,961	12.135	$210,609	$412,198
Natalizumab (Tysabri)	$518,796	12.294	$469,192	$791,103
Dominated treatments				
Interferon beta-1b (Betaseron)	$377,968	12.065	$208,719	Dominated by interferon beta-1b 250 mcg (Extavia)

Table 50: Univariate Sensitivity Analysis Regarding Time Horizon				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a 22 mcg (Rebif)	$380,483	11.835	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$388,472	11.819	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$409,354	11.924	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$449,676	12.107	$577,073	Dominated by dimethyl fumarate
35-year time horizon				
Glatiramer acetate (Copaxone)	$371,676	12.369	Ref	Ref
Interferon beta-1b (Extavia)	$384,978	12.516	$90,342	$90,342
Dimethyl fumarate 240 mg (Tecfidera)	$414,588	12.590	$194,293	$402,184
Natalizumab (Tysabri)	$543,884	12.766	$434,210	$735,729
Dominated treatments				
Interferon beta-1b (Betaseron)	$399,186	12.516	$186,840	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$401,359	12.255	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$409,552	12.243	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 50: Univariate Sensitivity Analysis Regarding Time Horizon				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a 44 mcg (Rebif)	$430,992	12.355	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$472,534	12.556	$539,682	Dominated by dimethyl fumarate
40-year time horizon				
Glatiramer acetate (Copaxone)	$384,886	12.641	Ref	Ref
Interferon beta-1b (Extavia)	$398,591	12.803	$84,636	$84,636
Dimethyl fumarate 240 mg (Tecfidera)	$428,684	12.879	$183,945	$395,027
Natalizumab (Tysabri)	$560,295	13.068	$411,300	$698,683
Dominated treatments				
Interferon beta-1b (Betaseron)	$413,009	12.803	$173,678	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$414,781	12.518	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$423,125	12.508	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$444,953	12.626	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$487,368	12.840	$514,761	Dominated by dimethyl fumarate

ICUR = incremental cost-utility ratio; mcg = microgram; mg = milligram; QALY = quality-adjusted life-year.

Table 51: Sensitivity Analysis Regarding Inclusion of EDSS Improvements				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Improvements on EDSS scale (Base case)				
Glatiramer acetate (Copaxone)	$321,589	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	11.376	$118,242	$118,242
Dimethyl fumarate (Tecfidera)	$361,688	11.442	$236,518	$425,655
Natalizumab (Tysabri)	$482,436	11.580	$522,472	$872,972
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	11.376	$246,411	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.187	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.167	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.262	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	11.422	$632,608	Dominated by dimethyl fumarate
No improvements on EDSS scale				
Glatiramer acetate (Copaxone)	$333,903	10.983	Ref	Ref
Interferon beta-1b (Extavia)	$345,173	11.091	$104,221	$104,221
Dimethyl fumarate 240 mg (Tecfidera)	$370,227	11.148	$219,803	$438,617
Natalizumab (Tysabri)	$480,443	11.281	$491,432	$829,108
Dominated treatments				
Interferon beta-1b (Betaseron)	$357,299	11.091	$216,357	Dominated by interferon beta-1b 250 mcg (Extavia)

Table 51: Sensitivity Analysis Regarding Inclusion of EDSS Improvements				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a (Rebif 22)	$359,324	10.898	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$366,452	10.886	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1b (Betaseron)	$357,299	11.091	$216,357	Dominated by interferon beta-1b 250 mcg (Extavia)
Fingolimod (Gilenya)	$419,629	11.124	$607,069	Dominated by dimethyl fumarate

ICUR = incremental cost-utility ratio; mcg = microgram; QALY = quality-adjusted life-year.

Table 52: Sensitivity Analysis Regarding Annual Relapse Rate				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Annual Relapse Rate: Patzold time-dependent (base case)				
Glatiramer acetate (Copaxone)	$321,589	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	11.376	$118,242	$118,242
Dimethyl fumarate (Tecfidera)	$361,688	11.442	$236,518	$425,655
Natalizumab (Tysabri)	$482,436	11.580	$522,472	$872,972
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	11.376	$246,411	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.187	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.167	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.262	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	11.422	$632,608	Dominated by dimethyl fumarate
Annual Relapse Rate: ScHARR				
Glatiramer acetate (Copaxone)	$329,642	11.207	Ref	Ref
Interferon beta-1b (Extavia)	$342,234	11.308	$124,172	$124,172
Dimethyl fumarate(Tecfidera)	$368,915	11.384	$222,244	$354,333
Natalizumab (Tysabri)	$488,499	11.533	$487,985	$803,519
Dominated treatments				
Interferon beta-1b (Betaseron)	$355,604	11.308	$256,000	Dominated by interferon beta-1b 250 mcg (Extavia)

Table 52: Sensitivity Analysis Regarding Annual Relapse Rate				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a 22 mcg (Rebif)	$358,108	11.121	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$366,808	11.092	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$385,828	11.196	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$423,211	11.368	$580,351	Dominated by dimethyl fumarate
Annual Relapse Rate: Prosser				
Glatiramer acetate (Copaxone)	$340,857	11.068	Ref	Ref
Interferon beta-1b (Extavia)	$354,059	11.162	$140,432	$140,432
Dimethyl fumarate(Tecfidera)	$378,597	11.263	$192,872	$241,362
Natalizumab (Tysabri)	$495,959	11.440	$417,046	$665,950
Dominated treatments				
Interferon beta-1b (Betaseron)	$367,428	11.162	$282,646	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$369,503	10.979	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$380,170	10.926	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 52: Sensitivity Analysis Regarding Annual Relapse Rate				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a 44 mcg (Rebif)	$397,069	11.057	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$432,006	11.259	$477,004	Dominated by dimethyl fumarate
Annual Relapse Rate: Patzold (constant)				
Glatiramer acetate (Copaxone)	$331,487	11.147	Ref	Ref
Interferon beta-1b (Extavia)	$344,377	11.245	$132,012	$132,012
Dimethyl fumarate(Tecfidera)	$370,396	11.332	$210,101	$297,194
Natalizumab (Tysabri)	$489,356	11.494	$455,524	$737,176
Dominated treatments				
Interferon beta-1b (Betaseron)	$357,746	11.245	$268,930	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$359,939	11.060	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$369,272	11.020	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$387,673	11.136	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$424,379	11.322	$531,136	Dominated by dimethyl fumarate

ICUR = incremental cost-utility ratio; mcg = microgram; QALY = quality-adjusted life-year.

Table 53: Analysis of Variability Regarding Stopping Rule				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Stopping rule: EDSS 5 and progression to SPMS				
Glatiramer acetate (Copaxone)	$318,270	11.252	Ref	Ref
Interferon beta-1b (Extavia)	$330,313	11.348	$126,624	$126,625
Dimethyl fumarate 240 mg (Tecfidera)	$357,010	11.412	$243,077	$415,430
Natalizumab (Tysabri)	$473,941	11.544	$533,839	$884,286
Dominated treatments				
Interferon beta-1b (Betaseron)	$343,252	11.348	$262,658	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$345,648	11.174	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$353,305	11.152	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$372,552	11.243	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$409,832	11.395	$641,406	Dominated by dimethyl fumarate
Stopping rule: EDSS 5 (regardless of progression to SPMS)				
Glatiramer acetate (Copaxone)	$332,248	11.252	Ref	Ref
Interferon beta-1b (Extavia)	$344,979	11.348	$133,844	$133,844
Dimethyl fumarate 240 mg (Tecfidera)	$375,402	11.412	$270,764	$473,407
Natalizumab (Tysabri)	$504,469	11.544	$590,591	$976,069
Dominated treatments				
Interferon beta-1b (Betaseron)	$359,442	11.348	$285,916	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$363,753	11.174	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$371,505	11.152	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 53: Analysis of Variability Regarding Stopping Rule				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a 44 mcg(Rebif)	$393,819	11.243	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$435,340	11.395	$722,169	Dominated by dimethyl fumarate
Stopping rule: EDSS 6 and progression to SPMS				
Glatiramer acetate (Copaxone)	$318,055	11.266	Ref	Ref
Interferon beta-1b (Extavia)	$329,990	11.367	$117,669	$117,669
Dimethyl fumarate 240 mg (Tecfidera)	$356,694	11.432	$232,241	$411,190
Natalizumab (Tysabri)	$473,658	11.568	$513,701	$856,682
Dominated treatments				
Interferon beta-1b (Betaseron)	$342,938	11.367	$245,320	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$345,521	11.182	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$353,155	11.162	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$372,371	11.255	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$409,588	11.413	$619,908	Dominated by dimethyl fumarate
Stopping rule: EDSS 6 (regardless of progression to SPMS)				
Glatiramer acetate (Copaxone)	$332,035	11.266	Ref	Ref
Interferon beta-1b (Extavia)	$344,659	11.367	$124,453	$124,453
Dimethyl fumarate 240 mg (Tecfidera)	$375,089	11.432	$258,777	$468,576
Natalizumab (Tysabri)	$504,196	11.568	$568,360	$945,611
Dominated treatments				
Interferon beta-1b (Betaseron)	$359,132	11.367	$267,146	Dominated by interferon beta-1b 250 mcg (Extavia)

Table 53: Analysis of Variability Regarding Stopping Rule				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a 22 mcg (Rebif)	$363,627	11.182	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$371,357	11.162	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$393,641	11.255	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$435,100	11.413	$698,011	Dominated by dimethyl fumarate
Stopping rule: EDSS 7 and progression to SPMS (base case)				
Glatiramer acetate (Copaxone)	$321,589	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$333,923	11.376	$118,242	$118,242
Dimethyl fumarate 240 mg (Tecfidera)	$361,688	11.442	$236,518	$425,655
Natalizumab (Tysabri)	$482,436	11.580	$522,472	$872,972
Dominated treatments				
Interferon beta-1b (Betaseron)	$347,292	11.376	$246,411	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$349,937	11.187	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$357,658	11.167	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$377,759	11.262	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$416,414	11.422	$632,608	Dominated by dimethyl fumarate
Stopping rule: EDSS 7 (regardless of progression to SPMS)				
Glatiramer acetate (Copaxone)	$348,140	11.272	Ref	Ref
Interferon beta-1b (Extavia)	$361,679	11.376	$129,799	$129,799

Table 53: Analysis of Variability Regarding Stopping Rule				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Dimethyl fumarate 240 mg (Tecfidera)	$396,482	11.442	$285,135	$533,535
Natalizumab (Tysabri)	$540,010	11.580	$623,243	$1,037,670
Dominated treatments				
Interferon beta-1b (Betaseron)	$377,935	11.376	$285,645	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$384,401	11.187	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$392,276	11.167	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$418,166	11.262	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$464,733	11.422	$777,836	Dominated by dimethyl fumarate
Progression to SPMS only				
Glatiramer acetate (Copaxone)	$329,599	11.277	Ref	Ref
Interferon beta-1b (Extavia)	$342,097	11.383	$117,977	$117,977
Dimethyl fumarate (Tecfidera)	$371,762	11.448	$246,140	$453,862
Natalizumab (Tysabri)	$498,224	11.587	$543,516	$910,107
Dominated treatments				
Interferon beta-1b (Betaseron)	$356,267	11.383	$251,737	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$360,302	11.190	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$368,034	11.171	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 53: Analysis of Variability Regarding Stopping Rule				
Treatment	**Total Cost**	**Total QALYs**	**ICUR Glatiramer Acetate**	**Sequential ICUR**
Interferon beta-1a 44 mcg (Rebif)	$389,727	11.267	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$430,323	11.428	$666,133	Dominated by dimethyl fumarate
No-stopping rule				
Glatiramer acetate (Copaxone)	$388,705	11.277	Ref	Ref
Interferon beta-1b (Extavia)	$402,980	11.383	$134,754	$134,754
Dimethyl fumarate 240 mg (Tecfidera)	$447,952	11.448	$345,876	$688,054
Natalizumab (Tysabri)	$622,781	11.587	$754,485	$1,258,198
Dominated treatments				
Interferon beta-1b (Betaseron)	$423,482	11.383	$328,295	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$437,757	11.190	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$445,581	11.171	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$479,785	11.267	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$536,691	11.428	$978,704	dominated by dimethyl fumarate

EDSS = Expanded Disability Status Scale; ICUR = Incremental cost-utility ratio; mcg = microgram; mg = milligram; QALY = quality-adjusted life-year; SPMS = secondary-progressive multiple sclerosis.

Table 54: Sensitivity Analysis Regarding Starting EDSS Score				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Starting EDSS = 1				
Glatiramer acetate (Copaxone)	$269,624	12.598	Ref	Ref
Interferon beta-1b (Extavia)	$288,206	12.644	$407,272	$407,272
Dimethyl fumarate 240 mg (Tecfidera)	$328,150	12.739	$416,147	$420,409
Natalizumab (Tysabri)	$494,938	12.868	$836,310	$1,295,178
Dominated treatments				
Interferon beta-1b (Betaseron)	$307,091	12.644	$821,174	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$310,677	12.538	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$321,392	12.472	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$351,421	12.591	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$406,398	12.753	$884,487	Dominated by dimethyl fumarate
Starting EDSS = 2				
Glatiramer acetate (Copaxone)	$310,572	11.624	Ref	Ref
Interferon beta-1b (Extavia)	$323,204	11.735	$114,012	$114,012
Dimethyl fumarate 240 mg (Tecfidera)	$352,924	11.807	$231,298	$411,018
Natalizumab (Tysabri)	$482,176	11.957	$515,804	$864,051
Dominated treatments				
Interferon beta-1b (Betaseron)	$337,508	11.735	$243,115	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$341,106	11.532	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$349,193	11.509	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 54: Sensitivity Analysis Regarding Starting EDSS Score				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Interferon beta-1a 44 mcg (Rebif)	$370,499	11.613	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$411,588	11.788	$618,278	Dominated by dimethyl fumarate
Starting EDSS = 3				
Glatiramer acetate (Copaxone)	$365,103	10.269	Ref	Ref
Interferon beta-1b (Extavia)	$373,599	10.400	$64,817	$64,817
Dimethyl fumarate 240 mg (Tecfidera)	$392,101	10.437	$160,360	$496,260
Natalizumab (Tysabri)	$478,137	10.565	$381,776	$673,644
Dominated treatments				
Interferon beta-1b (Betaseron)	$382,924	10.400	$135,961	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$384,123	10.178	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$390,143	10.190	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$402,961	10.258	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$429,443	10.398	$500,931	Dominated by dimethyl fumarate
Starting EDSS = 4				
Glatiramer acetate (Copaxone)	$389,984	9.220	Ref	Ref
Interferon beta-1b (Extavia)	$396,669	9.350	$51,293	$51,293
Dimethyl fumarate (Tecfidera)	$409,824	9.376	$126,842	$504,176
Natalizumab (Tysabri)	$470,957	9.494	$295,453	$519,610
Dominated treatments				
Interferon beta-1a 22 mcg (Rebif)	$403,118	9.350	$100,781	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1b (Betaseron)	$402,284	9.135	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 54: Sensitivity Analysis Regarding Starting EDSS Score				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Interferon beta-1a (Avonex)	$406,378	9.154	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$415,778	9.209	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$435,328	9.332	$402,552	Dominated by dimethyl fumarate

EDSS = Expanded Disability Status Scale; ICUR = Incremental cost-utility ratio; mcg = microgram; mg = milligram; QALY = quality-adjusted life-year.

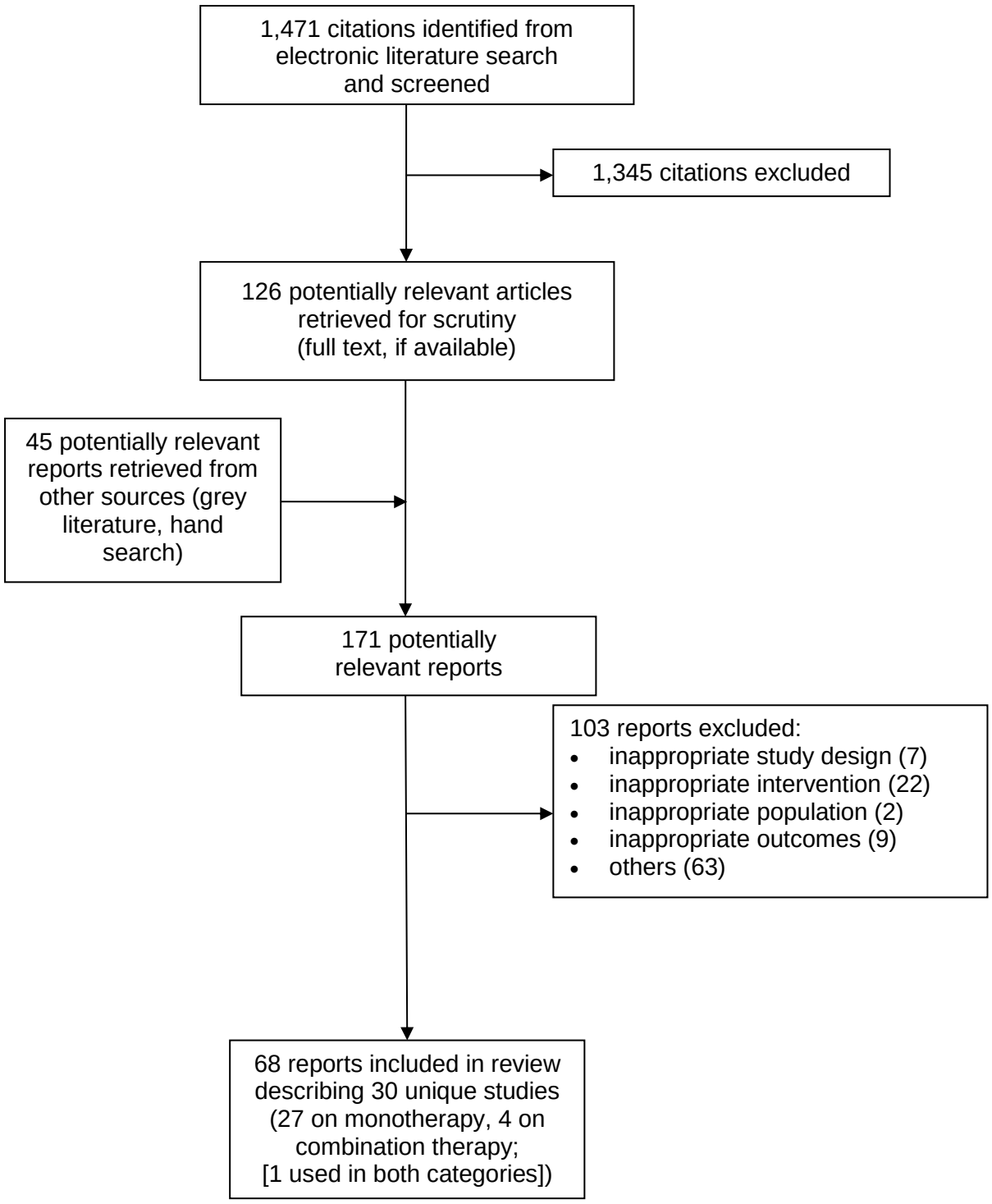
Table 55: Sensitivity Analysis Regarding Patient's Starting Age				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Patient Starting Age = 20				
Glatiramer acetate (Copaxone)	$324,555	11.353	Ref	Ref
Interferon beta-1b (Extavia)	$336,962	11.459	$116,736	$116,736
Dimethyl fumarate (Tecfidera)	$364,928	11.525	$234,563	$424,763
Natalizumab (Tysabri)	$486,575	11.665	$518,677	$867,355
Dominated treatments				
Interferon beta-1b (Betaseron)	$350,427	11.459	$243,425	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$353,098	11.266	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$360,868	11.246	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$381,107	11.342	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$420,041	11.505	$628,620	Dominated by dimethyl fumarate
Patient starting age = 30				
Glatiramer acetate (Copaxone)	$323,380	11.321	ref	ref
Interferon beta-1b (Extavia)	$335,760	11.427	$117,367	$117,367
Dimethyl fumarate(Tecfidera)	$363,649	11.492	$235,385	$425,139
Natalizumab (Tysabri)	$484,949	11.632	$520,274	$869,720
Dominated treatments				
Interferon beta-1b (Betaseron)	$349,188	11.427	$244,678	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$351,848	11.235	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate

Table 55: Sensitivity Analysis Regarding Patient's Starting Age				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Interferon beta-1a (Avonex)	$359,600	11.215	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$379,786	11.311	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$418,613	11.472	$630,298	Dominated by dimethyl fumarate
Patient Starting Age = 40				
Glatiramer acetate (Copaxone)	$319,657	11.219	Ref	Ref
Interferon beta-1b (Extavia)	$331,942	11.322	$119,204	$119,204
Dimethyl fumarate(Tecfidera)	$359,574	11.387	$237,759	$426,214
Natalizumab (Tysabri)	$479,724	11.524	$524,874	$876,522
Dominated treatments				
Interferon beta-1b (Betaseron)	$345,247	11.322	$248,316	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$347,875	11.134	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$355,564	11.114	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$375,573	11.208	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$414,041	11.367	$635,131	Dominated by dimethyl fumarate
Patient Starting Age = 50				
Glatiramer acetate (Copaxone)	$310,124	10.953	Ref	Ref
Interferon beta-1b (Extavia)	$322,160	11.050	$124,133	$124,133
Dimethyl fumarate(Tecfidera)	$349,123	11.113	$244,023	$428,976

Table 55: Sensitivity Analysis Regarding Patient's Starting Age				
Treatment	**Total Cost**	**Total QALYs**	**ICUR versus glatiramer acetate**	**Sequential ICUR**
Natalizumab (Tysabri)	$466,288	11.244	$536,964	$894,322
Dominated treatments				
Interferon beta-1b (Betaseron)	$335,147	11.050	$258,073	Dominated by interferon beta-1b 250 mcg (Extavia)
Interferon beta-1a 22 mcg (Rebif)	$337,688	10.873	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a (Avonex)	$345,215	10.853	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia) and glatiramer acetate
Interferon beta-1a 44 mcg (Rebif)	$364,761	10.944	Dominated	Dominated by interferon beta-1b 250 mcg (Extavia), glatiramer acetate and dimethyl fumarate
Fingolimod (Gilenya)	$402,298	11.096	$647,777	Dominated by dimethyl fumarate

ICUR = Incremental cost-utility ratio; mcg = microgram; mg = milligram; QALY = quality-adjusted life-year.

APPENDIX 6: SELECTION OF INCLUDED STUDIES



APPENDIX 7: INCLUDED STUDY LIST

Monotherapy

Study AFFIRM
Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):899-910.

Related references:
Phillips JT, Giovannoni G, Lublin FD, O'Connor PW, Polman CH, Willoughby E, et al. Sustained improvement in Expanded Disability Status Scale as a new efficacy measure of neurological change in multiple sclerosis: treatment effects with natalizumab in patients with relapsing multiple sclerosis. MultScler. 2011 Aug;17(8):970-9.

Rudick RA, Miller D, Hass S, Hutchinson M, Calabresi PA, Confavreux C, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. Ann Neurol. 2007 Oct;62(4):335-46.

Miller DH, Soon D, Fernando KT, MacManus DG, Barker GJ, Yousry TA, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. Neurology. 2007 Apr 24;68(17):1390-401.

Hutchinson M, Kappos L, Calabresi PA, Confavreux C, Giovannoni G, Galetta SL, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. J Neurol. 2009 Mar;256(3):405-15.

Study BECOME
Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K, et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology. 2009 Mar 11;72(23):1976-83.

Related references:
Cadavid D, Cheriyan J, Skurnick J, Lincoln JA, Wolansky LJ, Cook SD. New acute and chronic black holes in patients with multiple sclerosis randomised to interferon beta-1b or glatiramer acetate. Journal of Neurology, Neurosurgery and Psychiatry. 2009;80(12):1337-43.

Cheriyan J, Kim S, Wolansky LJ, Cook SD, Cadavid D. Impact of inflammation on brain volume in multiple sclerosis. Arch Neurol. 2012;69(1):82-8.

Study BEYOND
O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 mug or 500 mug interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009 Oct;8(10):889-97.

Related references:
Filippi M, Rocca MA, Camesasca F, Cook S, O'Connor P, Arnason BG, et al. Interferon beta-1b and glatiramer acetate effects on permanent black hole evolution. Neurology [Internet]. 2011 Apr 5 [cited 2012 Nov 19];76(14):1222-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3068007/pdf/znl1222.pdf

Calabrese 2012
Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. MultScler. 2012 Apr;18(4):418-24.

Study CAMMS223
The CAMMS223 Trial Investigators, Compston DAS, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. Alemtuzumab versus interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008;359(17):1786-801.

Related references:
Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. Lancet Neurol. 2011 Apr;10(4):338-48.

Coles A, Fox E, Vladic A, Gazda S, Brinar V, Selmaj K, et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. Supplementary appendix. Lancet Neurol. 2013;10:338-48.
Study CARE-MS I
Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet.2012 Oct 31.

Study CARE-MS II
Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet.2012 Oct 31.

Clanet 2002
Clanet M, Radue EW, Kappos L, Hartung HP, Hohlfeld R, Sandberg-Wollheim M, et al. A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS. Neurology. 2002 Nov 26;59(10):1507-17.

Comi 2001
Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol. 2001 Mar;49(3):290-7.

Study CONFIRM
Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1087-97.

Related references:
Supplement to: Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367:1087-97.

Hutchinson M, Fox RJ, Miller DH, Phillips JT, Kita M, Havrdova E, et al. Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the CONFIRM study. J Neurol. 2013 Jun 8.

Study DEFINE
Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1098-107.

Related references:
Supplement to: Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012;367:1098-107.

Etemadifar 2006
Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis.ActaNeurol Scand. 2006 May;113(5):283-7.

Study EVIDENCE
Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology. 2002 Nov 26;59(10):1496-506.

Related references:
Sandberg-Wollheim M, Bever C, Carter J, Farkkila M, Hurwitz B, Lapierre Y, et al. Comparative tolerance of IFN beta-1a regimens in patients with relapsing multiple sclerosis. The EVIDENCE study. J Neurol. 2005 Jan;252(1):8-13.

Panitch H, Goodin D, Francis G, Chang P, Coyle P, O'Connor P, et al. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. J Neurol Sci. 2005 Dec 15;239(1):67-74.

Schwid SR, Panitch HS. Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: A multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis. ClinTher. 2007;29(9):2031-48.

Traboulsee A, Al-Sabbagh A, Bennett R, Chang P, Li DK, EVIDENCE Study Group, et al. Reduction in magnetic resonance imaging T2 burden of disease in patients with relapsing-remitting multiple sclerosis: analysis of 48-week data from the EVIDENCE (EVidence of Interferon Dose-response: European North American Comparative Efficacy) study. BMC Neurol [Internet]. 2008 [cited 2012 Nov 19];8(11). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2374794/pdf/1471-2377-8-11.pdf

Study FREEDOMS

Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010 Feb 4;362(5):387-401.

Related references:
Supplement to: Kappos L, Radue E-W, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing
multiple sclerosis. N Engl J Med. 2012;362:387-401.

Devonshire V, Havrdova E, Radue EW, O'Connor P, Zhang-Auberson L, Agoropoulou C, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol. 2012 May;11(5):420-8.

Radue EW, O'Connor P, Polman CH, Hohlfeld R, Calabresi P, Selmaj K, et al. Impact of Fingolimod Therapy on Magnetic Resonance Imaging Outcomes in Patients With Multiple Sclerosis. Arch Neurol. 2012 Jul 2;69(10):1259-69.

Study IFNB-MS

The IFNB Multiple Sclerosis Study Group. Interferon beta-1a is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology. 1993 Apr;43(4):655-61.

Related references:
Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group.Neurology. 1993 Apr;43(4):662-7.

Sibley WA. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. Neurology. 1995;45(7):1277-85.

Study IMPROVE

De SN, Curtin F, Stubinski B, Blevins G, Drulovic J, Issard D, et al. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. MultScler. 2010 Jul;16(7):888-92.

Related references:
De SN, Sormani MP, Stubinski B, Blevins G, Drulovic JS, Issard D, et al. Efficacy and safety of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: further outcomes from the IMPROVE study. J Neurol Sci. 2012 Jan 15;312(1-2):97-101.

Study INCOMIN

Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet. 2002 Apr 27;359(9316):1453-60.

Related references:
Barbero P, Bergui M, Versino E, Ricci A, Zhong JJ, Ferrero B, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis (INCOMIN Trial) II: analysis of MRI responses to treatment and correlation with Nab. MultScler. 2006 Feb;12(1):72-6.

Johnson 1995
Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. Neurology. 1995 Jul;45(7):1268-76.

Related references:
Ge Y, Grossman RI, Udupa JK, Fulton J, Constantinescu CS, Gonzales-Scarano F, et al. Glatiramer acetate (Copaxone) treatment in relapsing-remitting MS: quantitative MR assessment. Neurology. 2000 Feb 22;54(4):813-7.

Weinstein A, Schwid SR, Schiffer RB, McDermott MP, Giang DW, Goodman AD. Neuropsychologic status in multiple sclerosis after treatment with glatiramer.ArchNeurol [Internet]. 1999 Mar [cited 2012 Nov 19];56(3):319-24. Available from: http://archneur.ama-assn.org/cgi/reprint/56/3/319

Kappos 2011
Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet. 2011 Nov 19;378(9805):1779-87.

Study MSCRG
Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol. 1996;39(3):285-94.

Related references:
Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: design and conduct of study and baseline characteristics of patients.Multiple Sclerosis Collaborative Research Group (MSCRG).MultScler. 1995;1(2):118-35.

Simon JH, Jacobs LD, Campion M, Wende K, Simonian N, Cookfair DL, et al. Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. Ann Neurol. 1998;43(1):79-87.

Miller DM, Weinstock-Guttman B, Bourdette D, You X, Foulds P, Rudick RA. Change in quality of life in patients with relapsing-remitting multiple sclerosis over 2 years in relation to other clinical parameters: results from a trial of intramuscular interferon beta-1a. MultScler. 2011 Jun;17(6):734-42.

Rudick RA, Goodkin DE, Jacobs LD, Cookfair DL, Herndon RM, Richert JR, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis.Neurology. 2001;57(12 Suppl 5):S25-S30.

O'Connor 2006
O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GP, Confavreux C, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology. 2006 Mar 28;66(6):894-900.

Study PRISMS
PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group.Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis.Lancet. 1998 Nov 7;352(9139):1498-504.

Related references:
Patten SB, Metz LM. Interferon beta-1 a and depression in relapsing-remitting multiple sclerosis: an analysis of depression data from the PRISMS clinical trial. MultScler. 2001 Aug;7(4):243-8.

Liu C, Blumhardt LD. Randomised, double blind, placebo-controlled study of interferon beta-1a in relapsing-remitting multiple sclerosis analysed by area under disability/time curves. J NeurolNeurosurg Psychiatry [Internet]. 1999 Oct [cited 2012 Nov 19];67(4):451-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1736573/pdf/v067p00451.pdf

Li DK, Paty DW. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-beta1a in relapsing-remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis. Ann Neurol. 1999 Aug;46(2):197-206.

Study REGARD
Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbifvsGlatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008 Oct;7(10):903-14.

Saida 2012
Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, et al. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis.MultScler. 2012;18(9):1269-77.

Study TEMSO
O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011 Oct 6;365(14):1293-303.

Related references:
O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. Supplementary appendix.NEngl J Med [Internet]. 2011 Oct 6 [cited 2012 Dec 7];365(14):1293-303. Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1014656/suppl_file/nejmoa1014656_appendix.pdf

Miller AE, O'Connor P, Wolinsky JS, Confavreux C, Kappos L, Olsson TP, et al. Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis. MultScler. 2012;18(11):1625-32.

Study TRANSFORMS
Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010 Feb 4;362(5):402-15.

Related references:
Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. Supplementary appendix.NEngl J Med [Internet]. 2010 Feb 4 [cited 2012 Dec 7];362(5):402-15. Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa0907839/suppl_file/nejm_cohen_402sa1.pdf

Study CombiRx
Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al. Randomized study combining interferon & glatiramer acetate in multiple sclerosis. Ann Neurol. 2013 Feb 19.

Combination Therapy

Study CombiRx
Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al. Randomized study combining interferon & glatiramer acetate in multiple sclerosis. Ann Neurol. 2013 Feb 19.

Freedman 2012
Freedman MS, Wolinsky JS, Wamil B, Confavreux C, Comi G, Kappos L, et al. Teriflunomide added to interferon-beta in relapsing multiple sclerosis: a randomized phase II trial. Neurology. 2012 Jun 5;78(23):1877-85.

Study GLANCE
Goodman AD, Rossman H, Bar-Or A, Miller A, Miller DH, Schmierer K, et al. GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study. Neurology [Internet]. 2009 Mar 3 [cited 2012 Nov 16];72(9):806-12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821836/pdf/6342.pdf

Study SENTINEL
Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue E-W, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):911-23.

Related references:
Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue E-W, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. Supplementary appendix.NEngl J Med [Internet]. 2006 Mar 2 [cited 2012 Dec 7];354(9):911-23. Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa044396/suppl_file/nejm_rudick_911sa1.pdf

Radue EW, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Rudick RA, et al. Natalizumab plus interferon beta-1a reduces lesion formation in relapsing multiple sclerosis. J Neurol Sci. 2010 May 15;292(1-2):28-35.
Rudick RA, Miller D, Hass S, Hutchinson M, Calabresi PA, Confavreux C, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. Ann Neurol. 2007 Oct;62(4):335-46.

Hutchinson M, Kappos L, Calabresi PA, Confavreux C, Giovannoni G, Galetta SL, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. J Neurol. 2009 Mar;256(3):405-15.

APPENDIX 8: EXCLUDED STUDY LIST

Inappropriate Study Design

Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Neurology. 1998 Mar;50(3):701-8.

Jongen PJ, Sindic C, Sanders E, Hawkins S, Linssen W, van ME, et al. Adverse events of interferon beta-1a: A prospective multi-centre international ich-gcp-based cro-supported external validation study in daily practice. PLoS ONE [Internet]. 2011 [cited 2012 Nov 26];6(10). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3201962/pdf/pone.0026568.pdf

O'Connor P, Comi G, Montalban X, Antel J, Radue EW, de Vera A, et al. Oral fingolimod (FTY720) in multiple sclerosis: two-year results of a phase II extension study. Neurology. 2009 Jan 6;72(1):73-9.

Manova MG, Kostadinova II, Akabaliev VC. A clinical study of multiple sclerosis patients treated with betaferon. Folia Med (Plovdiv). 2008 Jul;50(3):24-9.

Goodin DS, Reder AT, Ebers GC, Cutter G, Kremenchutzky M, Oger J, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNbeta-1b trial. Neurology. 2012 Apr 24;78(17):1315-22.

Schwid SR, Thorpe J, Sharief M, Sandberg-Wollheim M, Rammohan K, Wendt J, et al. Enhanced benefit of increasing interferon beta-1a dose and frequency in relapsing multiple sclerosis: The EVIDENCE study. Arch Neurol. 2005;62(5):785-92.

Wroe SJ. Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis.J Int Med Res [Internet]. 2005 May [cited 2013 Mar 13];33(3):309-18. Available from: http://www.jimronline.net/content/full/2005/60/0581.pdf

Inappropriate Intervention

Nafissi S, Azimi A, mini-Harandi A, Salami S, shahkarami MA, Heshmat R. Comparing efficacy and side effects of a weekly intramuscular biogeneric/biosimilar interferon beta-1a with Avonex in relapsing remitting multiple sclerosis: a double blind randomized clinical trial. ClinNeurolNeurosurg. 2012 Sep;114(7):986-9.

Patti F, L'Episcopo MR, Cataldi ML, Reggio A. Natural interferon-beta treatment of relapsing-remitting and secondary-progressive multiple sclerosis patients. A two-year study.ActaNeurol Scand. 1999 Nov;100(5):283-9.

Jacobs L, Salazar AM, Herndon R. Intrathecally administered natural human fibroblast interferon reduces exacerbations of multiple sclerosis: Results of a multicenter, double-blinded study. Arch Neurol. 1987;44(6):589-95.

Jacobs L, Salazar AM, Herndon R. Multicentre double-blind study of effect of intrathecally administered natural human fibroblast interferon on exacerbations of multiple sclerosis. Lancet. 1986;2(8521):1411-3.

Patti F, L'Episcopo MR, Cataldi ML, Reggio A. Natural interferon-beta treatment of relapsing-remitting and secondary-progressive multiple sclerosis patients. A two-year study. ActaNeurol Scand. 1999 Nov;100(5):283-9.

Jacques F, Gaboury I, Christie S, Grand'Maison F. Combination therapy of interferon beta-1b and tacrolimus: A pilot safety study. Multiple Sclerosis International [Internet]. 2012 [cited 2012 Nov 26]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3431088/pdf/MSI2012-935921.pdf

Filippi M, Wolinsky JS, Comi G, CORAL Study Group. Effects of oral glatiramer acetate on clinical and MRI-monitored disease activity in patients with relapsing multiple sclerosis: a multicentre, double-blind, randomised, placebo-controlled study. Lancet Neurol. 2006 Mar;5(3):213-20.

Milanese C, Salmaggi A, La ML, Campi A, Eoli M, Savoiardo M, et al. Double blind study of intrathecal beta-interferon in multiple sclerosis: Clinical and laboratory results. Journal of Neurology Neurosurgery and Psychiatry [Internet]. 1990;53(7):554-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC488128/pdf/jnnpsyc00517-0014.pdf

Polman C, Barkhof F, Kappos L, Pozzilli C, Sandbrink R, Dahlke F, et al. Oral interferon beta-1a in relapsing-remitting multiple sclerosis: a double-blind randomized study. MultScler. 2003 Aug;9(4):342-8.

Fernandez O, Antiquedad A, Arbizu T, Capdevila A, de CP, Correa de Sa JC, et al. Treatment of relapsing-remitting multiple sclerosis with natural interferon beta: a multicenter, randomized clinical trial. MultScler. 1995;1(Suppl 1):S67-S69.

Bornstein MB, Miller A, Slagle S, Weitzman M, Crystal H, Drexler E, et al. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. N Engl J Med. 1987 Aug 13;317(7):408-14.

Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med. 2006 Sep 14;355(11):1124-40.

Montalban X, Comi G, O'Connor P, Gold S, De VA, Eckert B, et al. Oral fingolimod (FTY720) in relapsing multiple sclerosis: impact on health-related quality of life in a phase II study. MultScler. 2011 Nov;17(11):1341-50

Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2003 Jan 2;348(1):15-23.

Dalton CM, Miszkiel KA, Barker GJ, MacManus DG, Pepple TI, Panzara M, et al. Effect of natalizumab on conversion of gadolinium enhancing lesions to T1 hypointense lesions in relapsing multiple sclerosis. J Neurol. 2004;251(4):407-13.

O'Connor PW, Goodman A, Willmer-Hulme AJ, Libonati MA, Metz L, Murray RS, et al. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. Neurology. 2004 Jun 8;62(11):2038-43.

Comi G, Cohen JA, Arnold DL, Wynn D, Filippi M, FORTE Study Group. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. Ann Neurol. 2011 Jan;69(1):75-82.

Cohen JA, Rovaris M, Goodman AD, Ladkani D, Wynn D, Filippi M, et al. Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS. Neurology. 2007 Mar 20;68(12):939-44.

The Once Weekly Interferon for MS Study Group. Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. Neurology. 1999 Sep 11;53(4):679-86.

Saida T, Tashiro K, Itoyama Y, Sato T, Ohashi Y, Zhao Z, et al. Interferon beta-1b is effective in Japanese RRMS patients: a randomized, multicenter study. Neurology. 2005 Feb 22;64(4):621-30.

Wynn D, Meyer C, Allen N, O'Brien D. Optimal dosing of immunomodulating drugs: A dose-comparison study of GA in RRMS. Progress in Neurotherapeutics and Neuropsychopharmacology. 2008;3(1):137-51.

Koch-Henriksen N, Sorensen PS, Christensen T, Frederiksen J, Ravnborg M, Jensen K, et al. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology. 2006 Apr 11;66(7):1056-60.

Inappropriate Population

Rieckmann P, Heidenreich F, Sailer M, Zettl UK, Zessack N, Hartung HP, et al. Treatment de-escalation after mitoxantrone therapy: Results of a phase IV, multicentre, open-label, randomized study of subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis. TherAdvNeurolDisord [Internet]. 2012 [cited 2012 Nov 26];5(1):3-12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3251902/pdf/10.1177_1756285611428503.pdf

Comi G, De SN, Freedman MS, Barkhof F, Polman CH, Uitdehaag BMJ, et al. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): A phase 3 randomised controlled trial. The Lancet Neurology. 2012;11(1):33-41.

Inappropriate Outcomes

Hurwitz BJ, Jeffery D, Arnason B, Bigley K, Coyle P, Goodin D, et al. Tolerability and safety profile of 12- to 28-week treatment with interferon beta-1b 250 and 500 microg QOD in patients with relapsing-remitting multiple sclerosis: a multicenter, randomized, double-blind, parallel-group pilot study. ClinTher. 2008 Jun;30(6):1102-12.

Rovaris M, Comi G, Ladkani D, Wolinsky JS, Filippi M, European/Canadian Glatiramer Acetate Study Group. Short-term correlations between clinical and MR imaging findings in relapsing-remitting multiple sclerosis. AJNR Am J Neuroradiol [Internet]. 2003 Jan [cited 2012 Nov 19];24(1):75-81. Available from: http://www.ajnr.org/cgi/reprint/24/1/75

Balcer LJ, Galetta SL, Polman CH, Eggenberger E, Calabresi PA, Zhang A, et al. Low-contrast acuity measures visual improvement in phase 3 trial of natalizumab in relapsing MS. J Neurol Sci. 2012 Jul 15;318(1-2):119-24.

Others

Kappos L, McDougall A, Frith J. Erratum: Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing-remitting multiple sclerosis (The Lancet (1998) November 7 (1498-1504)). Lancet. 1999;353(9153):678.

Kristoferitsch W, Seeldrayers P, Kyriallis K, Brochet B, Confavreux C, Clanet M, et al. Double-blind randomized multicenter dose-comparison study of interferon-beta-1a (AVONEX): Rationale, design and baseline data. MultScler. 2001;7(3):179-83.

Koch-Henriksen N, Sorensen PS. The Danish National Project of interferon-beta treatment in relapsing-remitting multiple sclerosis. The Danish Multiple Sclerosis Group.MultScler. 2000 Jun;6(3):172-5.

Lindsey JW, Scott TF, Lynch SG, Cofield SS, Nelson F, Conwit R, et al. The CombiRx trial of combined therapy with interferon and glatiramer acetate in relapsing remitting MS: Design and baseline characteristics. Multiple Sclerosis and Related Disorders. 2012;1(2):81-6.

Balcer LJ, Galetta SL, Calabresi PA, Confavreux C, Giovannoni G, Havrdova E, et al. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. Neurology. 2007 Apr 17;68(16):1299-304.

Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind, placebo-controlled trial. Neurology. 2001;57(12 Suppl 5):S16-S24.

Knobler RL, Greenstein JI, Johnson KP, Lublin FD, Panitch HS, Conway K, et al. Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up. J Interferon Res. 1993 Oct;13(5):333-40.

Kappos L, Gold R, Miller DH, MacManus DG, Havrdova E, Limmroth V, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet. 2008 Oct 25;372(9648):1463-72.

MacManus DG, Miller DH, Kappos L, Gold R, Havrdova E, Limmroth V, et al. BG-12 reduces evolution of new enhancing lesions to T1-hypointense lesions in patients with multiple sclerosis. J Neurol. 2011;258(3):449-56.

Kappos L, Gold R, Miller DH, MacManus DG, Havrdova E, Limmroth V, et al. Effect of BG-12 on contrast-enhanced lesions in patients with relapsing--remitting multiple sclerosis: subgroup analyses from the phase 2b study. MultScler. 2012 Mar;18(3):314-21.

APPENDIX 9: CHARACTERISTICS OF INCLUDED STUDIES

1. AFFIRM (2006)[9]

Methods	Phase 3, multi-centre, multi-country, randomized, double-blind, placebo-controlled trial.
Participants	942 patients were enrolled at 99 centres in Europe, North America, Australia, and New Zealand. *Inclusion criteria*: Age = 18 years to 50 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.0; had MRI lesions with MS, with ≥1 medially documented relapse within 12 months before the study began. *Exclusion criteria*: Primary-progressive, secondary-progressive, or progressive-relapsing; a relapse within 50 days before administration of the first dose of the study drug; treatment with cyclophosphamide or mitoxantrone within the previous year, or treatment with IFN beta, glatiramer acetate, cyclosporine, azathioprine, methotrexate, or IV immune globulin within the previous 6 months; treatment with IFN beta, glatiramer acetate, or both for more than 6 months.
Interventions	Patients were randomly assigned in a 2:1 ratio to receive natalizumab or placebo by IV infusion every 4 weeks for up to 116 weeks. **Natalizumab** 300 mg IV every 4 weeks (n = 627) **Placebo** (n = 315)
Outcomes	*Primary end points*: Rate of clinical relapse at 1 year; cumulative probability of sustained progression of disability at 2 years. *Secondary end points*: Different MRI outcomes at 1 and 2 years; proportion of relapse-free patients at 1 year; progression of disability at 2 years, measured by MSFC. *Tertiary end points*: HRQoL was assessed by SF-36 (PCS and MCS) and Subject Global Assessment Visual Analogue Scale.
Definitions	*Relapses*: New or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new neurologic signs found by the examining neurologist. *Sustained progression of disability*: An increase of 1.0 or more on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 12 weeks (progression could not be confirmed during a relapse).
Treatment history	Unclear (inadequate information to characterize).

2. BECOME (2009)[10]

Methods	Single-centre, rater-blinded, randomized controlled trial.
Participants	75 patients were enrolled at one centre in the US. *Inclusion criteria*: Age = 18 years to 55 years; treatment-naïve patients with RRMS (79%) or CIS (21%) suggestive of MS. Details of inclusion and exclusion criteria were reported in the website appendix.
Interventions	Patients were randomly assigned in a 1:1 ratio to receive IFN beta-1b (Betaseron) or glatiramer acetate (Copaxone) for 2 years. **Interferon beta-1b 250 mcg SC every other day** (n = 36) **Glatiramer acetate 20 mg SC q.d.** (n = 39)
Outcomes	Different MRI outcomes at 1 and 2 years. Confirmed relapse occurrences (annualized relapse rate, percent relapse-free).
Definitions	*Relapses*: All new or worsening symptoms lasting ≥ 24 hours and not explained by fever or infection that were confirmed by a blinded examining neurologist using worsening scores on SNRS or EDSS.
Treatment history	Treatment-naive (based on reported baseline characteristics).

3. BEYOND (2009)[11]

Methods	Phase 3, multi-centre, multi-country, randomized, rater-blinded, randomized controlled trial.
Participants	2,244 patients were enrolled at 198 centres in 26 countries worldwide. *Inclusion criteria*: Age = 18 years to 55 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.0; had MRI lesions with MS, with ≥ 1 relapse in the year before entry into the study. *Exclusion criteria*: Those who had signs or symptoms of other diseases not MS; progressive forms of MS; heart disease; treatment-experienced or participated in the previous trials of drug for MS; history of severe depression; alcohol or drug misuse; suicide attempts; serious or acute live, renal, or bone marrow dysfunction; monoclonal gammaglobulinopathy, or uncontrolled epilepsy; contraindication or allergy to the drug used in the study; unable to have MRI.
Interventions	Patients were randomly assigned in a 2:2:1 ratio to either 250 mcg or 500 mcg interferon beta-1b or 20 mg glatiramer for 2 to 3.5 years. **Interferon beta-1b 250 mcg SC every other day** (n = 897) **Glatiramer acetate 20 mg SC q.d.** (n = 448)
Outcomes	*Primary end points*: Relapse-based outcomes at year 2 (ARR, days to first relapse, proportion relapse-free). *Secondary end points*: Confirmed EDSS progression; MS-related admission to hospital, MS-related steroid course, different MRI outcomes.
Definitions	*Relapses*: New or recurrent neurological abnormalities that were separated by at least 30 days from the onset of the preceding event, lasted at least 24 hours, and occurred without fever or infection. *EDSS progression*: Measured as a 1-point change in the score that was sustained for 3 months.
Treatment history	Treatment-naive (based on inclusion criteria).

4. Calabrese et al. (2012)[12]

Methods	Single-centre, rater-blinded, randomized controlled trial.
Participants	165 patients were enrolled at one centre in Italy. *Inclusion criteria*: Age = 18 years to 55 years, diagnosis of RRMS (McDonald/Polman criteria), EDSS = 0 to 5.0 *Exclusion criteria*: Those previously treated with immunosuppressive drugs.
Interventions	Patients were randomly assigned (1:1:1) to receive IFN beta-1a (Rebif), IFN beta-1a (Avonex), or glatiramer acetate (Copaxone) for 2 years. **Interferon beta-1a 44 mcg SC t.i.w. (n = 55)** **Interferon beta-1a 30 mcg IM q.w. (n = 55)** **Glatiramer acetate 20 mg SC q.d. (n = 55)**
Outcomes	Different MRI outcomes. Annualized relapse rate. EDSS change.
Definitions	*Relapses*: Not reported.
Treatment history	Unclear (inadequate information to characterize).

5. CAMMS223 (2008)[13]

Methods	Phase 2 multi-centre, multi-country, rater-blinded, randomized controlled trial.
Participants	334 patients were enrolled at 49 centres in Europe and US. *Inclusion criteria*: Diagnosis of RRMS (McDonald criteria) with an onset of symptoms no more than 36 months before the time of screening, EDSS = 0 to 3.0; had one or more enhancing lesions on MRI; with ≥ 2 relapses during the previous 2 years. *Exclusion criteria*: Previous disease-modifying treatment; presence of serum antithyrotropin-receptor antibodies.
Interventions	Patients were randomly assigned (1:1:1) to receive alemtuzumab (either 12 mg per day or 24 mg per day) or IFN beta-1a (Rebif) for 3 years. **Alemtuzumab 12 mg IV q.d., 5 consecutive days at 1st month, 3 consecutive days at months 12 and 24** (n = 113) **Alemtuzumab 24 mg IV q.d.** (n = 110) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 111)
Outcomes	*Co-primary end points*: Sustained accumulation of disability and rate of relapse. *Secondary end points*: Proportion of patients with relapse-free MS, different MRI outcomes.
Definitions	*Relapses*: New or worsening symptoms with an objective change in neurologic examination attributable to MS that lasted 48 hours, that were present at normal body temperature, and that were preceded by at least 30 days of clinical stability. *Sustained accumulation of disability*: An increase of at least 1.5 points for patients with baseline score of 0, and at least 1.0 point for patients with a baseline score of 1.0 or more; all scores were confirmed twice during a 6-month period.
Treatment history	Treatment-naive (based on inclusion criteria),

6. CARE-MS I (2012)[14]

Methods	Phase 3 multi-centre, multi-country, rater-blinded, randomized controlled trial.
Participants	581 patients were enrolled at 101 centres in 16 countries including Europe, Canada, and US. *Inclusion criteria*: Age = 18 years to 50 years, diagnosis of RRMS (McDonald criteria) with disease duration up to 5 years, EDSS = 0 to 3.0; had cranial abnormalities on MRI attributable to MS; with ≥ 2 relapses during the previous 2 years. *Exclusion criteria*: Progressive disease course, previous MS disease therapy (apart from corticosteroids), previous immunosuppressive; investigational or monoclonal antibody therapy, clinically significant autoimmunity other than MS.
Interventions	Patients were randomly assigned (2:1) to receive alemtuzumab 12 mg per day or IFN beta-1a (Rebif) for 2 years. **Alemtuzumab 12 mg IV q.d., 5 consecutive days at month 0, 3 consecutive days at month 12** (n=386) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 195)
Outcomes	*Co-primary end points*: Relapse rate and time to 6 months sustained accumulation of disability. *Secondary end points*: Proportion of patients with relapse-free, change in EDSS, change in MSFC, different MRI outcomes.
Definitions	*Relapses*: New or worsening neurologic symptoms attributable to MS, lasting at least 48 hours, with pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination assessed by a masked rater. *Sustained accumulation of disability*: An increase from baseline of at least one EDSS point (or ≥ 1.5 points if baseline EDSS score was 0) confirmed over 6 months.
Treatment history	Treatment-naive (based on inclusion criteria).

7. CARE-MS II (2012)[15]

Methods	Phase 3 multi-centre, multi-country, rater-blinded, randomized controlled trial.
Participants	840 patients were enrolled at 194 centres in 23 countries including Europe, Canada, and US. *Inclusion criteria*: Age = 18 years to 50 years, diagnosis of RRMS (McDonald criteria) with disease duration up to 5 years, EDSS = 0 to 5.0; had cranial and spinal MRI lesions; with ≥ 2 relapses during the previous 2 years and at least one in the previous year. *Exclusion criteria*: Progressive forms of MS, previous cytotoxic drug use or investigational therapy, treatment within the previous 6 months with natalizumab, methotrexate, azathioprine or cyclosporine, and a history of clinically significant autoimmunity other than MS.
Interventions	Patients were randomly assigned (2:2:1) to receive alemtuzumab 12 mg per day, alemtuzumab 24 mg per day, or IFN beta-1a (Rebif) for 2 years. In December 2008, randomization in the alemtuzumab 24 mg group was discontinued to accelerate recruitment to the other two study groups. **Alemtuzumab 12 mg IV q.d., 5 consecutive days at month 0, 3 consecutive days at month 12** (n = 436) **Alemtuzumab 24 mg IV q.d.** (n = 173) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 231)
Outcomes	*Co-primary end points*: Relapse rate and time to 6 months sustained accumulation of disability. *Secondary end points*: Proportion of patients with relapse-free, change in EDSS, change in MSFC, different MRI outcomes.
Definitions	*Relapses*: New or worsening neurologic symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination. *Sustained accumulation of disability*: An increase from baseline of at least one EDSS point (or ≥ 1.5 points if baseline EDSS score was 0) confirmed over 6 months.
Treatment history	Treatment-experienced (based on inclusion criteria).

8. Clanet et al. (2002)[16]

Methods	Multi-centre, multi-country, double-blind, dose-comparison, randomized controlled trial.
Participants	840 patients were enrolled at 38 centres in Europe. *Inclusion criteria*: Age = 18 years to 55 years, with a relapsing form of MS (Poser et al.), EDSS = 2.0 to 5.5; had a clinical diagnosis of definite MS; with ≥ 2 relapses within 3 years before randomization. *Exclusion criteria*: Progressive forms of MS (defined as a continuous deterioration in neurologic function during the previous 6 months, without superimposed relapses during the previous 1 year); had a relapse within 2 months before randomization; pregnant or breastfeeding; with history of uncontrolled seizure, suicidal ideation, or severe depression; received treatment with IFN beta products within 3 months of randomization; investigational products for MS treatment or non-MS indications; chronic immunosuppressant therapy or chronic steroid therapy.
Interventions	Patients were randomly assigned (1:1) to receive IFN beta-1a 30 mcg or 60 mcg for at least 36 months. **Interferon beta-1a 30 mcg IM q.w.** (n = 402) **Interferon beta-1a 60 mcg IM q.w.** (n = 400)
Outcomes	*Primary end point*: Disability progression. *Secondary end point*: Relapse rate, annualized IV steroid use, percent of patients with relapse-free, different MRI outcomes.
Definitions	*Relapses*: Not reported. *Disability progression*: Time to a sustained increase of ≥ 1.0 point on the EDSS persisting for 6 months for subjects with baseline EDSS scores ≤ 4.5, or a 0.5 point increase for subjects with a baseline EDSS score ≥ 5.0.
Treatment history	Unclear (inadequate information to characterize).

9. Comi et al. (2001)[17]

Methods	Multi-centre, multi-country, randomized, double-blind, placebo-controlled trial.
Participants	239 patients were enrolled at 29 centres in 6 European countries and Canada. *Inclusion criteria*: Age = 18 years to 50 years, with relapse-remitting course, a diagnosis of MS for at least 1 year (Poser et al.), EDSS = 0 to 5.0; ≥1 documented relapse in the preceding 2 years, ≥ 1 enhancing lesion on screening brain MRI. *Exclusion criteria*: Previous use of glatiramer or oral myelin; prior lymphoid irradiation; use of immunosuppressant or cytotoxic agents in the past 2 years; use of azathioprine, cyclosporine, interferons, deoxyspergualine, or chronic corticosteroids during previous 6 months; receiving concomitant therapy with an experimental drug for MS or for another disease; serious intercurrent systemic or psychiatric illnesses; pregnant; unwilling to use contraceptive; hypersensitivity to gadolinium-diethylenetriaminepentaacetic acid; unable to undergo repeat MRI study.
Interventions	Patients were randomly assigned (1:1) to receive glatiramer acetate or placebo for 9 months. **Glatiramer acetate 20 mg SC q.d.** (n = 119) **Placebo** (n = 120)
Outcomes	*Primary end point*: Total number of enhancing lesions. *Secondary end points*: Other different MRI outcomes. *Tertiary end points*: Relapse rate, per cent of patients with relapse-free, steroid courses, relapse-related hospitalizations.
Definitions	*Relapses*: The appearance of one or more new neurological symptoms, or the reappearance of one or more previously experienced ones. An event was counted as a relapse only when the patient's symptoms were accompanied by objective changes in the neurological examination corresponding to an increase of at least 0.5 points on the EDSS, or one grade in the score of the two or more functional systems, or two grades in one functional system.
Treatment history	Unclear (inadequate information to characterize).

10. CONFIRM (2012)[18]

Methods	Phase 3, multi-centre, multi-country, rater-blinded, randomized, placebo-controlled trial.
Participants	14,30 patients were enrolled at 200 centres in 28 countries including Europe and North America. *Inclusion criteria*: Age = 18 years to 55 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.0; ≥1 clinically documented relapse in the previous 12 months, or ≥ 1 gadolinium-enhancing lesion 0 to 6 weeks before randomization. *Exclusion criteria*: Progressive forms of MS, other clinically significant illness, pre-specified laboratory abnormalities, and prior exposure to glatiramer acetate or contraindicated medications.
Interventions	Patients were randomly assigned (1:1:1:1) to receive oral placebo, dimethyl fumarate (BG-12) at dose of 240 mg b.i.d., BG-12 240 mg t.i.d., or glatiramer acetate for 2 years. **Dimethyl fumarate 240 mg oral b.i.d.** (n = 359) **Dimethyl fumarate 240 mg oral t.i.d.** (n = 345) **Placebo** (n = 363) **Glatiramer acetate 20 mg SC q.d.** (n = 350)
Outcomes	*Primary end point*: Annualized relapse rate at 2 years. *Secondary end points*: Different MRI outcomes at 2 years, disability progression. *Tertiary end points*: Relative benefits and risks of BG-12 or glatiramer acetate versus placebo and the number of gadolinium-enhancing lesions at 2 years.
Definitions	*Relapses*: New or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by at least 30 days. *Disability progression*: An increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later.
Treatment history	Mixed (based on reported baseline characteristics).

11. DEFINE (2012)[19]

Methods	Phase 3, multi-centre, multi-country, double-blind, randomized, placebo-controlled trial.
Participants	1,234 patients were enrolled at 198 centres in 28 countries including Europe, Canada, and US. *Inclusion criteria*: Age = 18 years to 55 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.0; ≥1 clinically documented relapse within 12 months before randomization, or ≥ 1 gadolinium-enhancing lesion within 6 weeks before randomization. *Exclusion criteria*: Progressive forms of MS, another major disease that would preclude participation in the clinical trial, abnormal results on the pre-specified laboratory tests, or recent exposure to contraindicated medications.
Interventions	Patients were randomly assigned (1:1:1) to receive oral placebo, dimethyl fumarate (BG-12) at dose of 240 mg b.i.d., or BG-12 240 mg t.i.d. for 2 years. **Dimethyl fumarate 240 mg oral b.i.d.** (n = 410) **Dimethyl fumarate 240 mg oral t.i.d.** (n = 416) **Placebo** (n = 408)
Outcomes	*Primary end point*: Proportion of patients who had a relapse by 2 years *Secondary end points*: Different MRI outcomes at 2 years, annualized relapse rate, time to progression disability.
Definitions	*Relapses*: New or recurrent neurologic symptoms, not associated with fever or infection, that lasted at least 24 hours and that were accompanied by new objective neurologic findings according to neurologist's evaluation. *Disability progression*: At least a 1.0-point increase on the EDSS in patients with a baseline score of 1.0 or higher or at least a 1.5-point increase in patients with a baseline score of 0, with the increased score sustained for at least 12 weeks.
Treatment history	Mixed (based on reported baseline characteristics).

12. Etemadifar et al. (2006)[20]

Methods	Single-centre, rater-blinded, randomized controlled trial.
Participants	90 patients were enrolled at one centre in Iran. *Inclusion criteria*: Age = 15 years to 50 years, diagnosis of relapsing MS (Poser et al.), EDSS = 0 to 5.0; ≥ 2 relapses within the 2-year period to treatment initiation documented by a neurologist. *Exclusion criteria*: History of severe allergic or anaphylactic reaction to any IFN, or to other components of drug formulation; evidence of neurologic, psychiatric, cardiac, endocrinologic, hematologic, hepatic, renal, active malignancy, autoimmune diseases, or other chronic disease; history of uncontrolled seizure or suicidal ideation or severe depression; lactation and pregnancy.
Interventions	Patients were randomly assigned (1:1:1) to receive Betaseron, Avonex and Rebif for 24 months. **Interferon beta-1b 250 mcg SC every other day** (n = 30) **Interferon beta-1a 30 mcg IM q.w.** (n = 30) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 30)
Outcomes	Number of relapses, proportion of relapse-free patients, EDSS scores.
Definitions	*Relapses*: The appearance of a new neurologic symptom, or severe deterioration in a pre-existing symptom that lasted 24 hours causing the deterioration in the EDSS with 1 point.
Treatment history	Unclear (inadequate information to characterize).

13. EVIDENCE (2002)[21]

Methods	Multi-centre, multi-country, rater-blinded, randomized, placebo-controlled trial.
Participants	677 patients were enrolled at 56 centres in Europe, Canada, and US. *Inclusion criteria*: Age = 18 years to 55 years, IFN-naive patients with definite RRMS (Poser et al.), EDSS = 0 to 5.5; ≥ 2 exacerbations of MS in the prior 2 years. *Exclusion criteria*: Previous use of IFN, cladribine, or total lymphoid irradiation; use of glatiramer acetate or cytokine therapy in the prior 3 months; use of IV immunoglobulin in the prior 6 months; and use of other immunomodulatory agents in the prior 12 months.
Interventions	Patients were randomly assigned (1:1) to receive either Avonex or Rebif for 24 weeks. **Interferon beta-1a 30 mcg IM q.w.** (n = 338) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 339)
Outcomes	*Primary end point*: Proportion of patients who were relapse-free at 24 weeks. *Secondary end points*: Relapse, disability, and MRI outcomes at 48 weeks.
Definitions	*Relapses*: The appearance of new symptoms or worsening of an old symptom, accompanied by an appropriate objective finding on neurologic examination by the blinded evaluator, lasting at least 24 hours in the absence of fever and preceded by at least 30 days of clinical stability or improvement. *Disability*: Progression by one point on the EDSS scale confirmed at a visit 3 or 6 months later without an intervening EDSS value that would not meet the criteria for progression.
Treatment history	Unclear (inadequate information to characterize).

14. FREEDOMS (2010)[22]

Methods	Phase 3, multi-centre, multi-country, double-blind, randomized, placebo-controlled trial.
Participants	1,272 patients were enrolled at centres in Australia, Canada, Europe, and South Africa. *Inclusion criteria*: Age = 18 years to 55 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.5; ≥ 1 relapse in the previous year or ≥ 2 relapses in the previous 2 years. *Exclusion criteria*: Relapse or corticosteroid treatment within 30 days before randomization, active infection, macular edema, diabetes mellitus, immune suppression (drug- or disease-induced), or clinically significant systemic disease.
Interventions	Patients were randomly assigned (1:1;1) to receive oral fingolimod capsules in a dose of 0.5 mg or 1.25 mg, or matching placebo, for 24 months. **Fingolimod oral 0.5 mg q.d.** (n = 425) **Placebo** (n = 418)
Outcomes	*Primary end point*: Annualized relapse rate. *Secondary end points*: Disability progression, time to a first relapse, EDSS change, MSFC change, different MRI outcomes.
Definitions	*Relapses*: A confirmed relapse constituted symptoms that must have been accompanied by an increase of at least half a point in the EDSS score, of 1 point in each of two EDSS functional system scores, or of 2 points in one EDSS functional system score (excluding scores for the bowel-bladder or cerebral functional systems). *Disability progression*: An increase of 1 point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.
Treatment history	Mixed (based on reported baseline characteristics).

15. IFNB-MS (1993)[23]

Methods	Multi-centre, double-blind, randomized, placebo-controlled trial.
Participants	372 patients were enrolled at different centres in Canada and the US. *Inclusion criteria*: Age = 18 years to 50 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.5; had ≥ 2 exacerbations during the previous 2 years; clinically stable for at least 30 days before entry and received no adrenocorticotrophic hormone or prednisone during this period. *Exclusion criteria*: Prior treatment with azathioprine or cyclophosphamide.
Interventions	Patients were randomly assigned (1:1:1) to receive Betaseron at dose of 50 mcg or 250 mcg or placebo for 3 years. **Interferon beta-1b 250 mcg SC every other day** (n = 124) **Placebo** (n = 123)
Outcomes	*Primary end points*: Annualized relapse rate, proportion of relapse-free patients *Secondary end points*: Time to first relapse, relapse duration and severity, change in EDSS, MRI outcomes.
Definitions	*Relapses*: The appearance of a new symptoms or worsening of an old symptom, attributable to MS; accompanied by an appropriate new neurologic abnormality; lasting at least 24 hours in the absence of fever; and preceded by stability or improvement for at least 30 days. *Disability progression*: A patient was considered to have progression in disability when there was a persistent increase of 1 or more EDSS points confirmed on two consecutive evaluations separated by at least 3 months.
Treatment history	Treatment-naive (based on year of study and clinical expert input).

16. IMPROVE (2010)[24]

Methods	Phase 3b, multi-centre, multi-country, double-blind, randomized, placebo-controlled trial.
Participants	180 patients were enrolled at centres in European countries. *Inclusion criteria*: Age = 18 years to 60 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.5; active disease (≥ 1 clinical event and ≥ 1 gadolinium-enhancing MRI lesion) within the 6 months period before randomization. *Exclusion criteria*: Not specified.
Interventions	Patients were randomly assigned (2:1) to receive Rebif or placebo for 16 weeks. **Interferon beta-1a 44 mcg SC t.i.w.** (n = 120) **Placebo** (n = 60)
Outcomes	*Primary end point*: Number of combined unique active MRI brain lesions at week 16. *Secondary end points*: Number of combined unique active lesions/patient/scan, other MRI outcomes, relapse rate.
Definitions	*Relapses*: Not reported.
Treatment history	Unclear (inadequate information to characterize).

17. INCOMIN (2002)[25]

Methods	Multi-centre, open label, rater-masked, randomized controlled trial.
Participants	188 patients were enrolled at 15 centres in Italy. *Inclusion criteria*: Age = 18 years to 50 years, clinically definite RRMS (Poser et al.), EDSS = 1-3.5; had two clinically documented relapses during the preceding 2 years, and no relapse (and no corticosteroid treatment) for at least 30 days before the study entry. *Exclusion criteria*: Previous systemic treatment with IFN beta or treatment with other immunosuppressive or immunomodulatory drugs (except corticosteroids); pregnancy, lactation, or an unwillingness to practice acceptable birth control; major depression or suicidal attempt; and clinically significant heart, liver, renal, or bone marrow disease.
Interventions	Patients were randomly assigned (1:1) to receive Avonex or Betaseron for 2 years. **Interferon beta-1a 30 mcg IM q.w.** (n = 92) **Interferon beta-1b 250 mcg SC every other day** (n = 96)
Outcomes	*Primary end point*: Proportions of patients free from relapses during 24 months. *Secondary end points*: Annualized relapse rate, annualized treated relapse rate, proportion of patients free from sustained and confirmed progression from disability, EDSS score, time to sustained and confirmed progression in disability.
Definitions	*Relapses*: The occurrence of new neurological symptoms or worsening of an old one, with an objective change of at least one point in Kurtzke Functional System Scores, lasting at least 24 hours, without fever, and which followed a period of clinical stability or of improvement of at least 30 days. *Disability progression*: An increase in EDSS of at least 1 point sustained for at least 6 months and confirmed at the end of follow-up.
Treatment history	Treatment-naive (based on exclusion criteria).

18. Johnson et al. (1995)[26]

Methods	Multi-centre, double-blind, randomized, placebo-controlled trial.
Participants	251 patients were enrolled at 11 centres in the US. *Inclusion criteria*: Age = 18 years to 45 years, clinically definite RRMS (Poser et al.), EDSS = 0 to 5.0; had ≥ 2 clinically documented relapses in the 2 years before entry; onset of the first relapse at least 1 year before randomization; and a period of neurologic stability and freedom from corticosteroid therapy of at least 30 days prior to entry. *Exclusion criteria*: Received copolymer 1 or previous immunosuppressive therapy with cytotoxic chemotherapy (azathioprine, cyclophosphamide, or cyclosporine) or lymphoid irradiation; pregnancy or lactation; insulin-dependent diabetes mellitus, positive HIV or HTL V-I serology, evidence of Lyme disease, or required use of aspirin or chronic nonsteroidal antiinflammatory drugs during the course of the trial.
Interventions	Patients were randomly assigned (1:1) to receive glatiramer acetate or placebo for 24 months. **Glatiramer acetate 20 mg SC q.d.** (n = 125) **Placebo** (n = 126)
Outcomes	*Primary end points*: Relapse rate over 24 months, annualized relapse rate, number of relapse over 24 months. *Secondary end points*: Proportion of relapse-free patients, median time to first relapse, number of relapse per patient, proportion of patients with a change in disability, EDSS change, proportion of progression-free patients, ambulation index.
Definitions	*Relapses*: The appearance or reappearance of one or more neurologic abnormalities persisting for at least 48 hours and immediately proceeded by a relatively stable or improving neurologic state of at least 30 days. *Disability progression*: An increase of at least one full step on the EDSS that persisted of at least 3 months.
Treatment history	Treatment-naive (based on exclusion criteria, year of study, and clinical expert input).

19. Kappos et al.(2011)[34]

Methods	Phase 2, multi-centre, open label rater-masked, randomized, placebo-controlled trial.
Participants	220 patients were enrolled at 79 centres in 20 countries. *Inclusion criteria*: Age = 18 years to 55 years, diagnosis of RRMS, EDSS = 1-6.0; had ≥ 2 relapses in previous 3 years. *Exclusion criteria*: SPMS or PPMS, disease duration more than 15 years in patients with EDSS of 2 or less; history or presence of other neurological systemic autoimmune disorders; treatment with rituximab or lymphocyte-depleting therapies; use of lymphocyte trafficking disorders within previous 24 weeks; use of beta interferons, glatiramer acetate, intravenous immunoglobulin, plasmapheresis, and immunosuppressive treatments within previous 12 weeks, use of systemic glucocorticoids within previous 4 weeks; or intolerance to IFN beta-1a.
Interventions	Patients were randomly assigned (1:1:1:1) to receive ocrelizumab low dose or high dose, IFN beta-1a, or placebo for 24 weeks. **Interferon beta-1a 30 mcg IM q.w.** (n = 55) **Placebo** (n = 54)
Outcomes	*Primary end point*: MRI outcomes. *Secondary end points*: Annualized relapse rate, proportion of relapse-free patients.
Definitions	*Relapses*: The occurrence of new or worsening neurological symptoms attributable to MS, and immediately preceded by a stable or improving neurological state of at least 30 days. *Disability progression*: An increase of 1 point or more from baseline EDSS score confirmed at the next scheduled examination 3 months after initial screening.
Treatment history	Mixed (based on reported baseline characteristics).

20. MSCRG (1996)[27]

Methods	Phase 3, multi-centre, double-blind, randomized, placebo-controlled trial.
Participants	301 patients were enrolled at 4 centres in the US. *Inclusion criteria*: Age = 18 years to 55 years, diagnosis of relapsing MS (complete and incomplete remissions) (Poser et al.), EDSS = 1 to 3.5; had ≥ 2 relapses in previous 3 years. *Exclusion criteria*: Prior immunosuppressant or IFN therapy; adrenocorticotropic hormone or corticosteroid treatment with 2 months of entry; pregnancy or nursing; unwillingness to practice contraception; presence of chronic-progressive MS, or any disease other than MS compromising organ function.
Interventions	Patients were randomly assigned (1:1) to receive Avonex or placebo for 2 years. **Interferon beta-1a 30 mcg IM q.w.** (n = 158) **Placebo** (n = 143)
Outcomes	*Primary end point*: Time to onset of sustained worsening in disability. *Secondary end points*: Proportion of patients with relapses, annualized relapse rate, different MRI outcomes.
Definitions	*Relapses*: The appearance of new neurological symptoms or worsening of pre-existing neurological symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days, accompanied by objective change on neurological examination. *Disability progression*: Deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months.
Treatment history	Treatment-naive (based on exclusion criteria, year of study, and clinical expert input).

21. O'Connor et. al (2006)[28]

Methods	Phase 2, multi-centre, double-blind, randomized, placebo-controlled trial.
Participants	179 patients were enrolled at centres in Canada. *Inclusion criteria*: Age = 18 years to 65 years, with RRMS (n = 157) or secondary-progressive MS with relapses (n = 22) (Poser et al.), EDSS = 0 to 6.0; had ≥ 2 documented relapses in previous 3 years, and one clinical relapse during the preceding year. *Exclusion criteria*: Prior treatment with IFN, gamma-globulin, glatiramer, or other non-corticosteroid immunomodulatory therapies in the 4 months prior to the trial.
Interventions	Patients were randomly assigned (1:1:1) to receive placebo or teriflunomide at 7 mg or 14 mg for 36 weeks. **Teriflunomide oral 7 mg q.d.** (n = 61) **Teriflunomide oral 14 mg q.d.** (n = 57) **Placebo** (n=61)
Outcomes	*Primary end point*: Number of combined unique active (new and persisting) lesions per MRI scan during 36 weeks. *Secondary end points*: Other MRI outcomes, number of patients experienced relapses, annualized relapse rate, number of relapsing patients required a course of steroids, EDSS change.
Definitions	*Relapses*: 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.
Treatment history	Treatment-naive (based in exclusion criteria, year of study, and clinical expert input).

22. PRISMS (1998)[29]

Methods	Multi-centre, multi-country, double-blind, randomized, placebo-controlled trial.
Participants	560 patients were enrolled at 22 centres in 9 countries including Australia, Canada, and Europe. *Inclusion criteria*: Adult RRMS patients (Poser et al.), EDSS = 0 to 5.0; had ≥ 2 relapses in previous 2 years. *Exclusion criteria*: Previous systemic treatment with IFN, lymphoid irradiation, or cyclophosphamide, or with other immunomodulatory or immunosuppressive treatments in the preceding 12 months.
Interventions	Patients were randomly assigned (1:1:1) to receive placebo or Rebif at 22 mcg or 44 mcg dose for 2 years. **Interferon beta-1a 22 mcg SC t.i.w.** (n = 189) **Interferon beta-1a 44 mcg SC t.i.w.** (n = 184) **Placebo** (n = 187)
Outcomes	*Primary end point*: Number of relapses. *Secondary end points*: Times to first and second relapse, proportion of relapse-free patients, disability progression, ambulation index, need for steroid therapy and hospitalization, and disease activity under MRI and burden of disease.
Definitions	*Relapses*: The appearance of a new symptom or worsening of an old symptom over at least 24 hours that could be attributed to MS activity and was preceded by stability or improvement for at least 30 days. *Disability progression*: An increase in EDSS of at least 1 point sustained over at least 3 months.
Treatment history	Treatment-naive (based on exclusion criteria, year of study, and clinical expert input).

23. REGARD (2008)[30]

Methods	Multi-centre, multi-country, randomized, comparative, parallel-group, open-label study, rater-masked.
Participants	764 patients were enrolled at 81 centres in 14 countries including Canada, South America, and Europe. *Inclusion criteria*: Adult RRMS patients (McDonald criteria), EDSS = 0 to 5.5; had ≥ 1 relapse in the preceding 12 months, and clinically stable or neurologically improving during the 4 weeks before randomization. *Exclusion criteria*: Pregnancy or breastfeeding; treatment with steroids or adrenocorticotropic hormone with the previous 4 weeks; previous treatment with IFN beta, glatiramer acetate, or cladribine; total lymphoid irradiation; plasma exchange within the previous 3 months; intravenous gamma-globulin use within the previous 6 months; cytokine or anti-cytokine therapy within the previous 3 months; or immunosuppressant use within the past 12 months.
Interventions	Patients were randomly assigned (1:1) to receive Rebif or glatiramer acetate for 96 weeks. **Interferon beta-1a 44 mcg SC t.i.w.** (n = 386) **Glatiramer acetate 20 mg SC q.d.** (n = 378)
Outcomes	*Primary end point*: Time to first relapse over 96 weeks. *Secondary end points*: Mean number T2 active lesions, mean number gadolinium-enhancing lesions, change in T2 lesion volume. *Tertiary outcomes*: Other MRI outcomes, relapse outcomes, disability progression.
Definitions	*Relapses*: New or worsening neurological symptoms, without fever, that lasted for 48 hours or more and was accompanied by a change in the Kurtzke Functional Systems Scores. *Disability progression*: Disability progression at the 6-month follow-up visit was confirmed, as follows — if the EDSS score at the baseline was 0, then a change of 1.5 points or more was required; if the EDSS was 0.5 - 4.5 at baseline, then a change of 1.0 point or more was required; and if the EDSS at baseline was 5 points or more, then the change required was 0.5 points or more.
Treatment history	Treatment-naive (based on inclusion criteria, year of study, and clinical expert input).

24. Saida et al. (2012)[31]

Methods	Phase 2, multi-centre, double-blind, randomized, placebo-controlled trial.
Participants	171 patients were enrolled at centres in Japan. *Inclusion criteria*: Age = 18 years to 60 years, diagnosis of RRMS (McDonald criteria), EDSS = 0 to 6.0; had ≥ 1 relapse in the previous year or ≥ 2 relapses in the previous 2 years; ≥ 1 gadolinium-enhancing lesion within 30 days before study commencement. *Exclusion criteria*: Primary-progressive MS; relapse or corticosteroid treatment within 30 days before randomization; malignancy, macular edema, diabetes mellitus, active infection, immunosuppression, or significant systemic disease; received cladribine, cyclophosphamide, mitoxantrone, or other immunosuppressive or immunoglobulin medication in the six months before randomization, or had plasmapheresis immunoadsorption or IFN beta therapy in the three months before randomization.
Interventions	Patients were randomly assigned (1:1:1) to receive placebo or fingolimod at 0.5 mg or 1.5 mg for 6 months. **Fingolimod oral 0.5 mg q.d.** (n = 57) **Placebo** (n = 57)
Outcomes	*Primary end point*: Percentage of patients free from GdE lesions at 3 and 6 months. *Secondary end points*: Percentage of patients free from relapse over 6 months, annualized relapse rate, and other MRI outcomes.
Definitions	*Relapses*: Not reported.
Treatment history	Unclear (inadequate information to characterize).

25. TEMSO (2011)[32]

Methods	Phase 3, multi-centre, multi-country, double-blind, randomized, placebo-controlled trial.
Participants	1,088 patients were enrolled at 127 centres in 21 countries including Canada, Europe, and US. *Inclusion criteria*: Age = 18 years to 55 years; diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.5; had ≥ 2 relapses in the previous 2 years or ≥ 1 relapse during the preceding year, but no relapse in the 60 days before randomization. *Exclusion criteria*: Had other systemic diseases; pregnant, or planned to conceive during the trial period.
Interventions	Patients were randomly assigned (1:1:1) to receive placebo or teriflunomide at 7 mg or 14 mg for 108 weeks. **Teriflunomide oral 7 mg q.d.** (n = 365) **Teriflunomide oral 14 mg q.d.** (n = 358) **Placebo** (n = 363)
Outcomes	*Primary end point*: Annualized relapse rate. *Secondary end points*: Disability progression (EDSS change), different MRI outcomes.
Definitions	*Relapses*: 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. *Disability progression*: 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.
Treatment history	Mixed (based on reported baseline characteristics).

26. TRANSFORMS (2010)[33]

Methods	Phase 3, multi-centre, multi-country, double-blind, randomized controlled trial.
Participants	1,292 patients were enrolled at 172 centres in 18 countries including Canada, Australia, Europe, and US. *Inclusion criteria*: Age = 18 years to 55 years; diagnosis of RRMS (McDonald criteria), EDSS = 0 to 5.5; had ≥ 1 relapse during the previous year or ≥ 2 relapses during the previous 2 years. *Exclusion criteria*: Documented relapse or corticosteroid treatment within 30 days before randomization; active infection, macular edema, immunosuppression, and clinically significant coexisting systemic disease.
Interventions	Patients were randomly assigned (1:1:1) to receive fingolimod at 0.5 mg or 1.25 mg or Avonex for 12 months. **Fingolimod oral 0.5 mg q.d.** (n = 431) **Interferon beta-1a 30 mcg IM q.w.** (n = 435)
Outcomes	*Primary end point*: Annualized relapse rate. *Secondary end points*: Number of new or enlarged T2-hyperintense lesions, time to confirmed disability progression.
Definitions	*Relapses*: New, worsening, or recurrent neurologic symptoms that occurred at least 30 days after the onset of preceding relapse, that lasted at least 24 hours without fever or infection. *Disability progression*: A one-point increase in the EDSS score (or a half-point increase for patients with a baseline score ≥ 5.5) that was confirmed 3 months later in the absence of relapse.
Treatment history	Mixed (based on reported baseline characteristics).

27. CombiRx (2013)[35]

Methods	Phase 3, multi-centre, US, and Canada, double-blind, randomized controlled trial.
Participants	1,008 patients were enrolled at 68 centres in the US and Canada. *Inclusion criteria*: Age = 18 years to 60 years, diagnosis or RRMS by Poser or McDonald criteria, EDSS = 0 to 5.5; had ≥ 2 relapses during the previous 3 years. *Exclusion criteria*: Not reported.
Interventions	Patients were randomly assigned (2:1:1) to receive IFN + glatiramer acetate or single agent with matching placebo for 3 years. **Interferon beta-1a 30 mcg IM q.w. + glatiramer acetate 20 mg SC q.d. (n = 499) Interferon beta-1a 30 mcg IM q.w. (n = 250) Glatiramer acetate 20 mg SC q.d. (n = 259)**
Outcomes	*Primary end point*: Annualized relapse rate. *Secondary end points*: Disability progression (EDSS change or MSFC change), different MRI outcomes.
Definitions	*Relapses*: New or worsening neurologic symptoms that lasted at least 24 hours without fever or infection, preceded by 30 days of stability. *Disability progression*: 1.0 increase in the EDSS from baseline, when baseline ≤ 5.0; or an increase of 0.5 from baseline, when baseline ≥ 5.5, sustained for 6 months (2 successive quarterly visits), as assessed by the blinded EDSS examiner and confirmed centrally.
Treatment history	Treatment-naive (based on exclusion criteria).

28. Freedman et al. (2012)[36]

Methods	Phase 2, multi-centre, multi-country, double-blind, randomized controlled trial.
Participants	118 patients were enrolled at 28 centres in 5 countries including Canada and the US. *Inclusion criteria*: Age = 18 years to 55 years, diagnosis of relapsing MS (with or without progression) by McDonald criteria, EDSS = 0 to 5.5; had no relapse for 8 weeks and clinically stable conditions for 4 weeks pre-study. All patients received a stable dose of IFN beta for at least 26 weeks before screening. *Exclusion criteria*: Not reported.
Interventions	Patients were randomly assigned (1:1:1) to receive placebo or teriflunomide 7 mg or 14 mg, in addition to IFN beta (Avonex, Rebif, Betaseron) for 24 weeks. **Teriflunomide 7 mg oral q.d. + interferon beta** (n = 37) **Teriflunomide 14 mg oral q.d. + interferon beta** (n = 38) **Placebo + interferon beta** (n = 41)
Outcomes	*Primary end points*: Safety outcomes. *Secondary end points*: MS relapses and MRI outcomes.
Definitions	Not reported.
Treatment history	Treatment-experienced (based on inclusion criteria).

29. GLANCE (2009)[37]

Methods	Phase 2, multi-centre, US and Canada, double-blind, randomized controlled trial.
Participants	110 patients were enrolled at 25 centres in the US and Canada. *Inclusion criteria*: Age = 18 years to 55 years, diagnosis of relapsing MS, EDSS = 0 to 5.0; had been treated with glatiramer acetate for at least 12 months before randomization and experienced one or more relapses during that time, and had cranial MRI lesions consistent with MS. *Exclusion criteria*: Progressive MS, MS relapse within 50 days before randomization, infectious illness within 30 days of randomization, abnormal laboratory results, history of severe allergic reaction, history of malignancy, pregnant women, planning to become pregnant or breastfeeding.
Interventions	Patients were randomly assigned (1:1) to receive placebo or natalizumab, in addition to glatiramer acetate for 24 weeks. **Natalizumab 300 mg IV every 4 weeks + glatiramer acetate 20 mg SC q.d.** (n = 55) **Placebo + glatiramer acetate 20 mg SC q.d.** (n = 55)
Outcomes	*Primary end points*: MRI outcomes. *Secondary end points*: MS relapses, disability.
Definitions	Not reported.
Treatment history	Treatment-experienced (based on inclusion criteria).

30. SENTINEL (2006)[38]

Methods	Phase 3, multi-centre, multi-country, double-blind, randomized controlled trial.
Participants	1,171 patients were enrolled at 124 centres in the US and Europe. *Inclusion criteria*: age = 18 years to 55 years, diagnosis of RRMS, EDSS = 0-5.0; had ≥ 1 relapse during the previous 12 months and an MRI scan revealing lesions of MS; had received treatment with IFN beta-1a for at least 12 months before randomization. *Exclusion criteria*: Primary-progressive, secondary-progressive, or progressive-relapsing MS; had a relapse within 50 days before randomization; had been treated with approved disease-modifying therapy other than IFN beta-1a IM q.w. within a 12-month period before randomization.
Interventions	Patients were randomly assigned (1:1) to receive placebo or natalizumab 300 mg IV every 4 weeks, in addition to IFN beta-1a IM q.w. for 116 weeks. **Natalizumab 300 mg IV every 4 weeks + interferon beta-1a 30 mcg IM q.w.** (n = 589) **Placebo + interferon beta-1a 30 mcg IM q.w.** (n = 582)
Outcomes	*Primary end point*: Disability progression. *Secondary end points*: MRI outcomes, rate of relapse.
Definitions	*Relapses*: New or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new, objective neurologic findings. *Disability progression*: An increase by at least 1.0 point in the EDSS score from a baseline score of at least 1.0, or an increase by at least 1.5 points in the EDSS score from a baseline score of 0, sustained for 12 weeks.
Treatment history	Treatment-experienced (based on inclusion criteria).

ARR = annualized relapse rate; b.i.d. = twice daily; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhanced; HRQoL = health-related quality of life; IFN = interferon; IV = intravenous; MCS = Mental Component Summary; MFSC = Multiple Sclerosis Functional Composite; mcg = microgram; mg = milligram; MRI = magnetic resonance imaging; MS = multiple sclerosis; PCS = Physical Component Summary; PPMS = primary-progressive multiple sclerosis; q.d. = once daily; q.w. = once weekly; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; t.i.d. = three times daily; t.i.w. = three times weekly.

APPENDIX 10: CRITICAL APPRAISAL OF INCLUDED STUDIES

Table A10.1: Assessment of Individual Study Quality

Study	Interventions	Randomization	Allocation Concealment	Double-Blinding	Baseline Characteristics Similarity	Outcome Measures	WDs	ITT Analysis	Funding
Monotherapy									
AFFIRM (2006)[9] (N = 942)	Natalizumab 300 mg IV e4w Placebo	Adequate	Adequate	Yes	Yes	Adequate	9%	Yes	Manufacturer
BECOME (2009)[10] (N = 75)	Interferon beta-1b 250 mcg SC q.o.d. Glatiramer acetate 20 mg SC q.d.	Insufficient reporting	Not reporting	No	Yes	Adequate	15%	Yes	Manufacturer
BEYOND (2009)[11] (N = 2,244)	Interferon beta-1b 250 mcg SC q.o.d. Glatiramer acetate 20 mg SC q.d.	Adequate	Adequate	No	Yes	Adequate	15%	Unclear	Manufacturer
Calabrese et al. (2012)[12] (N = 165)	Interferon beta-1a 44 mcg SC t.i.w. Interferon beta-1a 30 mcg IM q.w. Glatiramer acetate 20 mg SC q.d.	Adequate	Adequate	No	Yes	Adequate	15%	No	Manufacturer
CAMMS223 (2008)[13] (N = 334)	Alemtuzumab 12 mg IV q.d. Alemtuzumab 24 mg IV q.d. Interferon beta-1a 44 mcg SC t.t.w.	Adequate	Insufficient reporting	No	Yes	Adequate	25%	Yes	Manufacturer
CARE-MS I (2012)[14] (N = 581)	Alemtuzumab 12 mg IV q.d. Interferon beta-1a 44 mcg SC t.i.w.	Adequate	Adequate	No	Yes	Adequate	9%	Yes	Manufacturer
CARE-MS II (2012)[15] (N = 840)	Alemtuzumab 12 mg IV q.d. Alemtuzumab 24 mg IV q.d. Interferon beta-1a 44 mcg SC t.i.w.	Adequate	Adequate	No	Yes	Adequate	15%	Yes	Manufacturer
Clanet et al. (2002)[16] (N = 802)	Interferon beta-1a 30 mcg IM q.w. Interferon beta-1a 60 mcg IM q.w.	Insufficient reporting	Insufficient reporting	Yes	Yes	Adequate	30%	Yes	Manufacturer
Comi et al.	Glatiramer acetate 20 mg SC	Adequate	Adequate	Yes	Yes	Adequate	6%	Yes	Manufacturer

Table A10.1: Assessment of Individual Study Quality									
Study	**Interventions**	**Randomization**	**Allocation Concealment**	**Double-Blinding**	**Baseline Characteristics Similarity**	**Outcome Measures**	**WDs**	**ITT Analysis**	**Funding**
(2001)[17] (N = 239)	q.d. Placebo								
CONFIRM (2012)[18] **(**N = 1,430)	Dimethyl fumarate 240 mg oral b.i.d. Dimethyl fumarate 240 mg oral t.i.d. Placebo Glatiramer acetate 20 mg SC q.d.	Adequate	Adequate	No	Yes	Adequate	21%	Yes	Manufacturer
DEFINE (2012)[19] (N = 1,234)	Dimethyl fumarate 240 mg oral b.i.d. Dimethyl fumarate 240 mg oral t.i.d. Placebo	Adequate	Adequate	Yes	Yes	Adequate	23%	Yes	Manufacturer
Etemadifar et al. (2006)[20] (N = 90)	Interferon beta-1b 250 mcg SC q.o.d. Interferon beta-1a 30 mcg IM q.w. Interferon beta-1a 44 mcg SC t.i.w.	Insufficient reporting	Not reporting	No	No	Adequate	0%	Yes	Not reporting
EVIDENCE (2002)[21] (N = 677)	Interferon beta-1a 30 mcg IM q.w. Interferon beta-1a 44 mcg SC t.i.w.	Adequate	Adequate	No	Yes	Adequate	4%	Yes	Manufacturer
FREEDOMS (2010)[22] (N = 1,272)	Fingolimod oral 0.5 mg q.d. Placebo	Adequate	Adequate	Yes	Yes	Adequate	19%	Yes	Manufacturer
IFNB-MS (1993)[23] (N = 372)	Interferon beta-1b 250 mcg SC q.o.d. Placebo	Insufficient reporting	Not reporting	Yes	Yes	Adequate	33%	Yes	Not reporting
IMPROVE (2010)[24] (N = 180)	Interferon beta-1a 44 mcg SC t.i.w. Placebo	Insufficient reporting	Not reporting	Yes	Not reporting	Adequate	Not reporting	Yes	Manufacturer
INCOMIN (2002)[25] (N = 188)	Interferon beta-1a 30 mcg IM q.w. Interferon beta-1b 250 mcg SC q.o.d.	Adequate	Adequate	No	Yes	Adequate	16%	Yes	Public

Table A10.1: Assessment of Individual Study Quality									
Study	**Interventions**	**Randomization**	**Allocation Concealment**	**Double-Blinding**	**Baseline Characteristics Similarity**	**Outcome Measures**	**WDs**	**ITT Analysis**	**Funding**
Johnson et al.(1995)[26] (N = 251)	Glatiramer acetate 20 mg SC q.d. Placebo	Insufficient reporting	Not reporting	Yes	Yes	Adequate	14%	Yes	Manufacturer, Public
Kappos et al (2011)[34] (N = 218)	Interferon beta-1a 30 mcg IM q.w. Placebo	Insufficient reporting	Not reporting	No	No	Adequate	6%	Yes	Manufacturer
MSCRG (1996)[27] (N = 301)	Interferon beta-1a 30 mcg IM q.w. Placebo	Adequate	Adequate	Yes	Yes	Adequate	8%	Yes	Public, Manufacturer
O'Connor et al. (2006)[28] (N = 179)	Teriflunomide oral 7 mg q.d. Teriflunomide oral 14 mg q.d. Placebo	Insufficient reporting	Not reporting	Yes	Yes	Adequate	11%	Yes	Manufacturer
PRISMS (1998)[29] (N = 560)	Interferon beta-1a 22 mcg SC t.i.w. Interferon beta-1a 44 mcg SC t.i.w. Placebo	Adequate	Adequate	Yes	Yes	Adequate	10%	Yes	Manufacturer
REGARD (2008)[30] (N = 764)	Interferon beta-1a 44 mcg SC t.i.w. Glatiramer acetate 20 mg SC q.d.	Adequate	Adequate	Yes	Yes	Adequate	18%	Yes	Manufacturer
Saida et al. (2012)[31] (N = 171)	Fingolimod oral 0.5 mg q.d. Placebo	Insufficient reporting	Not reporting	Yes	Yes	Adequate	14%	No	Manufacturer
TEMSO (2011)[32] (N = 1,088)	Teriflunomide oral 7 mg q.d. Teriflunomide oral 14 mg q.d. Placebo	Adequate	Adequate	Yes	Yes	Adequate	27%	Yes	Manufacturer
TRANSFORMS (2010)[33] (N = 1,292)	Fingolimod oral 0.5 mg q.d. Interferon beta-1a 30 mcg IM q.w.	Adequate	Adequate	Yes	Yes	Adequate	11%	Yes	Manufacturer

Table A10.1: Assessment of Individual Study Quality									
Study	**Interventions**	**Randomization**	**Allocation Concealment**	**Double-Blinding**	**Baseline Characteristics Similarity**	**Outcome Measures**	**WDs**	**ITT Analysis**	**Funding**
CombiRx (2013)[35] (N = 1,008)	Interferon beta-1a 30 mcg IM q.w. + glatiramer acetate 20 mg SC q.d. Glatiramer acetate 20 mg SC q.d. Interferon beta-1a 30 mcg IM q.w.	Adequate	Adequate	Yes	Yes	Adequate	19%	Yes	Public
Combination Therapy									
CombiRx (2013)[35] (N = 1,008)	Interferon beta-1a 30 mcg IM q.w. + glatiramer acetate 20 mg SC q.d. Glatiramer acetate 20 mg SC q.d. Interferon beta-1a 30 mcg IM q.w.	Adequate	Adequate	Yes	Yes	Adequate	19%	Yes	Public
Freedman et al. (2012)[36] (N = 118)	Teriflunomide oral 7 mg q.d. + interferon beta Teriflunomide oral 14 mg q.d. + interferon beta Placebo + Interferon beta	Adequate	Not reporting	Yes	Yes	Adequate	8%	Yes	Manufacturer
GLANCE (2009)[37] (N = 110)	Natalizumab 300 mg IV e4w + glatiramer acetate 20 mg SC q.d. Placebo + Glatiramer acetate	Adequate	Not reporting	Yes	No	Adequate	6%	Yes	Manufacturer
SENTINEL (2006)[38] (N = 1,171)	Natalizumab 300 mg IV e4w + interferon beta-1a Placebo + interferon beta-1a	Adequate	Adequate	Yes	Yes	Adequate	14%	Yes	Manufacturer

b.i.d. = twice daily; e2w = every 2 weeks; e4w = every 4 weeks; q.o.d. = every other day; IM = intramuscular; IV = intravenous; ITT = intention to treat; mcg = microgram; mg = milligram; ; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.d. = three times daily; t.i.w. = three times weekly; WDs = withdrawals.

Table A10.2: MRI Populations Having Data on Number of GdE Lesions and Number of New or Enlarged T2 Lesions				
Study	**Population (GdE Lesions)**	**Study**	**Population (New or Enlarged T2 Lesions)**	**Selection Criteria for MRI Scans**
AFFIRM (2006)[9]	Full	AFFIRM	Full	
BEYOND (2009)[11]	Full	BEYOND	Full	
Calabrese et al. (2012)[12]	Full	Calabrese	Full	
Clanet et al. (2002)[16]	Partial (38%)	Clanet	Partial (38%)	A subset of patients who had annual MRIs. The sample size was calculated to provide 80% power. Selection criteria: unclear
CONFIRM (2012)[18]	Partial (42%)	CONFIRM	Partial (40%)	Patients in the ITT population for whom any post-baseline MRI data were available. Selection criteria: unclear
DEFINE (2012)[19]	Partial (38%)	DEFINE	Partial (38%)	Subgroups of patients at sites with full capabilities. Selection criteria: unclear
		EVIDENCE	Full	
FREEDOMS (2010)[22]	Partial (82%)	FREEDOMS	Partial (82%)	Appears to test full population, and the reported numbers were patients with available MRI data. Selection criteria: not reported
Johnson et al. (1995)[26]	Partial (11%)	Johnson	Partial (11%)	The cohort (n = 27) was from one centre of the multi-centre phase 3 trial. Selection criteria: not reported
MSCRG (1996)[27]	Partial (60%)	MSCRG	Partial (58%)	A subset of patients followed at year 2. Selection criteria: unclear
O'Connor et al. (2006)[28]	Full	O'Connor	Full	
REGARD (2008)[30]	Partial (60%)	REGARD	Partial (60%)	MRI scans were assessed in 60% of patients. The sample size was calculated to provide 85% power. Selection criteria: unclear
Saida et al. (2012)[31]	Full	Saida	Full	
TEMSO	Full			
TRANSFORM (2010)[33]	Partial (84%)	TRANSFORM	Partial (85%)	Appears to test full population, and the reported numbers were patients with available MRI data. Selection criteria: not reported

GdE = gadolinium-enhancing; ITT = intention to treat; MRI = magnetic resonance imaging; n = number.

APPENDIX 11: SUMMARY OF RESULTS FROM DIRECT AND INDIRECT COMPARISONS

Table A11.1: Summary of Efficacy Results From Direct Pairwise Meta-Analyses

			Relapse		Disability			MRI			
	Treatment Versus Comparator	**Study**	**ARR**	**Relapse-Free Patients**	**Disability Progression**	**Mean hange EDSS**	**Mean Change MSFC**	**Patients With GdE Lesions**	**Mean No. GdE Lesions**	**Patients With T2 Lesions**	**Mean No. T2 Lesions**
	Active compared with placebo										
1	IFN beta-1b 250 mcg SC versus placebo	IFNB-MS (1993)[23]	↑[a]	↔[b]	↔	nr	nr	nr	nr	nr	nr
2	IFN beta-1a 22 mcg SC versus placebo	PRISMS (1998)[29]	↑	↑	↔	↔	nr	nr	nr	nr	nr
3	IFN beta-1a 44 mcg SC versus placebo	IMPROVE (2010),[24] PRISMS (1998)[29]	↑	↑	↑	↑	nr	nr	nr	↑	nr
4	IFN beta-1a 30 mcg IM versus placebo	MSCRG (1996),[27] Kappos et al. (2011)[34]	↑	↔	↑	↑	nr	nr	↔	nr	↑
5	Glatiramer acetate versus placebo	Comi et al. (2001),[17] CONFIRM (2012),[18] Johnson et al. (1995)[26]	↑	↑	↔	↔	nr	nr	↑	nr	↑
6	Natalizumab versus placebo	AFFIRM (2006)[9]	↑	↑	↑	nr	nr	↑	↑	↑	↑
7	Fingolimod versus placebo	FREEDOMS (2010),[22] Saida et al. (2012)[31]	↑	↑	↑	↑	↑	↑	↑	↑	↑
8	Teriflunomide 7 mg versus placebo	O'Connor et al. (2006),[28] TEMSO (2011)[32]	↑	↑	↔	nr	nr	↑	↑	↑	↑
9	Teriflunomide 14 mg versus placebo	O'Connor et al. (2006),[28] TEMSO (2011)[32]	↑	↑	↑	nr	nr	↑	↑	↔	↑
10	Dimethyl fumarate 240 mg b.i.d. versus placebo	CONFIRM(2012),[18] DEFINE (2012)[19]	↑	↑	↑	nr	nr	↑	↑	nr	↑
	Interferon compared with interferon										
11	IFN beta-1a 44 mcg SC versus IFN beta-1b 250 mcg SC	Etemadifar et al. (2006)[20]	↔	↔	nr	↓[c]	nr	nr	nr	nr	nr
12	IFN beta-1b 250 mcg SC versus IFN beta-1a 30 mcg IM	Etemadifar et al. (2006),[20] INCOMIN (2002)[25]	↑	↑	↑	↑	nr	↑	nr	↑	nr
13	IFN beta-1a 44 mcg SC versus IFN beta-1a 30 mcg IM	Calabrese et al. (2012),[12] Etemadifar et al. (2006),[20] EVIDENCE (2002)[21]	↑	↑	↔	↔	nr	nr	↔	↑	↔
	Head-to-head comparisons										
14	IFN beta-1b 250 mcg SC versus glatiramer acetate	BECOME (2009),[10] BEYOND (2009)[11]	↔	↔	↔	nr	nr	nr	↔	nr	↑
15	IFN beta-1a 44 mcg SC versus glatiramer acetate	Calabrese et al. (2012),[12] REGARD (2008)[30]	↔	↔	↔	↔	nr	↑	↔	↔	↔
16	IFN beta-1a 30 mcg IM versus glatiramer acetate	Calabrese et al. (2012),[12] CombiRx (2013)[35]	↔	↔	↔	↔	↓	nr	↔	nr	↔
17	Dimethyl fumarate 240 mg b.i.d. versus glatiramer acetate	CONFIRM (2012)[18]	↑	↔	↔	nr	nr	nr	↔	nr	↑
18	Fingolimod versus IFN beta-1a 30 mcg IM	TRANSFORMS (2010)[33]	↑	↑	↔	↔	↑	↑	↑	↑	↑

Table A11.1: Summary of Efficacy Results From Direct Pairwise Meta-Analyses											
			Relapse		**Disability**			**MRI**			
19	Alemtuzumab 12 mg versus IFN beta-1a 44 mcg SC	CARE-MS I (2012),[14] CARE-MS II (2012),[15] CAMMS223 (2008)[13]	↑	↑	↑	↑ (CAMMS, MS II) ↔ (MS I)	↑	↑	nr	↑ (MS I, MS II) ↓ (CAMMS)	nr
20	Alemtuzumab 24 mg versus IFN beta-1a 44 mcg SC	CAMMS223 (2008)[13]	↑	↑	↑	↑	nr	nr	nr	↓	nr
	Dose comparisons										
21	Alemtuzumab 12 mg versus Alemtuzumab 24 mg	CAMMS223 (2008)[13]	↔	↔	↔	↔	nr	nr	nr	↔	nr
22	Teriflunomide 7 mg versus Teriflunomide 14 mg	O'Connor et al. (2006),[28] TEMSO (2011)[32]	↔	↔	↔	nr	nr	↓	↓	↔	↔
23	IFN beta-1a 22 mcg SC versus IFN beta-1a 44 mcg SC	PRISMS (1998)[29]	↔	↔	↔	↔	nr	nr	nr	nr	nr
24	IFN beta-1a 30 mcg IM versus IFN beta-1a 60 mcg IM	Clanet et al. (2002)[16]	↔	↔	↔	↔	nr	nr	↔	↓	↔

ARR = annualized relapse rate; b.i.d. = twice a day; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; IFN = interferon; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; nr = not reported; SC = subcutaneous.
↑[a] Superior; ↔[b] Not statistically significant; ↓ [c] Inferior.

Table A11.2: Summary of Safety Results From Direct Pairwise Meta-Analyses																
		Total Withdrawal	**Withdrawal Due to AE**	**Serious AEs**	**Flu-Like**	**Fatigue**	**Flushing**	**Infection**	**Depression**	**Infusion Reaction**	**Injection Site Reaction**	**Hyper-Sensitivity**	**Skin Disorders**	**Hepatic Disorders**	**Thyroid Disorders**	**GI Disorders**
Active compared with placebo																
1	IFN beta-1b 250 mcg	↔ [a]	↑ [b]	nr	nr	nr	nr	nr	↔	nr	↓ [c]	nr	nr	nr	nr	nr
2	IFN beta-1a 22 mcg	↔	↔	nr	↔	↔	nr	nr	↔	nr	↓	nr	nr	↓	nr	nr
3	IFN beta-1a 44 mcg	↔	↓	nr	↓	↔	nr	nr	↔	nr	↓	↔	↔	↓	↔	nr
4	IFN beta-1a 30 mcg	↔	↔	↔	↓	nr	nr	↑	nr	nr	nr	nr	nr	nr	nr	↓
5	Glatiramer acetate	↔	↔	↔	nr	↔	↔	↔	↔	nr	↓	↓	nr	↔	nr	↑
6	Natalizumab	↔	↔	↔	nr	↔	nr	↔	↔	↓	nr	↓	↓	↔	nr	↔
7	Fingolimod 0.5 mg	↑	↔	↔	nr	↔	nr	↔	↔	nr	nr	nr	↔	↓	nr	↓
8	Teriflunomide 7 mg	↔	↔	↔	nr	↔	nr	↔	nr	nr	nr	nr	↔	↓	nr	↓
9	Teriflunomide 14 mg	↔	↔	↔	nr	↔	nr	↔	nr	nr	nr	nr	↔	↓	nr	↓
10	Dimethyl fumarate	↔	↔	↔	nr	↔	↓	↔	↔	nr	nr	nr	nr	↓	nr	↓
Interferon compared with interferon																
11	IFN beta-1a 44 mcg versus IFN beta-1b 250 mcg	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
12	IFN beta-1b 250 mcg versus IFN beta-1a 30 mcg	↔	↔	nr	↔	↔	nr	nr	↔	nr	↓	nr	nr	↔	↔	nr
13	IFN beta-1a 44 mcg versus IFN beta-1a 30 mcg	↔	↔	↔	↔	nr	nr	nr	↔	nr	↓	nr	nr	↓	nr	nr
Head-to head comparisons																
14	IFN beta-1b 250 mcg versus glatiramer acetate	↑	↔	↔	↓	↔	nr	↔	↔	nr	↑	↑	nr	↓	nr	↔
15	IFN beta-1a 44 mcg versus glatiramer acetate	↓	↔	↔	↓	nr	nr	↑	↔	nr	↑	nr	nr	↓	nr	↔
16	IFN beta-1a 30 mcg versus glatiramer acetate	↓	↔	↔	↔	↔	nr	↔	↔	nr	↔	nr	↔	nr	nr	↔
17	Dimethyl fumarate versus glatiramer acetate	↔	↔	↔	nr	↔	↓	↔	↔	nr	nr	nr	nr	↔	nr	↓
18	Fingolimod versus IFN beta-1a 30 mcg	↔	↔	↔	↑	↔	nr	↔	↔	nr	nr	nr	nr	↓	nr	↓
19	Alemtuzumab 12 mg versus IFN beta-1a 44 mcg	↑	↑	↔	↑	↓	nr	↓	↔	nr	↑	nr	↓	↑	↓	↔
20	Alemtuzumab 24 mg versus IFN beta-1a 44 mcg	↑	↑	↔	↑	↓	nr	↓	↔	nr	↑	nr	↓	↑	↓	↔
Dose comparisons																
21	Alemtuzumab 12 mg versus Alemtuzumab 24 mg	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	nr	↔	↔	↔	↑
22	Teriflunomide 7 mg versus Teriflunomide 14 mg	↔	↔	↔	nr	↔	nr	↔	nr	nr	nr	nr	↔	↔	nr	↑
23	IFN beta-1a 22 mcg versus IFN beta-1a 44 mcg	↔	↔	nr	↔	↔	nr	nr	↔	nr	↔	nr	nr	↔	nr	nr
24	IFN beta-1a 30 mcg versus IFN beta-1a 60 mcg	↔	↑	nr	↑	nr	nr	nr	↔	nr	nr	nr	nr	nr	nr	nr

AE = adverse event; GI = gastrointestinal; IFN = interferon; mcg = microgram; mg = milligram; nr = not reported.

↔ [a] Not statistically significant.

↑ [b] Superior (lower incidence).

↓ [c] Inferior (higher incidence).

Table A11.3: Summary of Results for Pairwise Meta-Analysis and Network Meta-Analysis					
Treatment Versus Comparator		**Annualized Relapse Rate**		**Sustained Disability**	
		Pairwise MA RaR [95% CI]	**NMA RaR [95% CrI]**	**Pairwise MA RR [95% CI]**	**NMA RR [95% CrI]**
Active compared with placebo					
1	IFN beta-1b 250 mcg versus placebo	**0.71 [0.61, 0.81]**	**0.67 [0.59, 0.77]**	0.77 [0.56, 1.04]	**0.74 [0.50, 0.97]**
2	IFN beta-1a 22 mcg versus placebo	**0.71 [0.62, 0.82]**	**0.71 [0.60, 0.83]**	0.82 [0.63, 1.07]	0.89 [0.58, 1.23]
3	IFN beta-1a 44 mcg versus placebo	**0.67 [0.59, 0.78]**	**0.67 [0.59, 0.76]**	**0.71 [0.54, 0.95]**	0.84 [0.61, 1.08]
4	IFN beta-1a 30 mcg versus placebo	**0.81 [0.67, 0.96]**	**0.87 [0.76, 0.98]**	**0.63 [0.44, 0.92]**	0.87 [0.67, 1.09]
5	Glatiramer acetate versus placebo	**0.70 [0.55, 0.90]**	**0.67 [0.60, 0.74]**	0.92 [0.70, 1.20]	0.83 [0.65, 1.02]
6	Natalizumab versus placebo	**0.32 [0.27, 0.37]**	**0.32 [0.26, 0.38]**	**0.59 [0.46, 0.75]**	0.67 [0.40, 1.01]
7	Fingolimod 0.5 mg versus placebo	**0.46 [0.38, 0.54]**	**0.44 [0.37, 0.53]**	**0.72 [0.55, 0.94]**	0.76 [0.52, 1.04]
8	Teriflunomide 7 mg versus placebo	**0.69 [0.54, 0.84]**	**0.69 [0.56, 0.83]**	0.79 [0.61, 1.03]	0.85 [0.54, 1.19]
9	Teriflunomide 14 mg versus placebo	**0.68 [0.51, 0.84]**	**0.68 [0.56, 0.83]**	**0.74 [0.57, 0.96]**	0.80 [0.50, 1.15]
10	Dimethyl fumarate versus placebo	**0.51 [0.44, 0.60]**	**0.50 [0.42, 0.59]**	**0.66 [0.52, 0.84]**	**0.73 [0.53, 0.97]**
Interferon compared with interferon					
11	IFN beta-1a 44 mcg versus IFN beta-1b 250 mcg	0.86 [0.46, 1.61]	**0.97 [0.97, 0.98]**	NA	NA
12	IFN beta-1b 250 mcg versus IFN beta-1a 30 mcg	**0.69 [0.54, 0.87]**	**0.78 [0.77, 0.78]**	**0.44 [0.25, 0.80]**	**0.86 [0.76, 0.89]**
13	IFN beta-1a 44 mcg versus IFN beta-1a 30 mcg	**0.76 [0.59, 0.98]**	**0.78 [0.78, 0.78]**	0.87 [0.60, 1.28]	**0.96 [0.92, 0.99]**
Head-to-head Comparisons					
14	IFN beta-1b 250 mcg versus glatiramer acetate	1.06 [0.94, 1.20]	1.01 [0.99, 1.03]	1.04 [0.83, 1.31]	**0.90 [0.78, 0.94]**
15	IFN beta-1a 44 mcg versus glatiramer acetate	0.97 [0.78, 1.22]	1.01 [0.99, 1.02]	1.34 [0.87, 2.05]	1.01 [0.95, 1.06]

Table A11.3: Summary of Results for Pairwise Meta-Analysis and Network Meta-Analysis					
Treatment Versus Comparator		**Annualized Relapse Rate**		**Sustained Disability**	
		Pairwise MA RaR [95% CI]	**NMA RaR [95% CrI]**	**Pairwise MA RR [95% CI]**	**NMA RR [95% CrI]**
16	IFN beta-1a 30 mcg versus glatiramer acetate	1.25 [0.85, 1.85]	**1.30 [1.28, 1.32]**	0.87 [0.63, 1.20]	**1.05 [1.03, 1.07]**
17	Dimethyl fumarate versus glatiramer acetate	**0.76 [0.62, 0.93]**	**0.76 [0.71, 0.80]**	0.82 [0.57, 1.17]	**0.89 [0.82, 0.95]**
18	Fingolimod 0.5 mg versus IFN beta-1a 30 mcg	**0.49 [0.38, 0.63]**	**0.51 [0.48, 0.54]**	0.74 [0.45, 1.22]	**0.88 [0.78, 0.95]**
19	Alemtuzumab 12 mg versus IFN beta-1a 44 mcg	**0.44 [0.34, 0.55]**	**0.45 [0.42, 0.48]**	**0.59 [0.40, 0.86]**	**0.67 [0.52, 0.80]**
20	Alemtuzumab 24 mg versus IFN beta-1a 44 mcg	**0.22 [0.14, 0.35]**	**0.25 [0.17, 0.34]**	**0.42 [0.21, 0.84]**	**0.59 [0.32, 0.89]**
Dose comparisons					
21	Alemtuzumab 12 mg versus Alemtuzumab 24 mg	1.38 [0.82, 2.30]	**1.82 [1.41, 2.42]**	0.79 [0.32, 1.92]	1.13 [0.90, 1.62]
22	Teriflunomide 7 mg versus Teriflunomide 14 mg	1.04 [0.84, 1.29]	1.00 [1.00, 1.00]	1.08 [0.81, 1.43]	**1.05 [1.04, 1.07]**
23	IFN beta-1a 22 mcg versus IFN beta-1a 44 mcg	1.05 [0.90, 1.22]	**1.05 [1.02, 1.09]**	1.15 [0.85, 1.56]	1.06 [0.94, 1.14]
24	IFN beta-1a 30 mcg versus IFN beta-1a 60 mcg	0.95 [0.87, 1.04]	0.95 [0.88, 1.03]	1.00 [0.80, 1.26]	1.01 [0.86, 1.30]

CI = confidence interval; CrI = credible interval; IFN = interferon; MA = meta-analysis; mcg = microgram; mg = milligram; NMA = network meta-analysis; NA = not applicable; RaR = rate ratio.

APPENDIX 12: SUMMARY OF RESULTS FROM SUBGROUP ANALYSES

Table A12.1: Results of Sensitivity Analyses of ARR

Treatment	Base Case Results		Old Studies Removed[a]		Short-Duration Studies Removed[b]		Studies With Starting EDSS Score 0-3 or 1-3.5 Removed[c]	
		95% CrI		*95% CrI*		*95% CrI*		*95% CrI*
Alemtuzumab 12 mg	0.30	(0.25, 0.37)	0.31	(0.22, 0.41)	0.31	(0.25, 0.37)	0.34	(0.26, 0.44)
Alemtuzumab 24 mg	0.17	(0.1, 0.26)	0.17	(0.1, 0.28)	0.17	(0.1, 0.26)	NA	NA
Dimethyl fumarate 240 mg	0.50	(0.42, 0.59)	0.51	(0.42, 0.61)	0.51	(0.42, 0.61)	0.51	(0.42, 0.6)
Fingolimod 0.5 mg	0.44	(0.37, 0.53)	0.45	(0.36, 0.55)	0.44	(0.36, 0.53)	0.44	(0.37, 0.53)
Glatiramer acetate 20 mg	0.67	(0.6, 0.74)	0.67	(0.56, 0.8)	0.67	(0.59, 0.75)	0.67	(0.6, 0.75)
Interferon beta-1a 30 mcg	0.87	(0.76, 0.98)	0.90	(0.72, 1.11)	0.86	(0.76, 0.99)	0.87	(0.74, 1.04)
Interferon beta-1a 60 mcg	0.91	(0.75, 1.11)	0.95	(0.69, 1.26)	0.91	(0.74, 1.13)	0.92	(0.74, 1.16)
Interferon beta-1a 22 mcg	0.71	(0.6, 0.83)	NA	NA	0.71	(0.59, 0.85)	0.71	(0.6, 0.84)
Interferon beta-1a 44 mcg	0.67	(0.59, 0.76)	0.68	(0.52, 0.85)	0.68	(0.59, 0.77)	0.68	(0.59, 0.77)
Interferon beta-1b 250 mcg	0.67	(0.59, 0.77)	0.69	(0.54, 0.86)	0.67	(0.58, 0.77)	0.69	(0.59, 0.8)
Natalizumab 300 mg	0.32	(0.26, 0.38)	0.32	(0.25, 0.39)	0.31	(0.26, 0.39)	0.32	(0.26, 0.38)
Teriflunomide 7 mg	0.69	(0.56, 0.83)	0.69	(0.55, 0.86)	0.69	(0.55, 0.86)	0.69	(0.57, 0.84)
Teriflunomide 14 mg	0.68	(0.56, 0.83)	0.68	(0.54, 0.85)	0.69	(0.55, 0.86)	0.69	(0.56, 0.83)

ARR = annualized relapse rate; CrI = credible interval; EDSS = Expanded Disability Status Scale; mcg = microgram; mg = milligram; NA = not applicable.
[a]Published before year 2000 (IFNB-MS, Johnson, MSCRG, PRISMS).
[b]IMPROVE, Comi, O'Connor, Saida.
[c]CAMMS223, CARE-MS I, INCOMIN, MSCRG.

Table A12.2: Comparison of ARR Results between Base Case Model and Adjusted Models Using Select Covariates										
Treatment	**Base Case Results**		**Covariate: Time Since Symptom Onset**		**Covariate: Mean Relapses**		**Covariate: Baseline EDSS**		**Covariate: Treatment Duration**	
		95% CrI		*95% CrI*		*95% CrI*		*95% CrI*		*95% CrI*
Alemtuzumab 12 mg	0.30	(0.25, 0.37)	0.31	(0.25, 0.38)	0.30	(0.24, 0.37)	0.31	(0.24, 0.38)	0.30	(0.24, 0.37)
Alemtuzumab 24 mg	0.17	(0.1, 0.26)	0.17	(0.11, 0.28)	0.17	(0.1, 0.26)	0.17	(0.1, 0.27)	0.17	(0.1, 0.26)
Dimethyl fumarate 240 mg	0.50	(0.42, 0.59)	0.51	(0.43, 0.6)	0.50	(0.42, 0.6)	0.51	(0.42, 0.61)	0.50	(0.42, 0.6)
Fingolimod 0.5 mg	0.44	(0.37, 0.53)	0.45	(0.36, 0.56)	0.43	(0.33, 0.55)	0.44	(0.36, 0.53)	0.44	(0.37, 0.53)
Glatiramer acetate 20 mg	0.67	(0.6, 0.74)	0.68	(0.59, 0.78)	0.67	(0.59, 0.75)	0.67	(0.57, 0.79)	0.66	(0.59, 0.74)
Interferon beta-1a 30 mcg	0.87	(0.76, 0.98)	0.88	(0.76, 1.03)	0.86	(0.75, 0.99)	0.87	(0.76, 1.01)	0.86	(0.76, 0.98)
Interferon beta-1a 60 mcg	0.91	(0.75, 1.11)	0.92	(0.74, 1.16)	0.91	(0.73, 1.13)	0.92	(0.74, 1.14)	0.91	(0.74, 1.13)
Interferon beta-1a 22 mcg	0.71	(0.6, 0.83)	0.72	(0.6, 0.85)	0.71	(0.59, 0.85)	0.71	(0.59, 0.86)	0.71	(0.59, 0.84)
Interferon beta-1a 44 mcg	0.67	(0.59, 0.76)	0.69	(0.6, 0.79)	0.67	(0.58, 0.77)	0.68	(0.58, 0.8)	0.67	(0.59, 0.76)
Interferon beta-1b 250 mcg	0.67	(0.59, 0.77)	0.69	(0.58, 0.81)	0.68	(0.59, 0.78)	0.68	(0.56, 0.83)	0.67	(0.57, 0.77)
Natalizumab 300 mg	0.32	(0.26, 0.38)	0.31	(0.26, 0.38)	0.32	(0.26, 0.39)	0.31	(0.26, 0.38)	0.31	(0.26, 0.38)
Teriflunomide 7 mg	0.69	(0.56, 0.83)	0.72	(0.54, 0.98)	0.68	(0.56, 0.84)	0.70	(0.55, 0.88)	0.69	(0.56, 0.84)
Teriflunomide 14 mg	0.68	(0.56, 0.83)	0.72	(0.53, 0.98)	0.68	(0.55, 0.84)	0.69	(0.54, 0.89)	0.68	(0.56, 0.84)

ARR = annualized relapse rate; CrI = credible interval; EDSS = Expanded Disability Status Scale; mcg = microgram; mg = milligram.

Table A12.3: Results of Subgroup Analyses of ARR Based on Patient Treatment Experience						
Treatment	**Base Case Results**		**Treatment History — Naive[a]**		**Treatment History — Other[b]**	
		95% CrI		*95% CrI*		*95% CrI*
Alemtuzumab 12 mg	0.30	(0.25, 0.37)	0.27	(0.19, 0.37)	0.29	(0.17, 0.45)
Alemtuzumab 24 mg	0.17	(0.1, 0.26)	0.16	(0.09, 0.27)	NA	NA
Dimethyl fumarate 240 mg	0.50	(0.42, 0.59)	NA	NA	0.51	(0.4, 0.65)
Fingolimod 0.5 mg	0.44	(0.37, 0.53)	NA	NA	0.42	(0.32, 0.55)
Glatiramer acetate 20 mg	0.67	(0.6, 0.74)	0.64	(0.53, 0.77)	0.70	(0.55, 0.88)
Interferon beta-1a 30 mcg	0.87	(0.76, 0.98)	0.88	(0.72, 1.1)	0.76	(0.55, 1.03)
Interferon beta-1a 60 mcg	0.91	(0.75, 1.11)	NA	NA	0.80	(0.51, 1.22)
Interferon beta-1a 22 mcg	0.71	(0.6, 0.83)	0.71	(0.55, 0.91)	NA	NA
Interferon beta-1a 44 mcg	0.67	(0.59, 0.76)	0.67	(0.54, 0.83)	0.58	(0.38, 0.79)
Interferon beta-1b 250 mcg	0.67	(0.59, 0.77)	0.66	(0.54, 0.81)	0.52	(0.27, 0.95)
Natalizumab 300 mg	0.32	(0.26, 0.38)	NA	NA	0.31	(0.23, 0.44)
Teriflunomide 7 mg	0.69	(0.56, 0.83)	0.72	(0.39, 1.3)	0.68	(0.49, 0.96)
Teriflunomide 14 mg	0.68	(0.56, 0.83)	0.67	(0.37, 1.22)	0.68	(0.49, 0.96)

ARR = annualized relapse rate; CrI = credible interval; mcg = microgram; mg = milligram; NA = not applicable.
[a] Studies included BECOME, BEYOND, CAMMS223, CARE-MS I, IFNB-MS, INCOMIN, Johnson, MSCRG, O'Connor, PRIMS, and REGARD.
[b] Previous treatment status was unclear, experienced, or mixed. Studies included AFFIRM, Calabrese, CARE-MS II, Clanet., Comi, CONFIRM, DEFINE, Etemadifar, EVIDENCE, FREEDOMS, IMPROVE, Kappos, Saida, TEMSO, and TRANSFORMS.

Table A12.4: Results of Meta-Regression Analyses of ARR Based on Patient Treatment Experience						
Treatment	**Base Case Results**		**Treatment History — Naive[a]**		**Treatment History — Other[b]**	
		95% CrI		*95% CrI*		*95% CrI*
Alemtuzumab 12 mg	0.30	(0.25, 0.37)	0.30	(0.24, 0.37)	0.31	(0.24, 0.39)
Alemtuzumab 24 mg	0.17	(0.1, 0.26)	0.17	(0.1, 0.25)	0.17	(0.11, 0.26)
Dimethyl fumarate 240 mg	0.50	(0.42, 0.59)	0.49	(0.39, 0.62)	0.50	(0.42, 0.6)
Fingolimod 0.5 mg	0.44	(0.37, 0.53)	0.43	(0.35, 0.55)	0.45	(0.37, 0.53)
Glatiramer acetate 20 mg	0.67	(0.6, 0.74)	0.66	(0.58, 0.75)	0.68	(0.57, 0.79)
Interferon beta-1a 30 mcg	0.87	(0.76, 0.98)	0.86	(0.75, 0.99)	0.88	(0.73, 1.05)
Interferon beta-1a 60 mcg	0.91	(0.75, 1.11)	0.90	(0.74, 1.11)	0.94	(0.72, 1.17)
Interferon beta-1a 22 mcg	0.71	(0.6, 0.83)	0.71	(0.59, 0.84)	0.73	(0.57, 0.91)
Interferon beta-1a 44 mcg	0.67	(0.59, 0.76)	0.67	(0.58, 0.76)	0.69	(0.56, 0.82)
Interferon beta-1b 250 mcg	0.67	(0.59, 0.77)	0.67	(0.58, 0.77)	0.69	(0.56, 0.82)
Natalizumab 300 mg	0.32	(0.26, 0.38)	0.31	(0.24, 0.4)	0.32	(0.26, 0.38)
Teriflunomide 7 mg	0.69	(0.56, 0.83)	0.67	(0.53, 0.87)	0.69	(0.57, 0.84)
Teriflunomide 14 mg	0.68	(0.56, 0.83)	0.66	(0.52, 0.86)	0.68	(0.56, 0.83)

ARR = annualized relapse rate; CrI = credible interval; mcg = microgram; mg = milligram.

[a] Studies included BECOME, BEYOND, CAMMS223, CARE-MS I, IFNB-MS, INCOMIN, Johnson et al., MSCRG, O'Connor et al., PRIMS, and REGARD.

[b] Previous treatment status was unclear, experienced, or mixed. Studies included AFFIRM, Calabrese, CARE-MS II, Clanet, Comi, CONFIRM, DEFINE, Etemadifar, EVIDENCE, FREEDOMS, IMPROVE, Kappos, Saida., TEMSO, and TRANSFORMS.

Table A12.5: Results of Sensitivity Analyses for Sustained Disability Progression						
Treatment	**Base Case Results**		**Old Studies Removed[a]**		**Studies With Starting EDSS Score 0 to 3 or 1 to 3.5 Removed[b]**	
		95% CrI		*95% CrI*		*95% CrI*
Alemtuzumab 12 mg	0.56	(0.32, 0.87)	0.69	(0.25, 1.28)	0.60	(0.33, 0.97)
Alemtuzumab 24 mg	0.49	(0.2, 0.97)	0.62	(0.17, 1.37)	NA	NA
Dimethyl fumarate 240 mg	0.73	(0.53, 0.97)	0.75	(0.46, 1.1)	0.74	(0.56, 0.94)
Fingolimod 0.5 mg	0.76	(0.52, 1.04)	0.82	(0.46, 1.24)	0.76	(0.55, 1)
Glatiramer acetate 20 mg	0.83	(0.65, 1.02)	0.90	(0.53, 1.29)	0.86	(0.69, 1.03)
Interferon beta-1a 30 mcg	0.87	(0.67, 1.09)	1.01	(0.58, 1.45)	0.86	(0.64, 1.11)
Interferon beta-1a 60 mcg	0.86	(0.51, 1.27)	1.01	(0.42, 1.6)	0.86	(0.53, 1.23)
Interferon beta-1a 22 mcg	0.89	(0.58, 1.23)	NA	NA	0.89	(0.62, 1.19)
Interferon beta-1a 44 mcg	0.84	(0.61, 1.08)	0.99	(0.5, 1.49)	0.84	(0.64, 1.07)
Interferon beta-1b 250 mcg	0.74	(0.5, 0.97)	0.80	(0.33, 1.28)	0.85	(0.62, 1.09)
Natalizumab 300 mg	0.67	(0.4, 1.01)	0.67	(0.32, 1.15)	0.67	(0.44, 0.94)
Teriflunomide 7 mg	0.85	(0.54, 1.19)	0.85	(0.43, 1.33)	0.85	(0.58, 1.14)
Teriflunomide 14 mg	0.80	(0.5, 1.15)	0.80	(0.4, 1.29)	0.80	(0.54, 1.1)

CrI = credible interval; EDSS = Expanded Disability Status Scale; mcg = microgram; mg = milligram; NA = not applicable.
[a] Published before year 2000 (IFNB-MS, Johnson, MSCRG, PRISMS).
[b] CAMMS223, CARE-MS I, INCOMIN, MSCRG.

Table A12.6: Sustained Disability Progression Results Between Base Case Model and Adjusted Models Using Covariates										
Treatment	**Base Case**		**Covariate: Baseline EDSS**		**Covariate: Time Since Symptom Onset**		**Covariate: Treatment Duration**		**Covariate: Mean Relapses**	
		95% CrI		*95% CrI*		*95% CrI*		*95% CrI*		*95% CrI*
Alemtuzumab 12 mg	0.56	(0.32, 0.87)	0.56	(0.32, 0.86)	0.56	(0.32, 0.86)	0.56	(0.32, 0.86)	0.50	(0.27, 0.81)
Alemtuzumab 24 mg	0.49	(0.2, 0.97)	0.49	(0.2, 0.96)	0.49	(0.2, 0.96)	0.49	(0.2, 0.96)	0.44	(0.17, 0.91)
Dimethyl fumarate 240 mg	0.73	(0.53, 0.97)	0.73	(0.53, 0.97)	0.73	(0.53, 0.97)	0.73	(0.53, 0.97)	0.74	(0.54, 0.98)
Fingolimod 0.5 mg	0.76	(0.52, 1.04)	0.76	(0.52, 1.04)	0.76	(0.52, 1.04)	0.76	(0.52, 1.04)	0.76	(0.52, 1.03)
Glatiramer acetate 20 mg	0.83	(0.65, 1.02)	0.83	(0.65, 1.02)	0.83	(0.65, 1.02)	0.83	(0.65, 1.02)	0.86	(0.67, 1.07)
Interferon beta-1a 30 mcg	0.87	(0.67, 1.09)	0.87	(0.67, 1.09)	0.87	(0.67, 1.09)	0.87	(0.67, 1.09)	0.86	(0.67, 1.08)
Interferon beta-1a 60 mcg	0.86	(0.51, 1.27)	0.87	(0.51, 1.27)	0.87	(0.51, 1.27)	0.87	(0.51, 1.27)	0.86	(0.51, 1.26)
Interferon beta-1a 22 mcg	0.89	(0.58, 1.23)	0.89	(0.58, 1.23)	0.89	(0.58, 1.23)	0.89	(0.58, 1.23)	0.85	(0.55, 1.2)
Interferon beta-1a 44 mcg	0.84	(0.61, 1.08)	0.84	(0.61, 1.08)	0.84	(0.61, 1.08)	0.84	(0.61, 1.08)	0.76	(0.53, 1.04)
Interferon beta-1b 250 mcg	0.74	(0.5, 0.97)	0.74	(0.5, 0.97)	0.74	(0.5, 0.97)	0.74	(0.5, 0.97)	0.76	(0.52, 0.99)
Natalizumab 300 mg	0.67	(0.4, 1.01)	0.67	(0.41, 1.01)	0.67	(0.41, 1.01)	0.67	(0.41, 1.01)	0.67	(0.41, 1)
Teriflunomide 7 mg	0.85	(0.54, 1.19)	0.85	(0.54, 1.19)	0.85	(0.54, 1.19)	0.85	(0.54, 1.19)	0.85	(0.54, 1.19)
Teriflunomide 14 mg	0.80	(0.5, 1.15)	0.80	(0.5, 1.15)	0.80	(0.5, 1.15)	0.80	(0.5, 1.15)	0.80	(0.5, 1.14)

CrI = credible interval; EDSS = Expanded Disability Status Scale; mcg = microgram; mg = milligram.

Table A12.7: Results of Subgroup Analyses of Sustained Disability Progression Based on Patient Treatment Experience						
Treatment	**Base Case**		**Treatment History — Naive[a]**		**Treatment History — Other[b]**	
		95% CrI		*95% CrI*		*95% CrI*
Alemtuzumab 12 mg	0.56	(0.32, 0.87)	0.52	(0.14, 1.2)	0.64	(0, 1.99)
Alemtuzumab 24 mg	0.49	(0.2, 0.97)	0.48	(0.1, 1.33)	NA	NA
Dimethyl fumarate 240 mg	0.73	(0.53, 0.97)	NA	NA	0.76	(0.09, 1.79)
Fingolimod 0.5 mg	0.76	(0.52, 1.04)	NA	NA	0.80	(0.05, 1.9)
Glatiramer acetate 20 mg	0.83	(0.65, 1.02)	0.77	(0.42, 1.23)	0.92	(0.06, 1.92)
Interferon beta-1a 30 mcg	0.87	(0.67, 1.09)	0.81	(0.43, 1.32)	0.96	(0.03, 1.97)
Interferon beta-1a 60 mcg	0.86	(0.51, 1.27)	NA	NA	0.96	(0.01, 1.99)
Interferon beta-1a 22 mcg	0.89	(0.58, 1.23)	0.89	(0.36, 1.51)	NA	NA
Interferon beta-1a 44 mcg	0.84	(0.61, 1.08)	0.84	(0.4, 1.37)	0.88	(0.01, 1.99)
Interferon beta-1b 250 mcg	0.74	(0.5, 0.97)	0.68	(0.31, 1.14)	NA	NA
Natalizumab 300 mg	0.67	(0.4, 1.01)	NA	NA	0.68	(0.03, 1.91)
Teriflunomide 7 mg	0.85	(0.54, 1.19)	NA	NA	0.85	(0.04, 1.93)
Teriflunomide 14 mg	0.80	(0.5, 1.15)	NA	NA	0.80	(0.04, 1.93)

CrI = credible interval; mcg = microgram; mg = milligram; NA = not applicable.
[a] Studies included BECOME, BEYOND, CAMMS223, CARE-MS I, IFNB-MS, INCOMIN, Johnson, MSCRG, O'Connor, PRIMS, and REGARD.
[b] Previous treatment status was unclear, experienced, or mixed. Studies included AFFIRM, Calabrese, Johnson, CARE-MS II, Clanet, Comi, CONFIRM, DEFINE, Etemadifar, EVIDENCE, FREEDOMS, IMPROVE, Kappos, Saida, TEMSO, and TRANSFORMS.

Table A12.8: Results of Meta-Regression Analyses of Sustained Disability Progression Based on Patient Treatment Experience						
Treatment	**Base Case**		**Treatment History — Naive[a]**		**Treatment History — Other[b]**	
		95% CrI		*95% CrI*		*95% CrI*
Alemtuzumab 12 mg	0.56	(0.32, 0.87)	0.53	(0.3, 0.84)	0.65	(0.33, 1.07)
Alemtuzumab 24 mg	0.49	(0.2, 0.97)	0.46	(0.18, 0.94)	0.58	(0.22, 1.15)
Dimethyl fumarate 240 mg	0.73	(0.53, 0.97)	0.62	(0.35, 1)	0.75	(0.54, 1.01)
Fingolimod 0.5 mg	0.76	(0.52, 1.04)	0.66	(0.38, 1.04)	0.80	(0.54, 1.1)
Glatiramer acetate 20 mg	0.83	(0.65, 1.02)	0.77	(0.56, 1.02)	0.91	(0.64, 1.21)
Interferon beta-1a 30 mcg	0.87	(0.67, 1.09)	0.82	(0.6, 1.08)	0.97	(0.66, 1.29)
Interferon beta-1a 60 mcg	0.86	(0.51, 1.27)	0.81	(0.46, 1.25)	0.96	(0.53, 1.42)
Interferon beta-1a 22 mcg	0.89	(0.58, 1.23)	0.87	(0.56, 1.22)	1.02	(0.58, 1.45)
Interferon beta-1a 44 mcg	0.84	(0.61, 1.08)	0.80	(0.57, 1.07)	0.95	(0.6, 1.31)
Interferon beta-1b 250 mcg	0.74	(0.5, 0.97)	0.70	(0.47, 0.95)	0.85	(0.5, 1.19)
Natalizumab 300 mg	0.67	(0.4, 1.01)	0.54	(0.24, 1.02)	0.67	(0.4, 1.01)
Teriflunomide 7 mg	0.85	(0.54, 1.19)	0.70	(0.33, 1.21)	0.85	(0.53, 1.2)
Teriflunomide 14 mg	0.80	(0.5, 1.15)	0.66	(0.31, 1.16)	0.80	(0.5, 1.16)

CrI = credible interval; mcg = microgram; mg = milligram.
[a] Studies included BECOME, BEYOND, CAMMS223, CARE-MS I, IFNB-MS, INCOMIN, Johnson, MSCRG, O'Connor, PRIMS, and REGARD.
[b] Previous treatment status was unclear, experienced, or mixed. Studies included AFFIRM, Calabrese, CARE-MS II, Clanet, Comi, CONFIRM, DEFINE, Etemadifar, EVIDENCE, FREEDOMS, IMPROVE, Kappos, Saida, TEMSO, and TRANSFORMS.

APPENDIX 13: DETAILED DATA OF MONOTHERAPY TRIALS

Table A13.1: Data for Relapse — Annualized Relapse Rate

Study	Year	Treatment				1		2		3		4	
		1	2	3	4	Mean	SD	Mean	SD	Mean	SD	Mean	SD
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks (N = 627)	Placebo (N = 315)	NA	NA	0.23	0.57	0.73	1.19	NA	NA	NA	NA
BECOME (2009)[10]	2009	Interferon beta-1b 250 mcg SC every other day (N = 36)	Glatiramer acetate 20 mg SC q.d. (N = 39)	NA	NA	0.37	0.43	0.33	0.40	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day (N = 897)	Glatiramer acetate 20 mg SC q.d. (N = 448)	NA	NA	0.36	0.13	0.34	0.13	NA	NA	NA	NA
Calabrese et al. (2012)[12]	2012	Interferon beta-1a 44 mcg SC t.i.w. (N = 55)	Interferon beta-1a 30 mcg IM q.w. (N = 55)	Glatiramer acetate 20 mg SC q.d. (N = 55)	NA	0.40	0.60	0.50	0.60	0.50	0.40	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d. (N = 112)	Alemtuzumab 24 mg IV q.d. (N = 110)	Interferon beta-1a 44 mcg SC t.i.w. (N = 111)	NA	0.11	0.21	0.08	0.19	0.36	0.40	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d. (N = 386)	Interferon beta-1a 44 mcg SC t.i.w. (N = 195)	NA	NA	0.18	0.50	0.39	0.85	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d. (N = 436)	Alemtuzumab 24 mg IV q.d. (N = 173)	Interferon beta-1a 44 mcg SC t.i.w. (N = 231)	NA	0.26	0.63	NR	NR	0.52	0.90	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w. (N = 402)	Interferon beta-1a 60 mcg IM q.w. (N = 400)	NA	NA	0.77	0.58	0.81	0.58	NA	NA	NA	NA

Table A13.1: Data for Relapse — Annualized Relapse Rate													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Comi et al. (2001)[17]	2001	Glatiramer acetate 20 mg SC q.d. (N = 119)	Placebo (N = 120)	NA	NA	0.81	1.22	1.21	1.22	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d. (N = 359)	Placebo (N = 363)	Glatiramer acetate 20 mg SC q.d. (N = 350)	NA	0.22	0.48	0.40	0.78	0.29	0.57	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d. (N = 410)	Placebo (N = 408)	NA	NA	0.17	0.36	0.36	0.72	NA	NA	NA	NA
Etemadifar et al. (2006)[20]	2006	Interferon beta-1b 250 mcg SC every other day (N = 30)	Interferon beta-1a 30 mcg IM q.w. (N = 30)	Interferon beta-1a 44 mcg SC t.i.w. (N = 30)	NA	0.35	0.35	0.60	0.45	0.30	0.45	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w. (N = 338)	Interferon beta-1a 44 mcg SC t.i.w. (N = 339)	NA	NA	0.64	0.77	0.54	0.77	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d. (N = 425)	Placebo (N = 418)	NA	NA	0.18	0.37	0.40	0.68	NA	NA	NA	NA
IFNB-MS (1993)[23]	1993	Interferon beta-1b 250 mcg SC every other day (N = 124)	Placebo (N = 123)	NA	NA	0.78	0.48	1.12	0.59	NA	NA	NA	NA
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w. (N = 120)	Placebo (N = 60)	NA	NA	0.14	0.39	0.33	0.58	NA	NA	NA	NA

Table A13.1: Data for Relapse — Annualized Relapse Rate													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w. (N = 92)	Interferon beta-1b 250 mcg SC every other day (N = 96)	NA	NA	0.70	0.90	0.50	0.70	NA	NA	NA	NA
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d. (N = 125)	Placebo (N = 126)	NA	NA	0.59	0.56	0.84	0.68	NA	NA	NA	NA
Kappos et al. (2011)[34]	2011	Interferon beta-1a 30 mcg IM q.w. (N = 54)	Placebo (N = 54)	NA	NA	0.36	0.70	0.64	0.93	NA	NA	NA	NA
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w. (N = 158)	Placebo (N = 143)	NA	NA	0.67	0.63	0.82	0.63	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d. (N = 61)	Teriflunomide oral 14 mg q.d. (N = 57)	Placebo (N = 61)	NA	0.58	0.85	0.55	1.12	0.81	1.22	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w. (N = 189)	Interferon beta-1a 44 mcg SC t.i.w. (N = 184)	Placebo (N = 187)	NA	0.91	0.66	0.87	0.65	1.28	0.80	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w. (N = 386)	Glatiramer acetate 20 mg SC q.d. (N = 378)	NA	NA	0.30	0.64	0.29	0.64	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d. (N = 57)	Placebo (N = 57)	NA	NA	0.50	1.09	0.99	1.47	NA	NA	NA	NA

Table A13.1: Data for Relapse — Annualized Relapse Rate													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d. (N = 365)	Teriflunomide oral 14 mg q.d. (N = 358)	Placebo (N = 363)	NA	0.37	0.53	0.37	0.63	0.54	0.73	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d. (N = 431)	Interferon beta-1a 30 mcg IM q.w. (N = 435)	NA	NA	0.16	0.47	0.33	0.84	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w. (N = 250)	Glatiramer acetate 20 mg SC q.d. (N = 259)	NA	NA	0.16	0.30	0.11	0.30	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; SD = standard deviation; t.i.w. = three times weekly.

Table A13.2: Data for Relapse — Patients With Relapse-Free													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	454	627	146	315	NA	NA	NA	NA
BECOME (2009)[10]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	19	36	28	39	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	520	897	264	448	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	87	112	92	110	57	111	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	292	376	110	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	279	426	NR	NR	94	202	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 60 mcg IM q.w.	NA	NA	92	402	92	400	NA	NA	NA	NA
Comi et al. (2001)[17]	2001	Glatiramer acetate 20 mg SC q.d.	Placebo	NA	NA	66	119	59	120	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.	NA	255	359	214	363	238	350	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo (N = 408)	NA	NA	299	410	220	408	NA	NA	NA	NA

Table A13.2: Data for Relapse — Patients With Relapse-Free													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Etemadifar et al. (2006)[20]	2006	Interferon beta-1b 250 mcg SC every other day	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	13	30	6	30	17	30	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	177	338	209	339	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	299	425	191	418	NA	NA	NA	NA
IFNB-MS (1993)[23]	1993	Interferon beta-1b 250 mcg SC every other day	Placebo	NA	NA	27	124	17	123	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	33	92	49	96	NA	NA	NA	NA
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d.	Placebo	NA	NA	42	125	34	126	NA	NA	NA	NA
Kappos et al. (2011)[34]	2011	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	42	54	41	54	NA	NA	NA	NA
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	32	85	23	87	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	NR	NR	44	57	38	61	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	51	189	59	184	30	187	NA	NA

Table A13.2: Data for Relapse — Patients With Relapse-Free													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	239	386	234	378	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	45	57	37	57	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	196	365	202	358	166	363	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	354	429	299	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w. (N = 250)	Glatiramer acetate 20 mg SC q.d. (N = 259)	NA	NA	185	250	206	259	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; NR = not reported; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.3: Data for Disability — Patients With Disability Progression													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	107	627	91	315	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	188	897	90	448	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	8	112	10	110	24	111	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	30	376	20	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	54	426	NR	NR	40	202	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 60 mcg IM q.w.	NA	NA	109	402	108	400	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.	NA	47	359	62	363	56	350	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	NA	NA	66	409	110	408	NA	NA	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	49	338	43	339	NA	NA	NA	NA

Table A13.3: Data for Disability — Patients With Disability Progression													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	74	425	101	418	NA	NA	NA	NA
IFNB-MS (1993)[23]	1993	Interferon beta-1b 250 mcg SC every other day	Placebo	NA	NA	43	122	56	122	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	28	92	13	96	NA	NA	NA	NA
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d.	Placebo	NA	NA	27	125	31	126	NA	NA	NA	NA
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	35	158	50	143	NA	NA	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	64	189	54	184	77	187	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	45	386	33	378	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	79	365	72	358	99	363	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	25	429	34	431	NA	NA	NA	NA

Table A13.3: Data for Disability — Patients With Disability Progression													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w. (N = 250)	Glatiramer acetate 20 mg SC q.d. (N = 259)	NA	NA	52	241	61	246	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; NR = not reported; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; SD = standard deviation; t.i.w. = three times weekly.

Table A13.4: Data for Disability — Mean Change EDSS From Baseline													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Calabrese et al. (2012)[12]	2012	Interferon beta-1a 44 mcg SC t.i.w. (N = 55)	Interferon beta-1a 30 mcg IM q.w. (N = 55)	Glatiramer acetate 20 mg SC q.d. (N = 55)	NA	0.2	0.5	0.2	0.4	0.3	0.5	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d. (N = 107)	Alemtuzumab 24 mg IV q.d. (N = 108)	Interferon beta-1a 44 mcg SC t.i.w. (N = 104)	NA	-0.32	1.2	-0.45	1.22	0.38	1.33	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d. (N = 386)	Interferon beta-1a 44 mcg SC t.i.w. (N = 195)	NA	NA	-0.14	1.13	-0.14	1.04	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d. (N = 436)	Alemtuzumab 24 mg IV q.d. (N = 173)	Interferon beta-1a 44 mcg SC t.i.w. (N = 231)	NA	-0.17	1.26	NR	NR	0.24	1.23	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w. (N = 402)	Interferon beta-1a 60 mcg IM q.w. (N = 400)	NA	NA	0.36	1.40	0.33	1.40	NA	NA	NA	NA
Comi et al. (2001)[17]	2001	Glatiramer acetate 20 mg SC q.d. (N = 119)	Placebo (N = 120)	NA	NA	0.02	0.45	0.05	0.24	NA	NA	NA	NA
Etemadifar et al. (2006)[20]	2006	Interferon beta-1b 250 mcg SC every other day (N = 30)	Interferon beta-1a 30 mcg IM q.w. (N = 30)	Interferon beta-1a 44 mcg SC t.i.w. (N = 30)	NA	-0.70	0.54	-0.10	0.94	-0.30	0.63	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d. (N = 425)	Placebo (N = 418)	NA	NA	0.00	0.88	0.13	0.94	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w. (N = 92)	Interferon beta-1b 250 mcg SC every other day (N = 96)	NA	NA	0.54	0.96	0.13	0.89	NA	NA	NA	NA

Table A13.4: Data for Disability — Mean Change EDSS From Baseline													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d. (N = 125)	Placebo (N = 126)	NA	NA	-0.05	1.13	0.21	0.99	NA	NA	NA	NA
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w. (N = 158)	Placebo (N = 143)	NA	NA	0.02	1.04	0.61	1.35	NA	NA	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w. (N = 189)	Interferon beta-1a 44 mcg SC t.i.w. (N = 184)	Placebo (N = 187)	NA	0.23	1.30	0.24	1.10	0.48	1.30	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d. (N = 431)	Interferon beta-1a 30 mcg IM q.w. (N = 435)	NA	NA	-0.08	0.79	0.01	0.78	NA	NA	NA	NA

EDSS = Expanded Disability Status Scale; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; SD = standard deviation; t.i.w. = three times weekly.

Table A13.5: Data for Disability — Mean Change MSFC From Baseline													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d. (N = 386)	Interferon beta-1a 44 mcg SC t.i.w. (N = 195)	NA	NA	0.15	0.52	0.07	0.45	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d. (N = 436)	Alemtuzumab 24 mg IV q.d. (N = 173)	Interferon beta-1a 44 mcg SC t.i.w. (N = 231)	NA	0.08	0.42	NR	NR	-0.04	0.43	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d. (N = 425)	Placebo (N = 418)	NA	NA	0.03	0.39	–0.06	0.57	NA	NA	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d. (N = 431)	Interferon beta-1a 30 mcg IM q.w. (N = 435)	NA	NA	0.04	0.42	–0.03	0.48	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w. (N = 208)	Glatiramer acetate 20 mg SC q.d. (N = 215)	NA	NA	0.10	0.50	0.20	0.50	NA	NA	NA	NA

IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; MSFC = Multiple Sclerosis Functional Composite; N = number of patients in each arm; NA = not applicable; q.d. = once daily; q.w = once weekly; SC = subcutaneous; SD = standard deviation; t.i.w. = three times weekly.

Table A13.6: Data for MRI — Patients With Gadolinium-Enhancing Lesions													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	19	627	88	315	NA	NA	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	26	366	34	178	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d. (N = 173)	Interferon beta-1a 44 mcg SC t.i.w. (N = 231)	NA	38	410	NR	NR	44	190	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	NA	NA	10	152	62	165	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	38	369	116	332	NA	NA	NA	NA
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	NA	44	112	45	56	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	37	73	18	76	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	37	61	35	57	45	61	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	44	230	76	230	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	15	50	31	52	NA	NA	NA	NA

Table A13.6: Data for MRI — Patients With Gadolinium-Enhancing Lesions													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	170	350	122	340	211	346	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	37	374	68	354	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.7: Data for MRI — Mean Number of Gadolinium-Enhancing Lesions													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks (N = 627)	Placebo (N = 315)	NA	NA	0.2	2.7	2.4	6.3	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day (N = 897)	Glatiramer acetate 20 mg SC q.d. (N = 448)	NA	NA	0.9	3.33	1.20	3.33	NA	NA	NA	NA
Calabrese et al. (2012)[12]	2012	Interferon beta-1a 44 mcg SC t.i.w. (N = 55)	Interferon beta-1a 30 mcg IM q.w. (N = 55)	Glatiramer acetate 20 mg SC q.d. (N = 55)	NA	1.0	1.0	0.9	0.9	1.1	1.0	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w. (N = 152)	Interferon beta-1a 60 mcg IM q.w. (N = 152)	NA	NA	0.66	1.08	0.83	1.26	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d. (N = 147)	Placebo (N = 144)	Glatiramer acetate 20 mg SC q.d. (N = 161)	NA	0.5	1.7	2.0	5.6	0.7	1.8	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d. (N = 152)	Placebo (N = 165)	NA	NA	0.1	0.63	1.8	4.15	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d. (N = 369)	Placebo (N = 332)	NA	NA	0.2	0.8	1.1	2.4	NA	NA	NA	NA
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d. (N = 14)	Placebo (N = 13)	NA	NA	1.9	7.7	2.0	2.7	NA	NA	NA	NA
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w. (N = 83)	Placebo (N = 82)	NA	NA	0.8	2.0	1.65	4.35	NA	NA	NA	NA

Table A13.7: Data for MRI — Mean Number of Gadolinium-Enhancing Lesions													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d. (N = 61)	Teriflunomide oral 14 mg q.d. (N = 57)	Placebo (N = 61)	NA	0.87	2.42	0.86	2.42	2.25	2.50	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w. (N = 161)	Glatiramer acetate 20 mg SC q.d. (N = 174)	NA	NA	0.32	1.45	0.3	0.98	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d. (N = 50)	Placebo (N = 52)	NA	NA	0.1	0.3	1.4	2.2	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d. (N = 350)	Teriflunomide oral 14 mg q.d. (N = 340)	Placebo (N = 346)	NA	0.57	1.52	0.26	1.12	1.33	2.88	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d. (N = 374)	Interferon beta-1a 30 mcg IM q.w. (N = 354)	NA	NA	0.23	0.97	0.51	1.86	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; NA = not applicable; NR = not reported; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; SD = standard deviation; t.i.w. = three times weekly.

Table A13.8: Data for MRI — Patients With New or Enlarging T2-hyperintense Lesions													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	267	627	269	315	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	80	112	87	110	60	111	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	176	363	99	172	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	186	403	NR	NR	127	187	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 60 mcg IM q.w.	NA	NA	118	153	93	152	NA	NA	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	210	338	142	339	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	183	370	267	339	NA	NA	NA	NA
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	NA	25	112	28	56	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	54	73	34	76	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	32	61	34	57	46	61	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	137	230	144	230	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	17	48	32	50	NA	NA	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	168	372	196	361	NA	NA	NA	NA

IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.9: Data for MRI — Mean Number of New or Enlarging T2-hyperintense Lesions													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks (N = 627)	Placebo (N = 315)	NA	NA	1.9	9.2	11.0	15.7	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day (N = 897)	Glatiramer acetate 20 mg SC q.d. (N = 448)	NA	NA	3.3	8.8	4.6	8.8	NA	NA	NA	NA
Calabrese et al. (2012)[12]	2012	Interferon beta-1a 44 mcg SC t.i.w. (N = 55)	Interferon beta-1a 30 mcg IM q.w. (N = 55)	Glatiramer acetate 20 mg SC q.d. (N = 55)	NA	1.2	1.0	1.3	1.1	1.2	1.0	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w. (N = 153)	Interferon beta-1a 60 mcg IM q.w. (N = 152)	NA	NA	3.2	4.08	2.9	5.55	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d. (N = 140)	Placebo (N = 139)	Glatiramer acetate 20 mg SC q.d. (N = 153)	NA	5.1	8.08	17.4	26.53	8.0	12.21	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d. (N = 152)	Placebo (N = 165)	NA	NA	3.2	7.61	16.5	23.4	NA	NA	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w. (N = 338)	Interferon beta-1a 44 mcg SC t.i.w. (N = 339)	NA	NA	1.4	3.0	0.9	2.7	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d. (N = 370)	Placebo (N = 339)	NA	NA	2.5	7.2	9.8	13.2	NA	NA	NA	NA
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d. (N = 14)	Placebo (N = 13)	NA	NA	3.9	9.5	5.4	3.3	NA	NA	NA	NA

Table A13.9: Data for MRI — Mean Number of New or Enlarging T2-hyperintense Lesions													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w. (N = 78)	Placebo (N = 80)	NA	NA	3.2	3.6	4.8	4.4	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d. (N = 61)	Teriflunomide oral 14 mg q.d. (N = 57)	Placebo (N = 61)	NA	0.41	1.8	0.71	1.81	1.52	1.87	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w. (N = 161)	Glatiramer acetate 20 mg SC q.d. (N = 174)	NA	NA	0.77	2.28	0.58	1.5	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d. (N = 48)	Placebo (N = 50)	NA	NA	1.1	2.4	6.1	10.8	NA	NA	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d. (N = 372)	Interferon beta-1a 30 mcg IM q.w. (N = 361)	NA	NA	1.7	3.9	2.6	5.8	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; NA = not applicable; NR = not reported; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; SD = standard deviation; t.i.w. = three times weekly.

Table A13.10: Data for Safety — Death													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	2	627	0	312	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	0	897	1	448	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	1	113	1	110	0	111	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	1	376	0	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	2	435	0	161	0	202	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 60 mcg IM q.w.	NA	NA	1	402	1	400	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo (N = 363)	Glatiramer acetate 20 mg SC q.d.	NA	0	359	1	363	1	351	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo (N = 408)	NA	NA	1	410	0	408	NA	NA	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	0	337	1	339	NA	NA	NA	NA

Table A13.10: Data for Safety — Death													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	0	425	2	418	NA	NA	NA	NA
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	1	158	0	143	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	0	61	0	57	0	61	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	1	189	0	184	1	187	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	1	386	0	378	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	0	57	0	57	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	0	368	0	358	0	360	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	0	429	0	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	1	250	1	259	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.11: Data for Safety — Serious Adverse Events													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	119	627	75	312	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	100	897	57	448	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	43	108	73	108	87	107	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	69	376	27	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	85	435	30	161	44	202	NA	NA
Comi et al. (2001)[17]	2001	Glatiramer acetate 20 mg SC q.d.	Placebo	NA	NA	10	119	6	120	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.	NA	61	359	79	363	60	351	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	NA	NA	74	410	86	408	NA	NA	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	18	337	21	339	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	43	425	56	418	NA	NA	NA	NA

Table A13.11: Data for Safety — Serious Adverse Events													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Kappos et al. (2011)[34]	2011	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	2	54	2	54	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	5	61	7	57	7	61	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	29	381	27	375	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	5	57	3	57	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	52	368	57	358	46	360	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	30	429	25	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	38	250	30	259	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.12: Data for Safety — Treatment Discontinuation Due to Adverse Events													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	38	627	13	315	NA	NA	NA	NA
BECOME (2009)[10]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	4	36	4	39	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	13	897	8	448	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	2	113	1	110	13	111	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	5	376	11	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	14	426	6	170	15	202	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 60 mcg IM q.w.	NA	NA	45	402	64	400	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.	NA	44	359	38	363	35	351	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	NA	NA	65	410	55	408	NA	NA	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	14	337	16	339	NA	NA	NA	NA

Table A13.12: Data for Safety — Treatment Discontinuation Due to Adverse Events													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	32	425	32	418	NA	NA	NA	NA
IFNB-MS (1993)[23]	1993	Interferon beta-1b 250 mcg SC every other day	Placebo	NA	NA	1	124	10	123	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	1	92	5	96	NA	NA	NA	NA
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d.	Placebo	NA	NA	5	125	1	126	NA	NA	NA	NA
Kappos et al. (2011)[34]	2011	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	1	54	0	54	NA	NA	NA	NA
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	7	158	2	143	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7mg q.d.	Teriflunomide oral 14mg q.d.	Placebo	NA	3	61	8	57	4	61	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	6	189	9	184	2	187	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	23	386	19	378	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	6	57	3	57	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	36	368	39	358	29	360	NA	NA

Table A13.12: Data for Safety — Treatment Discontinuation Due to Adverse Events													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	24	429	16	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	17	250	11	259	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.13: Data for Safety — Total Withdrawal													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	52	627	31	315	NA	NA	NA	NA
BECOME (2009)[10]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	7	36	4	39	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	104	888	71	445	NA	NA	NA	NA
Calabrese et al. (2012)[12]	2012	Interferon beta-1a 44 mcg SC t.i.w.	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	9	55	8	55	7	55	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	21	113	18	110	45	111	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	9	376	14	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	10	426	6	170	27	202	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 60 mcg IM q.w.	NA	NA	84	402	84	400	NA	NA	NA	NA
COMI (2001)[17]	2001	Glatiramer acetate 20 mg SC q.d.	Placebo	NA	NA	7	119	7	120	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.	NA	75	359	85	363	58	350	NA	NA

Table A13.13: Data for Safety — Total Withdrawal													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	NA	NA	95	410	91	408	NA	NA	NA	NA
Etemadifar et al. (2006)[20]	2006	Interferon beta-1b 250 mcg SC every other day	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	0	30	0	30	0	30	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	14	338	14	339	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	56	425	86	418	NA	NA	NA	NA
IFNB-MS (1993)[23]	1993	Interferon beta-1b 250 mcg SC every other day	Placebo	NA	NA	24	124	23	123	NA	NA	NA	NA
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	NA	8	120	3	60	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	19	92	11	96	NA	NA	NA	NA
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d.	Placebo	NA	NA	19	125	17	126	NA	NA	NA	NA
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	14	158	9	143	NA	NA	NA	NA

Table A13.13: Data for Safety — Total Withdrawal													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Kappos et al. (2011)[34]	2011	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	3	54	0	54	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	2	61	11	57	4	61	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	12	189	5	184	10	187	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	85	386	54	378	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	9	57	6	57	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7mg q.d.	Teriflunomide oral 14mg q.d.	Placebo	NA	91	365	95	358	104	363	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	31	429	45	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	56	250	36	259	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.14: Data for Safety — Influenza-Like Symptoms													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	359	888	25	445	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	6	108	2	108	29	107	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	11	376	43	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	31	435	13	161	47	202	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 60 mcg IM q.w.	NA	NA	342	402	368	400	NA	NA	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	165	337	143	339	NA	NA	NA	NA
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	NA	64	120	11	60	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	68	88	72	94	NA	NA	NA	NA
Kappos et al. (2011)[34]	2011	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	10	54	0	54	NA	NA	NA	NA

Table A13.14: Data for Safety — Influenza-Like Symptoms													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	96	158	57	143	NA	NA	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	47	189	50	184	45	187	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	119	381	5	375	NA	NA	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	15	429	159	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	51	250	44	259	NA	NA	NA	NA

IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.15: Data for Safety — Fatigue													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	169	627	66	312	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	193	888	95	445	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	35	108	32	108	32	107	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	50	376	16	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	81	435	35	161	26	202	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.		37	359	33	363	30	351	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	48	425	45	418	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	52	88	45	94	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	6	61	7	57	10	61	NA	NA

Table A13.15: Data for Safety — Fatigue													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	27	189	34	184	29	187	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	44	429	45	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	40	250	42	259	NA	NA	NA	NA

IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.16: Data for Safety — Flushing													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	11	108	9	108	NR	NR	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.	NA	110	359	13	363	6	351	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	NA	NA	154	410	20	408	NA	NA	NA	NA
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d.	Placebo	NA	NA	13	125	2	126	NA	NA	NA	NA
Kappos et al. (2011)[34]	2008	Dimethyl fumarate 120 mg oral q.d.	Dimethyl fumarate 120 mg oral t.i.d.	Dimethyl fumarate 240 mg oral t.i.d.	Placebo	34	64	31	64	25	63	6	65

b.i.d. = twice daily; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; SC = subcutaneous; t.i.d. = three times daily; t.i.w. = three times weekly.

Table A13.17: Data for Safety — Infection													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	495	627	246	312	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	170	888	95	445	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	71	108	71	108	50	107	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	253	376	85	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	334	435	134	161	134	202	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.	NA	201	359	182	363	176	351	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	NA	NA	262	410	265	408	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	379	425	357	418	NA	NA	NA	NA
Kappos et al. (2011)[34]	2011	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	11	54	22	54	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	32	61	31	57	26	61	NA	NA

Table A13.17: Data for Safety — Infection													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	69	381	93	375	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	28	57	22	57	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7mg q.d.	Teriflunomide oral 14mg q.d.	Placebo	NA	121	368	130	358	133	360	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	183	429	181	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	69	250	75	259	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.d. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.18: Data for Safety — Depression													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	119	627	50	312	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	151	888	64	445	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	14	108	17	108	19	108	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 60 mcg IM q.w.	NA	NA	36	402	40	400	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.		24	359	35	363	30	351	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	61	337	58	339	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	33	425	28	418	NA	NA	NA	NA
IFNB-MS (1993)[23]	1993	Interferon beta-1b 250 mcg SC every other day	Placebo	NA	NA	19	124	15	123	NA	NA	NA	NA
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	NA	1	120	2	60	NA	NA	NA	NA

Table A13.18: Data for Safety — Depression													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	18	88	18	94	NA	NA	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	39	189	44	184	52	187	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	30	381	22	375	NA	NA	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	21	429	32	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	40	250	43	259	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.19: Data for Safety — Infusion Reactions													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	148	627	55	312	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	106	108	107	108	NA	NA	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	338	376	NA	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	393	435	156	161	NA	NA	NA	NA

IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.20: Data for Safety — Injection Site Reactions													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	427	888	259	445	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	4	108	3	108	58	107	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	19	376	87	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	40	435	17	161	56	202	NA	NA
Comi et al (2001)[17] .	2001	Glatirameracetate 20 mg SC q.d.	Placebo	NA	NA	84	119	34	120	NA	NA	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.		NA	359	0	363	60	351	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	93	337	282	339	NA	NA	NA	NA
IFNB-MS (1993)[23]	1993	Interferon beta-1b 250 mcg SC every other day	Placebo	NA	NA	86	124	7	123	NA	NA	NA	NA
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	NA	48	120	8	60	NA	NA	NA	NA

Table A13.20: Data for Safety — Injection Site Reactions													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	7	88	35	94	NA	NA	NA	NA
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d.	Placebo	NA	NA	113	125	74	126	NA	NA	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	115	189	114	184	41	187	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	21	381	142	375	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	15	250	26	259	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; NR = not reported; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.21: Data for Safety — Hypersensitivity													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks (N = 627)	Placebo (N = 315)	NA	NA	25	627	0	312	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day (N = 897)	Glatiramer acetate 20 mg SC q.d. (N = 448)	NA	NA	46	888	77	445	NA	NA	NA	NA
Comi et al. (2001)[17]	2001	Glatiramer acetate 20 mg SC q.d. (N = 119)	Placebo (N = 120)	NA	NA	45	119	16	120	NA	NA	NA	NA
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w. (N = 120)	Placebo (N = 60)	NA	NA	6	120	3	60	NA	NA	NA	NA
Johnson et al. (1995)[26]	1995	Glatiramer acetate 20 mg SC q.d. (N = 125)	Placebo (N = 126)	NA	NA	19	125	4	126	NA	NA	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w. (N = 386)	Glatiramer acetate 20 mg SC q.d. (N = 378)	NA	NA	0	381	19	375	NA	NA	NA	NA

IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; NR = not reported; q.d. = once daily; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.22: Data for Safety — Skin Disorders													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	138	627	47	312	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	28	108	27	108	15	107	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	44	376	7	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	193	435	96	161	11	202	NA	NA
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	NA	5	120	1	60	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	5	57	5	57	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	38	368	40	358	26	360	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	20	250	22	259	NA	NA	NA	NA

IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.23: Data for Safety — Cancer													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	5	627	1	312	NA	NA	NA	NA
BECOME (2009)[10]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	1	36	0	39	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	0	108	3	108	1	107	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	2	376	0	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	2	435	3	161	2	202	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.	NA	0	359	1	363	4	351	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	NA	NA	2	410	2	408	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	4	425	10	418	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	0	57	0	57	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	0	368	1	358	3	360	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	28	429	24	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	6	250	3	259	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.24: Data for Safety — Liver Enzyme Elevation													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	31	627	12	312	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	99	888	16	445	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	2	108	3	108	16	107	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	15	376	32	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	19	435	5	161	13	202	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Dimethyl fumarate 240 mg oral t.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.	20	359	20	344	23	363	24	351
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Dimethyl fumarate 240 mg oral t.i.d.	Placebo	NA	25	410	25	416	12	408	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	17	337	41	339	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	36	425	7	418	NA	NA	NA	NA

Table A13.24: Data for Safety — Liver Enzyme Elevation													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	NA	9	120	2	60	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	23	88	22	94	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	10	61	7	57	6	61	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	9	189	12	184	2	187	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	21	381	5	375	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	4	57	2	57	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	44	368	51	358	24	360	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	28	429	8	431	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.25: Data for Safety — Thyroid Disorders													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	28	108	21	108	3	107	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	68	376	12	187	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	69	435	31	161	10	202	NA	NA
IMPROVE (2010)[24]	2010	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	NA	5	120	1	60	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	2	88	5	94	NA	NA	NA	NA

IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.26: Data for Safety — Gastrointestinal Disorders													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	69	627	31	312	NA	NA	NA	NA
BEYOND (2009)[11]	2009	Interferon beta-1b 250 mcg SC every other day	Glatiramer acetate 20 mg SC q.d.	NA	NA	83	888	49	445	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	17	108	31	108	22	107	NA	NA
CONFIRM (2012)[18]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	Glatiramer acetate 20 mg SC q.d.	NA	85	359	57	363	29	351	NA	NA
DEFINE (2012)[19]	2012	Dimethyl fumarate 240 mg oral b.i.d.	Placebo	NA	NA	115	410	93	408	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	88	425	67	418	NA	NA	NA	NA
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	74	158	47	143	NA	NA	NA	NA
O'Connor et al. (2006)[28]	2006	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	12	61	17	57	6	61	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	25	381	28	375	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	13	57	6	57	NA	NA	NA	NA
TEMSO (2011)[32]	2011	Teriflunomide oral 7 mg q.d.	Teriflunomide oral 14 mg q.d.	Placebo	NA	87	368	113	358	58	360	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	72	429	50	431	NA	NA	NA	NA
CombiRx (2013)[35]	2013	Interferon beta-1a 30 mcg IM q.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	68	250	60	259	NA	NA	NA	NA

b.i.d. = twice daily; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.27: Data for Safety — Antibodies													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
AFFIRM (2006)[9]	2006	Natalizumab 300 mg IV every 4 weeks	Placebo	NA	NA	57	627	NA	NA	NA	NA	NA	NA
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg or 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	51	194	NR	NR	NA	NA	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	323	376	22	175	NA	NA	NA	NA
CARE-MS II (2012)[15]	2012	Alemtuzumab 12 mg or 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	483	596	23	178	NA	NA	NA	NA
Clanet et al. (2002)[16]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 60 mcg IM q.w.	NA	NA	9	402	23	400	NA	NA	NA	NA
EVIDENCE (2002)[21]	2002	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	7	330	84	335	NA	NA	NA	NA
IFNB-MS (1993)[23]	1993	Interferon beta-1b 250 mcg SC every other day	Placebo	NA	NA	56	124	14	123	NA	NA	NA	NA
INCOMIN (2002)[25]	2001	Interferon beta-1a 30 mcg IM q.w.	Interferon beta-1b 250 mcg SC every other day	NA	NA	4	67	15	69	NA	NA	NA	NA
MSCRG (1996)[27]	1996	Interferon beta-1a 30 mcg IM q.w.	Placebo	NA	NA	6	143	35	158	NA	NA	NA	NA
PRISMS (1998)[29]	1998	Interferon beta-1a 22 mcg SC t.i.w.	Interferon beta-1a 44 mcg SC t.i.w.	Placebo	NA	45	189	23	184	NR	NR	NA	NA
REGARD (2008)[30]	2008	Interferon beta-1a 44 mcg SC t.i.w.	Glatiramer acetate 20 mg SC q.d.	NA	NA	102	374	346	366	NA	NA	NA	NA

IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.28: Data for Safety — Cardiovascular Disorders (Bradycardia and Atrioventricular Block)													
Study	**Year**	**Treatment**				**1**		**2**		**3**		**4**	
		1	**2**	**3**	**4**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
CAMMS223 (2008)[13]	2008	Alemtuzumab 12 mg mg IV q.d.	Alemtuzumab 24 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	0	108	1	108	NR	NR	NA	NA
CARE-MS I (2012)[14]	2012	Alemtuzumab 12 mg IV q.d.	Interferon beta-1a 44 mcg SC t.i.w.	NA	NA	2	376	NR	NR	NA	NA	NA	NA
FREEDOMS (2010)[22]	2010	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	11	425	6	418	NA	NA	NA	NA
Saida et al. (2012)[31]	2012	Fingolimod oral 0.5 mg q.d.	Placebo	NA	NA	3	57	0	57	NA	NA	NA	NA
TRANSFORMS (2010)[33]	2010	Fingolimod oral 0.5 mg q.d.	Interferon beta-1a 30 mcg IM q.w.	NA	NA	4	429	0	431	NA	NA	NA	NA

IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; N = number of patients in each arm; n = number of patients with event; NA = not applicable; NR = not reported; q.d. = once daily; q.w. = once weekly; SC = subcutaneous; t.i.w. = three times weekly.

Table A13.29: Relapse-Related Data of Included Studies										
Study Number	**First Author**	**Study Name**	**Publication Year**	**Treatment**	**No. of Patients in Group**	**Total Person-years**	**Total Relapses**	**Mean ARR**	**SD**	**95% CI**
1	Polman	AFFIRM	2006	Natalizumab 300 mg IV	627	1200	276	0.23	0.57	0.19 to 0.28
				Placebo	315	578	422	0.73	1.19	0.62 to 0.87
2	Cadavid	BECOME	2009	Interferon beta-1b 250 mcg SC	36	68.04	25	0.37	0.43	0.24 to 0.53
				Glatiramer acetate 20 mg SC	39	70.59	23	0.33	0.4	0.21 to 0.48
3	O'Connor.	BEYOND	2009	Interferon beta-1b 250 mcg SC	897	2260	814	0.36	1.3	NR
				Glatiramer acetate 20 mg SC	448	1099.5	374	0.34	1.3	NR
4	Compston	CAMMS223	2008	Alemtuzumab 12 mg IV	112	309.09	34	0.11	0.21	0.08 to 0.16
				Alemtuzumab 24 mg IV	110	312.5	25	0.08	0.19	0.05 to 0.12
				Interferon beta-1a 44 mcg SC	111	247.22	89	0.36	0.4	0.29 to 0.44
5	Cohen	CARE-MS I	2012	Alemtuzumab 12 mg IV	376	661.11	119	0.18	0.5	0.13 to 0.23
				Interferon beta-1a 44 mcg SC	187	312.82	122	0.39	0.85	0.29 to 0.53
6	Coles	CARE-MS II	2012	Alemtuzumab 12 mg IV	426	907.69	236	0.26	0.63	0.21 to 0.33
				Interferon beta-1a 44 mcg SC	202	386.54	201	0.52	0.9	0.41 to 0.66
7	Comi		2001	Glatiramer acetate 20 mg SC	119	75.3	61	0.81	1.22	NR
				Placebo	120	75.2	91	1.21	1.22	NR
8	Panitch.	EVIDENCE	2002	Interferon beta-1a 30 mcg IM	338	304.2	195	0.64	0.77	NR
				Interferon beta-1a 44 mcg SC	339	304.71	165	0.54	0.77	NR
9	Kappos.	FREEDOMS	2010	Fingolimod oral 0.5 mg	425	810.3	146	0.18	0.37	0.15 to 0.22
				Placebo	418	766.3	307	0.4	0.68	0.34 to 0.47
10		IFNB-MS	1993	Interferon beta-1b 250 mcg SC	124	207	173	0.78	0.48	0.70 to 0.88
				Placebo	123	207	266	1.12	0.59	1.02 to 1.23
11	Durelli	INCOMIN	2002	Interferon beta-1a 30 mcg IM	92	180	126	0.7	0.9	NR
				Interferon beta-1b 250 mcg SC	96	190	95	0.5	0.7	NR
12	Johnson		1995	Glatiramer acetate 20 mg SC	125	273	161	0.59	0.56	0.5 to 0.7
				Placebo	126	250	210	0.84	0.68	0.73 to 0.97

Table A13.29: Relapse-Related Data of Included Studies										
Study Number	**First Author**	**Study Name**	**Publication Year**	**Treatment**	**No. of Patients in Group**	**Total Person-years**	**Total Relapses**	**Mean ARR**	**SD**	**95% CI**
13	Jacobs	MSCRG	1996	Interferon beta-1a 30 mcg IM	158	328	220	0.67	0.63	NR
				Placebo	143	305	250	0.82	0.63	NR
14		PRISMS	1998	Interferon beta-1a 22 mcg SC	189	378.02	344	0.91	0.66	0.82 to 1.01
				Interferon beta-1a 44 mcg SC	184	365.52	318	0.87	0.65	0.78 to 0.97
				Placebo	187	374.22	479	1.28	0.8	1.17 to 1.4
15	Mikol	REGARD	2008	Interferon beta-1a 44 mcg SC	386	669.5	201	0.3	0.64	NR
				Glatiramer acetate 20 mg SC	378	669.5	194	0.29	0.64	NR
16	Cohen	TRANSFORMS	2010	Fingolimod oral 0.5 mg	429	424.6	68	0.16	0.47	0.12 to 0.21
				Interferon beta-1a 30 mcg IM	431	415.7	137	0.33	0.84	0.26 to 0.42
17	Lublin	CombiRx	2013	Interferon beta-1a 30 mcg IM	250	604.4	97	0.16	0.30	NR
				Glatiramer acetate 20 mg SC	259	650.7	70	0.11	0.30	NR
Studies Requiring Imputation for Total Relapses and Observed Person-Years										
18	Saida		2012	Fingolimod oral 0.5 mg	57	24.51	12	0.5	1.09	0.29 to 0.87
				Placebo	57	24.51	24	0.99	1.47	0.67 to 1.45
19	O'Connor		2006	Teriflunomide oral 7 mg	61	37.6	22	0.58	0.85	NR
				Teriflunomide oral 14 mg	57	35	19	0.55	1.12	NR
				Placebo	61	37.59	30	0.81	1.22	NR
20	De Stefano	IMPROVE	2010	Interferon beta-1a 44 mcg SC	120	55.2	8	0.14	0.39	0.09 to 0.23
				Placebo	60	27.6	9	0.33	0.58	0.22 to 0.52
21	Fox	CONFIRM	2012	Dimethyl fumarate 240 mg oral	359	567.22	125	0.22	0.48	0.18 to 0.28
				Placebo	363	573.54	229	0.4	0.78	0.33 to 0.49
				Glatiramer acetate 20 mg SC	350	553	160	0.29	0.57	0.23 to 0.35
22	Gold	DEFINE	2012	Dimethyl fumarate 240 mg oral	410	631.4	107	0.17	0.36	0.14 to 0.21
				Placebo	408	628.32	226	0.36	0.72	0.30 to 0.44

Table A13.29: Relapse-Related Data of Included Studies										
Study Number	**First Author**	**Study Name**	**Publication Year**	**Treatment**	**No. of Patients in Group**	**Total Person-years**	**Total Relapses**	**Mean ARR**	**SD**	**95% CI**
23	Etemadifar		2006	Interferon beta-1b 250 mcg SC	30	60	21	0.35	0.35	NR
				Interferon beta-1a 30 mcg IM	30	60	36	0.6	0.45	NR
				Interferon beta-1a 44 mcg SC	30	60	18	0.3	0.45	NR
24	Calabrese		2012	Interferon beta-1a 44 mcg SC	55	93.5	37	0.4	0.6	NR
				Interferon beta-1a 30 mcg IM	55	93.5	47	0.5	0.6	NR
25	O'Connor	TEMSO	2011	Teriflunomide oral 7 mg	365	554.22	205	0.37	0.53	0.32 to 0.43
				Teriflunomide oral 14 mg	358	543.59	201	0.37	0.63	0.31 to 0.44
				Placebo	363	551.18	298	0.54	0.73	0.47 to 0.62
26	Kappos		2011	Interferon beta-1a 30 mcg IM	54	23.18	8	0.36	0.7	NR
				Placebo	54	23.18	15	0.64	0.93	NR
27	Clanet		2002	Interferon beta-1a 30 mcg IM	402	844.2	650	0.77	0.58	NR
				Interferon beta-1a 60 mcg IM	400	840	680	0.81	0.58	NR

ARR = annualized relapse rate; CI = confidence interval; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; No. = number; NR = not reported; SC = subcutaneous; SD = standard deviation.

APPENDIX 14: PAIRWISE META-ANALYSES

Table A14.1: Direct Estimates for Efficacy Outcomes					
Outcome	**No. of RCTs**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**Effect Size (Random)**	**[95% CI], *P* Value**
1. IFN beta-1b 250 mcg SC q.o.d. versus placebo					
Annualized relapse rate	1	247	NA	Ratio: 0.71	[0.61, 0.81], 0.000
Patients with relapse-free	1	247	NA	RR: 1.58	[0.91, 2.74], 0.11
Patients with disability progression	1	244	NA	RR: 0.77	[0.56, 1.04], 0.09
2. IFN beta-1a 22 mcg SC t.i.w. versus placebo					
Annualized relapse rate	1	376	NA	Ratio: 0.71	[0.62, 0.82], 0.000
Patients with relapse-free	1	376	NA	RR: 1.68	[1.12, 2.52], 0.01
Patients with disability progression	1	376	NA	RR: 0.82	[0.63, 1.07], 0.14
Mean change EDSS from baseline	1	376	NA	MD: –0.25	[–0.51, 0.01], 0.06
3. IFN beta-1a 44 mcg SC t.i.w. versus placebo					
Annualized relapse rate	2	551	--	Ratio: 0.67	[0.59, 0.78], 0.000
Patients with relapse-free	1	371	NA	RR: 2.00	[1.35, 2.95], 0.0005
Patients with disability progression	1	371	NA	RR: 0.71	[0.54, 0.95], 0.02
Mean change EDSS from baseline	1	371	NA	MD: –0.24	[–0.48, 0.00], 0.05
Patients with new or enlarging T2-hyperintense lesions	1	168	NA	RR : 0.45	[0.29, 0.69], 0.0003
4. IFN beta-1a 30 mcg IM q.w. versus placebo					
Annualized relapse rate	2	409	--	Ratio: 0.81	[0.67, 0.96], 0.016
Patients with relapse-free	2	280	56.4%, 0.13	RR: 1.15	[0.81, 1.65], 0.43
Patients with disability progression	1	301	NA	RR: 0.63	[0.44, 0.92], 0.02
Mean change EDSS from baseline	1	301	NA	MD: –0.59	[–0.86, –0.32], < 0.0001
Mean number of GdE lesions	1	165	NA	MD: –0.85	[–1.89, 0.19], 0.11
Mean number of new or enlarging T2-hyperintense lesions	1	158	NA	MD: –1.60	[–2.85, –0.35], 0.01
5. Glatiramer acetate 20 mg SC q.d. versus placebo					
Annualized relapse rate	3	1203	--	Ratio : 0.51	[0.27, 0.95], 0.034
Patients with relapse-free	3	1203	0%, 0.91	RR: 1.16	[1.05, 1.27], 0.004
Patients with disability progression	2	964	0%, 0.82	RR: 0.92	[0.70, 1.20], 0.52
Mean change EDSS from baseline	2	490	61.9%, 0.11	No pooling	

Table A14.1: Direct Estimates for Efficacy Outcomes					
Outcome	**No. of RCTs**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**Effect Size (Random)**	**[95% CI], *P* Value**
	1	251	NA	MD: –0.26	[–0.52, 0.00], 0.05
	1	239	NA	MD: –0.03	[–0.12, 0.06], 0.52
Mean Number of GdE lesions	2	332	0%, 0.59	MD: –1.24	[–2.18, –0.31], 0.009
Mean number of new or enlarging T2-hyperintense lesions	2	319	78.7%, 0.03	No pooling	
	1	27	NA	MD: –1.50	[–6.79, 3.79], 0.58
	1	292	NA	MD: –9.40	[–14.22, –4.58], 0.0001
Mean change EDSS from baseline	1	373	NA	MD: –0.01	[–0.25, 0.23], 0.94
6. Natalizumab 300 mg IV e4w versus placebo					
Annualized relapse rate	1	942	NA	Ratio: 0.32	[0.27, 0.37], 0.000
Patients with relapse-free	1	942	NA	RR: 1.56	[1.37, 1.78], < 0.00001
Patients with disability progression	1	942	NA	RR: 0.59	[0.46, 0.75], < 0.0001
Patients with GdE lesions	1	942	NA	RR: 0.11	[0.07, 0.17], < 0.00001
Mean number of GdE lesions	1	942	NA	MD: –2.20	[–2.93, –1.47], < 0.00001
Patients with new or enlarging T2-hyperintense lesions	1	942	NA	RR: 0.50	[0.45, 0.55], < 0.00001
Mean number of new or enlarging T2-hyperintense lesions	1	942	NA	MD: –9.10	[–10.98, –7.22], < 0.00001
7. Fingolimod 0.5 mg oral q.d. versus placebo					
Annualized relapse rate	2	957	--	Ratio: 0.46	[0.38, 0.54], 0.000
Patients with relapse-free	2	957	68.5%, 0.07	No pooling	
	1	843	NA	RR: 1.54	[1.36, 1.74], < 0.00001
	1	114	NA	RR: 1.22	[0.96, 1.54], 0.10
Patients with disability progression	1	843	NA	RR: 0.72	[0.55, 0.94], 0.02
Mean change EDSS from baseline	1	843	NA	MD: –0.13	[–0.25, –0.01], 0.04
Mean change MSFC from baseline	1	843	NA	MD: 0.09	[0.02, 0.16], 0.008
Patients with GdE lesions	2	803	69.9%, 0.07	No pooling	
	1	701	NA	RR: 0.29	[0.21, 0.41], < 0.00001
	1	102	NA	RR: 0.50	[0.31, 0.81], 0.005
Mean number of GdE lesions	2	803	28.8%, 0.24	MD: –1.01	[–1.35, –0.66], < 0.00001
Patients with new or enlarging T2-hyperintense lesions	2	807	0%, 0.58	RR: 0.62	[0.56, 0.70], < 0.00001
Mean number of new or enlarging T2-hyperintense lesions	2	807	41.3%, 0.19	MD: –6.54	[–8.66, –4.42], < 0.00001

Table A14.1: Direct Estimates for Efficacy Outcomes					
Outcome	**No. of RCTs**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**Effect Size (Random)**	**[95% CI], *P* Value**
8. Teriflunomide 7 mg oral q.d. versus placebo					
Annualized relapse rate	2	850	--	Ratio: 0.78	[0.64, 0.95], 0.014
Patients with relapse-free	1	728	NA	RR: 1.17	[1.01, 1.36], 0.03
Patients with disability progression	1	728	NA	RR: 0.79	[0.61, 1.03], 0.08
Patients with GdE lesions	2	818	0%, 0.83	RR: 0.80	[0.71, 0.90], 0.0003
Mean number of GdE lesions	2	818	40.4%, 0.20	MD: –0.93	[–1.48, –0.39], 0.0008
Patients with new or enlarging T2-hyperintense lesions	1	122	NA	RR: 0.70	[0.53, 0.92], 0.01
Mean number of new or enlarging T2-hyperintense lesions	1	122	NA	MD: –1.11	[–1.76, –0.46], 0.0008
9. Teriflunomide 14 mg oral q.d. versus placebo					
Annualized relapse rate	2	839	--	Ratio: 0.75	[0.61, 0.92], 0.005
Patients with relapse-free	2	839	0%, 0.98	RR: 1.24	[1.09, 1.40], 0.0008
Patients with disability progression	1	721	NA	RR: 0.74	[0.57, 0.96], 0.02
Patients with GdE lesions	2	804	81.0%, 0.02	No pooling	
	1	118	NA	RR: 0.83	[0.65, 1.07], 0.16
	1	686	NA	RR: 0.59	[0.50, 0.69], < 0.00001
Mean number of GdE lesions	2	804	0%, 0.51	MD: –1.11	[–1.41, –0.80], < 0.00001
Patients with new or enlarging T2-hyperintense lesions	1	118	NA	RR: 0.79	[0.61, 1.02], 0.07
Mean number of new or enlarging T2-hyperintense lesions	1	118	NA	MD: –0.81	[–1.47, –0.15], 0.02
10. Dimethyl fumarate 240 mg oral b.i.d. versus placebo					
Annualized relapse rate	2	1540	--	Ratio: 0.51	[0.44, 0.60], 0.000
Patients with relapse-free	2	1540	54.7%, 0.14	No pooling	
	1	722	NA	RR: 1.20	[1.08, 1.34]
	1	818	NA	RR: 1.35	[1.21, 1.51]
Patients with disability progression	2	1539	16.3%, 0.27	RR: 0.66	[0.52, 0.84], 0.0006
Patients with GdE lesions	1	317	NA	RR: 0.18	[0.09, 0.33], < 0.00001
Mean number of GdE lesions	2	608	0%, 0.73	MD: –1.64	[–2.17, –1.11], < 0.00001
Mean number of new or enlarging T2-hyperintense lesions	2	596	0%, 0.74	MD: –12.90	[–15.82, –9.98], < 0.00001
11. IFN beta-1a 44 mcg SC t.i.w. versus IFN beta-1b 250 mcg SC q.o.d.					
Annualized relapse rate	1	60	NA	Ratio: 0.86	[0.46, 1.61], 0.631
Patients with relapse-free	1	60	NA	RR: 1.31	[0.78, 2.19], 0.31

Table A14.1: Direct Estimates for Efficacy Outcomes					
Outcome	**No. of RCTs**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**Effect Size (Random)**	**[95% CI], *P* Value**
Mean change EDSS from baseline	1	60	NA	MD: 0.40	[0.10, 0.70], 0.008
12. IFN beta-1b 250 mcg SC q.o.d. versus IFN beta-1a 30 mcg IM q.w.					
Annualized relapse rate	2	248	--	Ratio: 0.69	[0.54, 0.87], 0.002
Patients with relapse-free	2	248	0%, 0.35	RR: 1.51	[1.11, 2.06], 0.009
Patients with disability progression	1	188	NA	RR: 0.44	[0.25, 0.80], 0.007
Mean change EDSS from baseline	2	248	0%, 0.43	MD: –0.47	[–0.69, –0.25], < 0.0001
Patients with GdE lesions	1	149	NA	RR: 0.47	[0.29, 0.74], 0.001
Patients with new or enlarging T2-hyperintense lesions	1	149	NA	RR: 0.60	[0.46, 0.80], 0.0005
13. IFN beta-1a 44 mcg SC t.i.w. versus IFN beta-1a 30 mcg IM q.w.					
Annualized relapse rate	3	847	--	Ratio: 0.76	[0.59, 0.98], 0.037
Patients with relapse-free	2	737	79.2%, 0.03	No pooling	
	1	677	NA	RR: 1.18	[1.03, 1.34], 0.02
	1	60	NA	RR: 2.83	[1.30, 6.19], 0.009
Patients with disability progression	1	677	NA	RR: 0.87	[0.60, 1.28], 0.49
Mean change EDSS from baseline	2	170	0%, 0.37	MD: –0.03	[–0.19, 0.13], 0.71
Mean number of GdE lesions	1	110	NA	MD: 0.10	[–0.26, 0.46], 0.58
Patients with new or enlarging T2-hyperintense lesions	1	677	NA	RR: 0.67	[0.58, 0.78], < 0.00001
Mean number of new or enlarging T2-hyperintense lesions	2	787	44.8%, 0.18	MD: –0.29	[–0.68, 0.10], 0.15
14. IFN beta-1b 250 mcg SC q.o.d. versus glatiramer acetate 20 mg SC q.d.					
Annualized relapse rate	2	1420	--	Ratio: 1.06	[0.94, 1.20], 0.326
Patients with relapse-free	2	1420	56.1%, 0.13	No pooling	
	1	75	NA	RR: 0.74	[0.51, 1.06], 0.10
	1	1345	NA	RR: 0.98	[0.89, 1.08], 0.74
Patients with disability progression	1	1345	NA	RR: 1.04	[0.83, 1.31], 0.71
Mean number of GdE lesions	1	1345	NA	MD: –0.30	[–0.68, 0.08], 0.12
Mean number of new or enlarging T2-hyperintense lesions	1	945	NA	MD: –1.30	[–2.30, –0.30], 0.01
15. IFN beta-1a 44 mcg SC t.i.w. versus glatiramer acetate 20 mg SC q.d.					
Annualized relapse rate	2	874	--	Ratio: 0.97	[0.78, 1.22], 0.806
Patients with relapse-free	1	764	NA	RR: 1.00	[0.89, 1.12], 1.00

Table A14.1: Direct Estimates for Efficacy Outcomes					
Outcome	**No. of RCTs**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**Effect Size (Random)**	**[95% CI], *P* Value**
Patients with disability progression	1	764	NA	RR: 1.34	[0.87, 2.05], 0.18
Mean change EDSS from baseline	1	110	NA	MD: –0.10	[–0.29, 0.09], 0.29
Patients with GdE lesions	1	460	NA	RR: 0.58	[0.42, 0.80], 0.0009
Mean number of GdE lesions	2	445	0%, 0.61	MD: –0.02	[–0.24, 0.20], 0.85
Patients with new or enlarging T2-hyperintense lesions	1	460	NA	RR: 0.95	[0.82, 1.10], 0.50
Mean number of new or enlarging T2-hyperintense lesions	2	445	0%, 0.51	MD: 0.08	[–0.19, 0.36], 0.56
16. IFN beta-1a 30 mcg IM q.w. versus glatiramer acetate 20 mg SC q.d.					
Annualized relapse rate	2	619	--	Ratio: 1.25	[0.85, 1.85], 0.26
Patients with relapse-free	1	509	NA	RR: 0.93	[0.85, 1.02], 0.14
Patients with disability progression	1	487	NA	RR: 0.87	[0.63, 1.20], 0.40
Mean change EDSS from baseline	1	110	NA	MD: –0.10	[–0.27, 0.07], 0.25
Mean change MSFC from baseline	1	423	NA	MD: –0.10	[–0.20, 0.00], 0.04
Mean number of GdE lesions	1	110	NA	MD: –0.20	[–0.58, 0.18], 0.30
Mean number of new or enlarging T2-hyperintense lesions	1	110	NA	MD: 0.10	[–0.29, 0.49], 0.62
17. Dimethyl fumarate 240 mg oral b.i.d. versus glatiramer acetate 20 mg SC q.d.					
Annualized relapse rate	1	709	NA	Ratio: 0.76	[0.62, 0.93], 0.009
Patients with relapse-free	1	709	NA	RR : 1.04	[0.95, 1.15], 0.38
Patients with disability progression	1	709	NA	RR : 0.82	[0.57, 1.17], 0.27
Mean number of GdE lesions	1	308	NA	MD : –0.20	[–0.59, 0.19], 0.32
Mean number of new or enlarging T2-hyperintense lesions	1	293	NA	MD : –2.90	[–5.25, –0.55], 0.02
18. Alemtuzumab 12 mg IV q.d. versus IFN beta-1a 44 mcg SC t.i.w.					
Annualized relapse rate	3	1471	--	Ratio: 0.44	[0.34, 0.55], 0.000
Patients with relapse-free	3	1414	0%, 0.54	RR: 1.38	[1.26, 1.52], < 0.00001
Patients with disability progression	3	1414	36.5%, 0.21	RR: 0.59	[0.40, 0.86], 0.007
Mean change EDSS from baseline	3	1459	87.7%, 0.0003	No pooling	
	1	211	NA	MD: –0.70	[–1.04, –0.36], < 0.0001
	1	581	NA	MD: 0.00	[–0.18, 0.18], 1.00
	1	667	NA	MD: –0.41	[–0.61, –0.21], < 0.0001
Mean change MSFC from baseline	2	1248	0%, 0.46	MD: 0.10	[0.05, 0.16], 0.0001
Patients with GdE lesions	2	1144	0%, 0.82	RR: 0.39	[0.29, 0.53], < 0.00001

Table A14.1: Direct Estimates for Efficacy Outcomes					
Outcome	**No. of RCTs**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**Effect Size (Random)**	**[95% CI], *P* Value**
Patients with new or enlarging T2-hyperintense lesions	3	1348	92.5%, < 0.00001	No pooling	
	1	223	NA	RR: 1.32	[1.07, 1.63], 0.009
	1	535	NA	RR: 0.84	[0.71, 0.99], 0.04
	1	590	NA	RR: 0.68	[0.59, 0.79], < 0.00001
19. Alemtuzumab 24 mg IV q.d. versus IFN beta-1a 44 mcg SC t.i.w.					
Annualized relapse rate	1	221	NA	Ratio: 0.22	[0.14, 0.35], 0.000
Patients with relapse-free	1	221	NA	RR: 1.63	[1.33, 1.99], < 0.00001
Patients with disability progression	1	221	NA	RR: 0.42	[0.21, 0.84], 0.01
Mean change EDSS from baseline	1	212	NA	MD: –0.83	[–1.17, –0.49], < 0.00001
Patients with new or enlarging T2-hyperintense lesions	1	221	NA	RR: 1.46	[1.20, 1.78], 0.0001
20. Fingolimod 0.5 mg oral q.d. versus IFN beta-1a 30 mcg IM q.w.					
Annualized relapse rate	1	866	NA	Ratio: 0.49	[0.38, 0.63], 0.000
Patients with relapse-free	1	860	NA	RR: 1.19	[1.10, 1.28], < 0.00001
Patients with disability progression	1	860	NA	RR: 0.74	[0.45, 1.22], 0.23
Mean change EDSS from baseline	1	866	NA	MD: –0.09	[–0.19, 0.01], 0.09
Mean change MSFC from baseline	1	866	NA	MD: 0.07	[0.01, 0.13], 0.02
Patients with GdE lesions	1	728	NA	RR: 0.52	[0.35, 0.75], 0.0005
Mean number of GdE lesions	1	728	NA	MD: –0.28	[–0.50, –0.06], 0.01
Patients with new or enlarging T2-hyperintense lesions	1	733	NA	RR: 0.83	[0.72, 0.96], 0.01
Mean number of new or enlarging T2-hyperintense lesions	1	733	NA	MD: –0.90	[–1.62, –0.18], 0.01
21. Alemtuzumab 12 mg IV q.d. versus Alemtuzumab 24 mg IV q.d.					
Annualized relapse rate	1	222	NA	Ratio: 1.38	[0.82, 2.30], 0.227
Patients with relapse-free	1	222	NA	RR: 0.93	[0.82, 1.06], 0.26
Patients with disability progression	1	222	NA	RR: 0.79	[0.32, 1.92], 0.60
Mean change EDSS from baseline	1	215	NA	MD: 0.13	[–0.19, 0.45], 0.43
Patients with new or enlarging T2-hyperintense lesions	1	222	NA	RR: 0.90	[0.78, 1.05], 0.19
22. Teriflunomide 7 mg oral q.d. versus teriflunomide 14 mg oral q.d.					
Annualized relapse rate	2	841	--	Ratio: 1.04	[0.84, 1.29], 0.694
Patients with relapse-free	1	723	NA	RR: 0.95	[0.83, 1.09], 0.46

Table A14.1: Direct Estimates for Efficacy Outcomes					
Outcome	**No. of RCTs**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**Effect Size (Random)**	**[95% CI], *P* Value**
Patients with disability progression	1	723	NA	RR: 1.08	[0.81, 1.43], 0.61
Patients with GdE lesions	2	808	70.7%, 0.06	No pooling	
	1	118	NA	RR: 0.99	[0.74, 1.32], 0.93
	1	690	NA	RR: 1.35	[1.13, 1.62], 0.0009
Mean number of GdE lesions	2	808	0%, 0.51	MD: 0.30	[0.10, 0.49], 0.003
Patients with new or enlarging T2-hyperintense lesions	1	118	NA	RR: 0.88	[0.64, 1.21], 0.43
Mean number of new or enlarging T2-hyperintense lesions	1	118	NA	MD: –0.30	[–0.95, 0.35], 0.37
23. IFN beta-1a 22 mcg SC t.i.w. versus IFN beta-1a 44 mcg SC t.i.w.					
Annualized relapse rate	1	373	NA	Ratio: 1.05	[0.90, 1.22], 0.563
Patients with relapse-free	1	373	NA	RR: 0.84	[0.61, 1.15], 0.28
Patients with disability progression	1	373	NA	RR: 1.15	[0.85, 1.56], 0.35
Mean change EDSS from baseline	1	373	NA	MD: –0.01	[–0.25, 0.23], 0.94
24. IFN beta-1a 30 mcg IM q.w. versus IFN beta-1a 60 mcg IM q.w.					
Annualized relapse rate	1	802	NA	Ratio: 0.95	[0.87, 1.04], 0.274
Patients with relapse-free	1	802	NA	RR: 1.00	[0.77, 1.28], 0.97
Patients with disability progression	1	802	NA	RR: 1.00	[0.80, 1.26], 0.97
Mean change EDSS from baseline	1	802	NA	MD: 0.03	[–0.16, 0.22], 0.76
Mean number of GdE lesions	1	304	NA	MD: –0.17	[–0.43, 0.09], 0.21
Patients with new or enlarging T2-hyperintense lesions	1	305	NA	RR: 1.26	[1.08, 1.47], 0.003
Mean number of new or enlarging T2-hyperintense lesions	1	305	NA	MD: 0.30	[–0.79, 1.39], 0.59

b.i.d. = twice daily; CI = confidence interval; EDSS = Expanded Disability Status Scale; e4w = every four weeks; q.o.d. = every other day; GdE = gadolinium-enhancing; IFN = interferon; IM = intramuscular; IV = intravenous; mcg = microgram; mg = milligram; MD = mean difference; MSFC = Multiple Sclerosis Functional Composite; NA = not applicable; q.d. = once daily; q.0.d. = every other day; q.w. = once weekly; RCT = randomized controlled trial; RR = relative risk; SC = subcutaneous; t.i.w. = three times weekly.

Table A14.2: Direct Estimates for Safety Outcomes					
Outcome	**No. of RCT**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**RR (Random)**	**[95% CI], *P* value**
1. IFN beta-1b 250 mcg SC q.o.d. versus placebo					
Total withdrawal	1	247	NA	1.04	[0.62, 1.73], 0.90
Treatment discontinuation because of adverse events	1	247	NA	0.10	[0.01, 0.76], 0.03
Depression	1	247	NA	1.26	[0.67, 2.36], 0.48
Injection site reactions	1	247	NA	12.19	[5.88, 25.26], < 0.00001
2. IFN beta-1a 22 mcg SC t.i.w. versus placebo					
Total withdrawal	1	376	NA	1.19	[0.53, 2.68], 0.68
Treatment discontinuation because of adverse events	1	376	NA	2.97	[0.61, 14.52], 0.18
Influenza-like illness	1	376	NA	1.03	[0.72, 1.47], 0.86
Fatigue	1	376	NA	0.92	[0.57, 1.49], 0.74
Depression	1	376	NA	0.74	[0.52, 1.07], 0.11
Injection site reactions	1	376	NA	2.78	[2.07, 3.72], < 0.00001
Liver enzyme elevation	1	376	NA	4.45	[0.97, 20.33], 0.05
3. IFN beta-1a 44 mcg SC t.i.w. versus placebo					
Total withdrawal	2	551	22.4%, 0.26	0.76	[0.30, 1.94], 0.57
Treatment discontinuation because of adverse events	1	371	NA	4.57	[1.00, 20.88], 0.05
Influenza-like illness	2	551	87.7%, 0.004	No pooling	
	1	371	NA	1.13	[0.80, 1.60]
	1	180	NA	2.91	[1.66, 5.09]
Fatigue	1	371	NA	1.19	[0.76, 1.87], 0.45
Depression	2	551	1.6%, 0.31	0.83	[0.55, 1.24], 0.37
Injection site reactions	2	551	0%, 0.87	2.85	[2.18, 3.73], < 0.00001
Hypersensitivity	1	180	NA	1.00	[0.26, 3.86], 1.00
Skin disorders	1	180	NA	2.50	[0.30, 20.92], 0.40
Liver enzyme elevation	2	551	0%, 0.35	3.73	[1.30, 10.70], 0.01
Thyroid disorders	1	180	NA	2.50	[0.30, 20.92], 0.40
4. IFN beta-1a 30 mcg IM q.w. versus placebo					
Total withdrawal	2	409	8.6%, 0.30	1.67	[0.62, 4.48], 0.31
Serious adverse events	1	108	NA	1.00	[0.15, 6.84], 1.00
Treatment discontinuation because of adverse events	2	409	0%, 0.98	3.13	[0.78, 12.67], 0.11
Influenza-like illness	2	409	73.6%, 0.05	No pooling	

Table A14.2: Direct Estimates for Safety Outcomes					
Outcome	**No. of RCT**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**RR (Random)**	**[95% CI], *P* value**
	1	301	NA	1.52	[1.20, 1.93], 0.0005
	1	108	NA	21.00	[1.26, 349.61], 0.03
Infection	1	108	NA	0.50	[0.27, 0.93], 0.03
Gastrointestinal disorders	1	301	NA	1.42	[1.07, 1.90], 0.02
5. Glatiramer acetate 20 mg SC q.d. versus placebo					
Total withdrawal	3	1203	2.9%, 0.36	0.79	[0.61, 1.04], 0.10
Serious adverse events	2	953	52.9%, 0.15	No pooling	
	1	239	NA	1.68	[0.63, 4.48], 0.30
	1	714	NA	0.79	[0.58, 1.06], 0.12
Treatment discontinuation because of adverse events	2	965	56.2%, 0.13	No pooling	
	1	251	NA	5.04	[0.60, 42.53], 0.14
	1	714	NA	0.95	[0.62, 1.47], 0.83
Fatigue	1	714	NA	0.94	[0.59, 1.51], 0.80
Flushing	2	965	88.7%, 0.70	No pooling	
	1	251	NA	6.55	[1.51, 28.44], 0.01
	1	714	NA	0.48	[0.18, 1.24], 0.13
Infection	1	714	NA	1.00	[0.86, 1.16], 1.00
Depression	1	714	NA	0.89	[0.56, 1.41], 0.61
Injection site reactions	3	1204	94.8%, < 0.00001	No pooling	
	1	251	NA	1.54	[1.32, 1.80], < 0.00001
	1	239	NA	2.49	[1.83, 3.39], < 0.00001
	1	714	NA	125.13	[7.77, 2015.64], 0.0007
Hypersensitivity	2	490	0%, 0.37	3.14	[1.98, 4.96], < 0.00001
Liver enzyme elevation	1	714	NA	1.08	[0.62, 1.88], 0.79
Gastrointestinal disorders	1	714	NA	0.53	[0.34, 0.80], 0.003
6. Natalizumab 300 mg IV e4w versus placebo					
Total withdrawal	1	978	NA	0.84	[0.55, 1.29], 0.43
Serious adverse events	1	939	NA	0.79	[0.61, 1.02], 0.07
Treatment discontinuation because of adverse events	1	942	NA	1.47	[0.79, 2.72], 0.22
Fatigue	1	939	NA	1.27	[0.99, 1.64], 0.06
Infection	1	939	NA	1.00	[0.93, 1.07], 0.97

Table A14.2: Direct Estimates for Safety Outcomes					
Outcome	**No. of RCT**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**RR (Random)**	**[95% CI], *P* value**
Depression	1	939	NA	1.18	[0.88, 1.60], 0.27
Infusion reactions	1	939	NA	1.34	[1.01, 1.77], 0.04
Hypersensitivity	1	939	NA	25.42	[1.55, 416.15], 0.02
Skin disorders	1	939	NA	1.46	[1.08, 1.98], 0.01
Liver enzyme elevation	1	939	NA	1.29	[0.67, 2.47], 0.45
Gastrointestinal disorders	1	939	NA	1.11	[0.74, 1.65], 0.62
7. Fingolimod 0.5 mg oral q.d. versus placebo					
Total withdrawal	2	957	63.1%, 0.10	No pooling	
	1	843	NA	0.64	[0.47, 0.87], 0.005
	1	114	NA	1.50	[0.57, 3.94], 0.41
Serious adverse events	2	957	14.7%, 0.28	0.84	[0.50, 1.42], 0.51
Treatment discontinuation because of adverse events	2	957	0%, 0.33	1.06	[0.68, 1.66], 0.79
Fatigue	1	843	NA	1.05	[0.71, 1.54], 0.81
Infection	2	957	0%, 0.32	1.05	[0.99, 1.10], 0.08
Depression	1	843	NA	1.16	[0.71, 1.88], 0.55
Skin disorders	1	114	NA	1.00	[0.31, 3.27], 1.00
Liver enzyme elevation	2	957	0%, 0.32	4.25	[2.07, 8.72], < 0.0001
Gastrointestinal disorders	2	957	14.1%, 0.28	1.40	[0.97, 2.01], 0.07
Cardiovascular disorders	2	957	0%, 0.39	2.07	[0.81, 5.26], 0.13
8. Teriflunomide 7 mg oral q.d. versus placebo					
Total withdrawal	2	850	0%, 0.52	0.86	[0.68, 1.09], 0.22
Serious adverse events	2	850	0%, 0.46	1.06	[0.75, 1.50], 0.75
Treatment discontinuation because of adverse events	2	850	0%, 0.54	1.16	[0.74, 1.81], 0.51
Fatigue	1	122	NA	0.60	[0.23, 1.55], 0.29
Infection	2	850	55.3%, 0.13	No pooling	
	1	122	NA	1.23	[0.84, 1.79], 0.28
	1	728	NA	0.89	[0.73, 1.09], 0.25
Skin disorders	1	728	NA	1.43	[0.89, 2.30], 0.14
Liver enzyme elevation	2	850	0%, 0.89	1.77	[1.16, 2.70], 0.009
Gastrointestinal disorders	2	850	0%, 0.53	1.51	[1.14, 2.01], 0.004
Hair loss	2	850	34.1%, 0.22	2.37	[1.19, 4.72], 0.01

Table A14.2: Direct Estimates for Safety Outcomes					
Outcome	**No. of RCT**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**RR (Random)**	**[95% CI], *P* value**
9. Teriflunomide 14 mg oral q.d. versus placebo					
Total withdrawal	2	839	76.2%, 0.04	No pooling	
	1	118	NA	2.94	[0.99, 8.72], 0.05
	1	721	NA	0.93	[0.73, 1.17], 0.53
Serious adverse events	2	836	0%, 0.78	1.22	[0.87, 1.72], 0.24
Treatment discontinuation because of adverse events	2	836	0%, 0.47	1.44	[0.94, 2.20], 0.09
Fatigue	1	118	NA	0.75	[0.31, 1.83], 0.53
Infection	2	836	32.2%, 0.22	1.06	[0.84, 1.35], 0.61
Skin disorders	1	718	NA	1.55	[0.97, 2.48], 0.07
Liver enzyme elevation	2	836	0%, 0.35	1.95	[1.28, 2.98], 0.002
Gastrointestinal disorders	2	836	0%, 0.34	2.04	[1.57, 2.67], < 0.00001
Hair loss	2	836	34.3%, 0.22	3.04	[1.56, 5.90], 0.001
10. Dimethyl fumarate 240 mg oral b.i.d. versus placebo					
Total withdrawal	2	1540	0%, 0.42	0.97	[0.80, 1.17], 0.74
Serious adverse events	2	1540	0%, 0.66	0.82	[0.67, 1.01], 0.06
Treatment discontinuation because of adverse events	2	1540	0%, 0.99	1.17	[0.91, 1.52], 0.22
Fatigue	1	722	NA	1.13	[0.73, 1.77], 0.58
Flushing	2	1540	0%, 0.76	8.00	[5.65, 11.32], < 0.00001
Infection	2	1540	53.3%, 0.14	No pooling	
	1	722	NA	1.12	[0.97, 1.28], 0.12
	1	818	NA	0.98	[0.89, 1.09], 0.75
Depression	1	722	NA	0.69	[0.42, 1.14], 0.15
Liver enzyme elevation	2	1540	72.0%, 0.06	No pooling	
	1	722	NA	0.88	[0.49, 1.57], 0.66
	1	818	NA	2.07	[1.06, 4.07], 0.03
Gastrointestinal disorders	2	1540	7.4%, 0.30	1.33	[1.10, 1.62], 0.004
11. IFN beta-1a 44 mcg SC t.i.w. versus IFN beta-1b 250 mcg SC q.o.d.					
No safety data					
12. IFN beta-1b 250 mcg SC q.o.d. versus IFN beta-1a 30 mcg IM q.w.					
Total withdrawal	1	188	NA	0.55	[0.28, 1.10], 0.09
Treatment discontinuation because of adverse events	1	188	NA	4.79	[0.57, 40.24], 0.15

Table A14.2: Direct Estimates for Safety Outcomes					
Outcome	**No. of RCT**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**RR (Random)**	**[95% CI], *P* value**
Influenza-like illness	1	182	NA	0.99	[0.85, 1.16], 0.91
Fatigue	1	182	NA	0.81	[0.62, 1.06], 0.13
Depression	1	182	NA	0.94	[0.52, 1.68], 0.83
Injection site reactions	1	182	NA	4.68	[2.19, 9.99], < 0.0001
Liver enzyme elevation	1	182	NA	0.90	[0.54, 1.49], 0.67
Thyroid disorders	1	182	NA	2.34	[0.47, 11.75], 0.30
13. IFN beta-1a 44 mcg SC t.i.w. versus IFN beta-1a 30 mcg IM q.w.					
Total withdrawal	3	847	0%, 0.83	1.05	[0.60, 1.83], 0.87
Serious adverse events	1	676	NA	1.16	[0.63, 2.14], 0.63
Treatment discontinuation because of adverse events	1	676	NA	1.14	[0.56, 2.29], 0.72
Influenza-like illness	1	676	NA	0.86	[0.73, 1.02], 0.08
Depression	1	676	NA	0.95	[0.68, 1.31], 0.74
Injection site reactions	1	676	NA	3.01	[2.52, 3.61], < 0.00001
Liver enzyme elevation	1	676	NA	2.40	[1.39, 4.13], 0.002
14. IFN beta-1b 250 mcg SC q.o.d. versus glatiramer acetate 20 mg SC q.d.					
Total withdrawal	2	1408	60.1%, 0.11	No pooling	
	1	75	NA	1.90	[0.61, 5.94], 0.27
	1	1333	NA	0.73	[0.56, 0.97], 0.03
Serious adverse events	1	1345	NA	0.88	[0.65, 1.19], 0.40
Treatment discontinuation because of adverse events	2	1420	0%, 0.72	0.89	[0.43, 1.83], 0.75
Influenza-like illness	1	1333	NA	7.20	[4.88, 10.62], < 0.00001
Fatigue	1	1333	NA	1.02	[0.82, 1.27], 0.87
Infection	1	1333	NA	0.90	[0.72, 1.12], 0.34
Depression	1	1333	NA	1.18	[0.90, 1.55], 0.22
Injection site reactions	1	1333	NA	0.83	[0.74, 0.92], 0.0003
Hypersensitivity	1	1333	NA	0.30	[0.21, 0.42], < 0.00001
Liver enzyme elevation	1	1333	NA	3.10	[1.85, 5.19], < 0.0001
Gastrointestinal disorders	1	1333	NA	0.85	[0.61, 1.19], 0.34
15. IFN beta-1a 44 mcg SC t.i.w. versus glatiramer acetate 20 mg SC q.d.					
Total withdrawal	2	874	0%, 0.71	1.51	[1.13, 2.03], 0.006
Serious adverse events	1	756	NA	1.06	[0.64, 1.75], 0.83

Table A14.2: Direct Estimates for Safety Outcomes					
Outcome	**No. of RCT**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**RR (Random)**	**[95% CI], *P* value**
Treatment discontinuation because of adverse events	1	764	NA	1.19	[0.66, 2.14], 0.57
Influenza-like illness	1	756	NA	23.43	[9.68, 56.66], < 0.00001
Infection	1	756	NA	0.73	[0.55, 0.96], 0.03
Depression	1	756	NA	1.34	[0.79, 2.28], 0.28
Injection site reactions	1	756	NA	0.15	[0.09, 0.22], < 0.00001
Hypersensitivity	1	756	NA	0.03	[0.00, 0.42], 0.01
Liver enzyme elevation	1	756	NA	4.13	[1.58, 10.85], 0.004
Gastrointestinal disorders	1	756	NA	0.88	[0.52, 1.48], 0.63
16. IFN beta-1a 30 mcg IM q.w. versus glatiramer acetate 20 mg SC q.d.					
Total withdrawal	2	619	0%, 0.51	1.54	[1.08, 2.19], 0.02
Serious adverse events	1	509	NA	1.31	[0.84, 2.05], 0.23
Treatment discontinuation because of adverse events	1	509	NA	1.60	[0.77, 3.35], 0.21
Influenza-like illness	1	509	NA	1.20	[0.83, 1.73], 0.32
Fatigue	1	509	NA	0.99	[0.66, 1.47], 0.95
Infection	1	509	NA	0.95	[0.72, 1.26], 0.73
Depression	1	509	NA	0.96	[0.65, 1.43], 0.85
Injection site reaction	1	509	NA	0.60	[0.32, 1.10], 0.10
Skin disorders	1	509	NA	0.94	[0.53, 1.68], 0.84
Gastrointestinal disorders	1	509	NA	1.17	[0.87, 1.59], 0.30
17. Dimethyl fumarate 240 mg oral b.i.d. versus glatiramer acetate 20 mg SC q.d.					
Total withdrawal	1	709	NA	1.26	0.93, 1.72], 0.14
Serious adverse events	1	710	NA	0.99	[0.72, 1.38], 0.97
Treatment discontinuation because of adverse events	1	710	NA	1.23	[0.81, 1.87], 0.33
Fatigue	1	710	NA	1.21	[0.76, 1.91], 0.42
Flushing	1	710	NA	17.92	[7.99, 40.23], < 0.00001
Infection	1	710	NA	1.12	[0.97, 1.28], 0.12
Depression	1	710	NA	0.78	[0.47, 1.31], 0.35
Liver enzyme elevation	1	710	NA	0.81	[0.46, 1.45], 0.48
Gastrointestinal disorders	1	710	NA	2.87	[1.93, 4.25], < 0.00001
18. Fingolimod 0.5 mg oral q.d. versus IFN beta-1a 30 mcg IM q.w.					
Total withdrawal	1	860	NA	0.69	[0.45, 1.07], 0.10

Table A14.2: Direct Estimates for Safety Outcomes					
Outcome	**No. of RCT**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**RR (Random)**	**[95% CI], *P* value**
Serious adverse events	1	860	NA	1.21	[0.72, 2.02], 0.48
Treatment discontinuation because of adverse events	1	860	NA	1.51	[0.81, 2.80], 0.19
Influenza-like illness	1	860	NA	0.09	[0.06, 0.16], < 0.00001
Fatigue	1	860	NA	0.98	[0.66, 1.46], 0.93
Infection	1	860	NA	1.02	[0.87, 1.19], 0.84
Depression	1	860	NA	0.66	[0.39, 1.12], 0.13
Liver enzyme elevation	1	860	NA	3.25	[1.62, 7.63], 0.001
Gastrointestinal disorders	1	860	NA	1.45	[1.03, 2.02], 0.03
Cardiovascular disorders	1	860	NA	9.04	[0.49, 167.43], 0.14
19. Alemtuzumab 12 mg IV q.d. versus IFN beta-1a 44 mcg SC t.i.w.					
Total withdrawal	3	1415	61.2%, 0.08	0.31	[0.17, 0.56], 0.0001
Serious adverse events	3	1415	0%, 0.42	1.02	[0.81, 1.28], 0.87
Treatment discontinuation because of adverse events	3	1415	12.9%, 0.32	0.31	[0.17, 0.56], 0.0001
Influenza-like illness	3	1415	61.8%, 0.07	No pooling	
	1	215	NA	0.20	[0.09, 0.47], 0.0002
	1	563	NA	0.13	[0.07, 0.24], < 0.00001
	1	637	NA	0.31	[0.20, 0.47], < 0.00001
Fatigue	3	1415	63.1%, 0.07	No pooling	
Excluding CAMMS223 2008	2	1200	0%, 0.83	1.49	[1.07, 2.06], 0.02
Infection	3	1415	70.5%, 0.03	No pooling	
	1	215	NA	1.41	[1.10, 1.80], 0.006
	1	563	NA	1.48	[1.25, 1.76], < 0.00001
	1	637	NA	1.16	[1.04, 1.29], 0.010
Depression	1	216	NA	0.74	[0.39, 1.39], 0.35
Injection site reactions	3	1415	89.9%, < 0.0001	No pooling	
	1	215	NA	0.07	[0.03, 0.18], < 0.00001
	1	563	NA	0.11	[0.07, 0.17], < 0.00001
	1	637	NA	0.33	[0.23, 0.48], < 0.00001
Skin disorders	3	1415	86.1%, 0.0007	No pooling	
	1	215	NA	1.85	[1.05, 3.26], 0.03
	1	563	NA	3.13	[1.44, 6.81], 0.004
	1	637	NA	8.15	[4.54, 14.61], < 0.00001
Liver enzyme elevation	3	1415	73.1%, 0.02	No pooling	

Table A14.2: Direct Estimates for Safety Outcomes					
Outcome	**No. of RCT**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**RR (Random)**	**[95% CI], *P* value**
	1	215	NA	0.12	[0.03, 0.53], 0.005
	1	563	NA	0.23	[0.13, 0.42], < 0.00001
	1	637	NA	0.68	[0.34, 1.35], 0.27
Thyroid disorders	3	1415	39.7%, 0.19	3.66	[2.11, 6.36], < 0.00001
Gastrointestinal disorders	1	215	NA	0.77	[0.43, 1.36], 0.36
20. Alemtuzumab 24 mg IV q.d. versus IFN beta-1a 44 mcg SC t.i.w.					
Total withdrawal	2	593	0%, 0.39	0.37	[0.24, 0.55], < 0.00001
Serious adverse events	2	578	0%, 0.41	0.96	[0.70, 1.31], 0.79
Treatment discontinuation because of adverse events	2	593	64.2%, 0.09	No pooling	
	1	221	NA	0.08	[0.01, 0.58], 0.01
	1	372	NA	0.48	[0.19, 1.20], 0.11
Influenza-like illness	2	578	79.0%, 0.03	No pooling	
	1	215	NA	0.07	[0.02, 0.28], 0.0002
	1	363	NA	0.35	[0.19, 0.62], 0.0003
Fatigue	2	578	65.2%, 0.09	No pooling	
	1	215	NA	0.99	[0.66, 1.49], 0.96
	1	363	NA	1.69	[1.06, 2.68], 0.03
Infection	2	578	0%, 0.39	1.28	[1.15, 1.43], < 0.00001
Depression	1	216	NA	0.89	[0.49, 1.63], 0.72
Injection site reactions	2	578	91.5%, 0.0006	No pooling	
	1	215	NA	0.05	[0.02, 0.16], < 0.00001
	1	363	NA	0.38	[0.23, 0.63], 0.0002
Skin disorders	2	578	95.0%, < 0.00001	No pooling	
	1	215	NA	1.78	[1.01, 3.16], 0.05
	1	363	NA	10.95	[6.08, 19.72], < 0.00001
Liver enzyme elevation	2	578	30.2%, 0.23	0.32	[0.12, 0.81], 0.02
Thyroid disorders	2	578	0%, 0.40	4.50	[2.49, 8.11], < 0.00001
Gastrointestinal disorders	1	215	NA	1.40	[0.87, 2.25], 0.17
21. Alemtuzumab 12 mg IV q.d. versus alemtuzumab 24 mg IV q.d.					
Total withdrawal	2	819	0%, 0.36	0.99	[0.61, 1.63], 0.98
Serious adverse events	2	812	0%. 0.59	0.99	[0.73, 1.32], 0.92
Treatment discontinuation because of adverse events	2	819	0%, 0.57	1.03	[0.43, 2.46], 0.95

Table A14.2: Direct Estimates for Safety Outcomes					
Outcome	**No. of RCT**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**RR (Random)**	**[95% CI], *P* value**
Influenza-like illness	2	812	50.5%, 0.16	No pooling	
	1	216	NA	3.00	[0.62, 14.53], 0.17
	1	596	NA	0.88	[0.47, 1.64], 0.69
Fatigue	2	812	0%, 0.37	0.95	[0.73, 1.24], 0.73
Flushing	1	216	NA	1.22	[0.53, 2.83], 0.64
Infection	2	812	0%, 0.44	0.94	[0.86, 1.01], 0.10
Depression	1	216	NA	0.82	[0.43, 1.59], 0.56
Infusion reactions	2	812	86.2%, 0.007	No pooling	
	1	216	NA	0.99	[0.96, 1.02], 0.56
	1	596	NA	0.93	[0.89, 0.97], 0.0009
Injection site reactions	2	812	0%, 0.59	0.92	[0.55, 1.52], 0.73
Skin disorders	2	812	46.9%,	0.82	[0.61, 1.11], 0.20
Liver enzyme elevation	2	812	0%, 0.47	1.18	[0.51, 2.77], 0.70
Thyroid disorders	2	812	55.6%, 0.13	No pooling	
	1	216	NA	1.33	[0.81, 2.20], 0.26
	1	596	NA	0.82	[0.56, 1.21], 0.32
Gastrointestinal disorders	1	216	NA	0.55	[0.32, 0.93], 0.03
22. Teriflunomide 7 mg oral q.d. versus teriflunomide 14 mg oral q.d.					
Total withdrawal	2	841	80.9%, 0.02	No pooling	
	1	118	NA	0.17	[0.04, 0.73], 0.02
	1	723	NA	0.94	[0.73, 1.20], 0.62
Serious adverse events	2	844	0%, 0.63	0.86	[0.62, 1.20], 0.39
Treatment discontinuation because of adverse events	2	844	46.8%, 0.17	0.68	[0.30, 1.58], 0.37
Fatigue	1	118	NA	0.80	[0.29, 2.24], 0.67
Infection	2	844	0%, 0.75	0.92	[0.77, 1.09], 0.35
Skin disorders	1	726	NA	0.92	[0.61, 1.41], 0.71
Liver enzyme elevation	2	844	0%, 0.35	0.90	[0.64, 1.27], 0.55
Gastrointestinal disorders	2	844	0%, 0.72	0.74	[0.59, 0.92], 0.008
Hair loss	2	844	0%, 0.95	0.78	[0.55, 1.12], 0.18
23. IFN beta-1a 22 mcg SC t.i.w. versus IFN beta-1a 44 mcg SC t.i.w.					
Total withdrawal	1	373	NA	2.34	[0.84, 6.50], 0.10
Treatment discontinuation because of adverse events	1	373	NA	0.65	[0.24, 1.79], 0.40

Table A14.2: Direct Estimates for Safety Outcomes					
Outcome	**No. of RCT**	**Total Patients**	**Heterogeneity (I^2, *P* Value)**	**RR (Random)**	**[95% CI], *P* value**
Influenza-like illness	1	373	NA	0.92	[0.65, 1.29], 0.61
Fatigue	1	373	NA	0.77	[0.49, 1.23], 0.28
Depression	1	373	NA	0.86	[0.59, 1.26], 0.45
Injection site reactions	1	373	NA	0.98	[0.84, 1.15], 0.83
Liver enzyme elevation	1	373	NA	0.73	[0.32, 1.69], 0.46
24. IFN beta-1a 30 mcg IM q.w. versus IFN beta-1a 60 mcg IM q.w.					
Total withdrawal	1	802	NA	1.00	[0.76, 1.30], 0.97
Treatment discontinuation because of adverse events	1	802	NA	0.70	[0.49, 1.00], 0.05
Influenza-like illness	1	802	NA	0.92	[0.88, 0.97], 0.002
Depression	1	802	NA	0.90	[0.58, 1.37], 0.61

b.i.d. = twice daily; CI = confidence interval; e4w = every four weeks; IFN = interferon; IM = intramuscular; mcg = microgram; mg = milligram; IV = intravenous; N = number of patients in each arm; n = number of patients with event; NA = not applicable; No. = number; q.d. = once daily; q.o.d. = every other day; q.w. = once weekly; RCT = randomized controlled trial; RR = relative risk; SC = subcutaneous; SD = standard deviation; t.i.w. = three times weekly.

Table A14.3: Treatment-Specific Serious Adverse Events				
Study	**Serious Adverse Events[a]**	**No. Patients with events (%)**	***P* value**	**Reasons**
AFFIRM (2006)[9]	Death	2 (0.3) versus 0	NR	Malignant melanoma; alcohol intoxication
	Cancer	6 (1) versus 1 (0.3)	NR	
Natalizumab versus placebo	Infections	20 (3.2) versus 8 (2.6)	NR	*Natalizumab*: Pneumonia (4), urinary tract infection (5), others (11) *Placebo*: Appendicitis (2), gastroenteritis (2), others (4)
	MS relapse	38 (6) versus 41 (13)	< 0.001	
BECOME (2009)[10] INF beta-1b versus glatiramer acetate	NR			
BECOME (2009)[11] IFN beta-1b versus glatiramer acetate	Specific SAEs were not reported			
Calabrese et al. (2012)[12] INF beta-1a 44 mcg versus INF beta-1a 30 mcg versus glatiramer acetate	NR			
CAMMS223 (2008)[13]	Death	2 (0.9) versus 0	NR	Cardiovascular disease, immune thrombocytopenic purpura
Alemtuzumab (12 and 24 mg) versus IFN beta-1a 44 mcg	Cancer	3 (1.4) versus 1 (0.9)	NR	*Alemtuzumab*: Burkitt lymphoma, breast cancer, cervical cancer *IFN beta-1a*: Colon cancer
	Infusion reaction	3 (1.4) versus 0	NR	
	Liver toxicity	2 (0.9) versus 2 (1.9)	NR	*Alemtuzumab*: Abnormal liver function test *IFN beta-1a*: Hepatic failure, abnormal liver-function test
	Infection	9 (4.2) versus 2 (1.9)	NR	*Alemtuzumab*: Gastroenteritis, bronchitis, cellulitis, cervicitis, meningitis, urinary tract infection *IFN beta-1a*: Appendicitis, central-venous catheter infection
	Thyroid disorders	3 (1.4) versus 0	NR	Hyperthyroidism
	Blood and lymphatic system disorders	5 (2.3) versus 0	NR	Immune thrombocytopenic purpura
CARE-MS I (2012)[14]	Death	2 (0.5) versus 0	NR	Car accident, sepsis
	Cancer	2 (0.5) versus 0	NR	Thyroid cancer
Alemtuzumab 12 mg versus	Infusion reaction	12 (3) versus 0	NR	
IFN beta-1a 44 mcg	Liver toxicity	1 (0.5) versus 0	NR	
	Infection	7 (2) versus 2 (1)	NR	*Alemtuzumab*: Appendicitis, tuberculosis, herpes, meningitis, wound infection, tooth infection, uterine infection *IFN beta-1a*: Appendicitis, hepatitis A

Table A14.4: Treatment-Specific Serious Adverse Events				
Study	**Serious Adverse Events**	**No. Patients with events (%)**	***P* value**	**Reasons**
	Thyroid disorders	4 (1) versus 0	NR	Basedow disease, goitre, hyperthyroidism, thyrotoxic crisis
	Blood and lymphatic system disorders	5 (1) versus 0	NR	Immune thrombocytopenic purpura, agranulocytosis
CARE-MS II (2012)[15]	Death	2 (0.3) versus 0		Car accident, aspiration pneumonia
Alemtuzumab (12 mg and 24 mg) versus IFN beta-1a 44 mcg	Cancer	5 (1) versus 2 (1)	NR	*Alemtuzumab*: Basal cell carcinoma, thyroid cancer, vulval cancer, colon cancer *IFN beta-1a*: Basal cell carcinoma, acute myeloid leukemia
	Infusion reaction	17 (3) versus 0	NR	
	Liver toxicity	5 (1) versus 5 (2)	NR	
	Infection	22 (4) versus 3 (1)	NR	*Alemtuzumab*: Pneumonia, gastroenteritis, appendicitis, febrile infection, herpes, influenza, labyrinthitis, esophageal candidiasis, pasteurella infection, pyelonephritis, tooth infection, upper respiratory tract infection, urinary tract infection *IFN beta-1a*: Catheter site infection, injection site abscess, chronic pyelonephritis
	Thyroid disorders	5 (1) versus 0	NR	*Hypothyroidism*, hyperthyroidism, goitre
	Blood and lymphatic system disorders	8 (1.3) versus 0	NR	Autoimmune thrombocytopenia, thrombocytopenia, anemia, febrile neutropenia
Clanet et al. (2002)[16] IFN beta-1a 30 mcg versus IFN beta-1a 60 mcg	Death	1 (0.2) versus 1 (0.2)	NR	Drowning, cervical carcinoma
Comi et al. (2001)[17] Glatiramer acetate versus placebo	Specific SAEs were not reported			
CONFIRM et al. (2012)[18]	Death	0 versus 1 (0.3) versus 1 (0.3)	NR	
Dimethyl fumarate versus	MS relapse	39 (11) versus 36 (10) versus 51 (14)	NR	
Glatiramer acetate versus placebo	Infection	4 (1) versus 2 (0.6) versus 1 (0.3)	NR	*Dimethyl fumarate*: Gastroenteritis, cellulitis *Glatiramer acetate*: Pneumonia *Placebo*: Pneumonia
	Pain	4 (1) versus 0 versus 0	NR	Abdominal pain, back pain
	Depression	0 versus 2 (0.6) versus 0	NR	
	Convulsion	0 versus 0 versus 2 (0.6)	NR	
	Spontaneous abortion	0 versus 0 versus 2 (0.6)	NR	
	Anaphylactic abortion	0 versus 2 (0.6) versus 0	NR	
DEFINE (2012)[19]	Death	1 (0.2) versus 0	NR	Road accident

Table A14.5: Treatment-Specific Serious Adverse Events				
Study	**Serious Adverse Events**	**No. Patients with events (%)**	***P* value**	**Reasons**
	Cancer	2 (0.5) versus 2 (0.5)	NR	
Dimethyl fumarate versus placebo	MS relapse	39 (10) versus 60 (15)	NR	
	Infection	10 (2) versus 7 (2)	NR	
	Depression	1 (0.2) versus 2 (0.5)	NR	
Etemadifar et al. (2006)[20] IFN beta-1b versus IFN beta-1a 30 mcg versus IFN beta-1a 44 mcg	NR			
EVIDENCE (2002)[21]	Death	0 versus 1 (0.3)	NR	Solo pilot airplane crash
	Lymphopenia	0 versus 1 (0.3)	NR	
IFN beta-1a 30 mcg versus IFN beta-1a 44 mcg	Spontaneous abortion	0 versus 1 (0.3)	NR	
	Depression	2 (0.6) versus 1 (0.3)	NR	
	Suicidal ideation	0 versus 1 (0.3)	NR	
	MS relapse	1 (0.3) versus 0	NR	
	Chest pain	1 (0.3) versus 0	NR	
FREEDOMS (2010)[22]	Death	0 versus 2 (0.5)	NR	Pulmonary embolism, traffic accident
Fingolimod versus placebo	Cancer	4 (0.9) versus 10 (2.4)	NR	*Fingolimod*: Basal cell carcinoma *Placebo*: Basal cell carcinoma, breast cancer, malignant melanoma, Bowen disease, cervical carcinoma, endometrial cancer, prostate cancer
	Bradycardia	4 (0.9) versus 1 (0.2)	NR	
	Myocardial infarction	0 versus 2 (0.5)	NR	
	MS relapse	4 (0.9) versus 1 (0.2)	NR	
	Depression	0 versus 1 (0.2)	NR	
	Musculoskeletal disorders	2 (0.5) versus 3 (0.7)	NR	
	Abortion	0 versus 3 (0.7)	NR	
	Urinary tract infection	2 (0.5) versus 0	NR	
IFNB-MS (1993)[23] IFN beta-1b versus placebo	NR			
IMPROVE (2010)[24] IFN beta-1a 44 mcg versus placebo	NR			
INCOMIN (2002)[25] IFN beta-1a 30 mcg versus IFN beta-1b	NR			

Table A14.6: Treatment-Specific Serious Adverse Events				
Study	**Serious Adverse Events**	**No. Patients with events (%)**	***P* value**	**Reasons**
Johnson et al. (1995)[26] Glatiramer acetate versus placebo	NR			
Kappos et al. (2011)[34] IFN beta-1a 30 mcg versus placebo	Death	1 (2%) versus 0	NR	
	Infection	1 (2) versus 1 (2)	NR	
MSCRG (1996)[27] IFN beta-1a 30 mcg versus placebo	Death	1 (0.6) versus 0	NR	Pulmonary embolism and cardiac arrhythmia
O'Connor et al. (2006)[28] Teriflunomide (7 and 14 mg) versus placebo	Specific SAEs were not reported			
PRISMS (1998)[29] IFN beta-1a (22 and 44 mcg) versus placebo	NR			
REGARD (2008)[30] IFN beta-1a 44 mcg versus glatiramer acetate	Death	1 (0.4) versus 0	NR	Suicide
Saida et al. (2012)[31] Fingolimod versus placebo	Bradycardia	3 (5.3) versus 0	NR	
TEMSO (2011)[32]	Infection	17 (2.3) versus 8 (2.2)	NR	
	Neoplasms	5 (0.7) versus 5 (1.4)	NR	
Teriflunomide (7 and 14 mg)	Blood and lymphatic system	3 (0.4) versus 0	NR	
versus placebo	Psychiatric	5 (0.7) versus 5 (1.4)	NR	
	Nervous system	10 (1.4) versus 6 (1.7)	NR	
	Ear and labyrinth	0 versus 1 (0.3)	NR	
	Cardiac	0 versus 2 (0.6)	NR	
	Vascular	5 (0.7) versus 0	NR	
	Respiratory	2 (0.3) versus 0	NR	
	Gastrointestinal	16 (2.2) versus 1 (0.3)	NR	
	Hepatobiliary	11 (1.5) versus 2 (0.6)	NR	
	Skin	2 (0.3) versus 1 (0.3)	NR	
	Musculoskeletal	8 (1.1) versus 4 (1.1)	NR	
	Renal and urinary	2 (0.3) versus 0	NR	

Table A14.7: Treatment-Specific Serious Adverse Events				
Study	**Serious Adverse Events**	**No. Patients with events (%)**	***P* value**	**Reasons**
	Reproductive system and breast	8 (1.1) versus 1 (0.3)	NR	
TRANSFORMS (2010)[33]	Bradycardia	2 (0.5) versus 0	NR	
	Atrioventricular block	2 (0.5) versus 0	NR	
Fingolimod versus	Infection	1 (0.2) versus 3 (0.7)	NR	
IFN beta-1a 30 mcg	Cancer	8 (2) versus 1 (0.2)	NR	*Fingolimod*: Basal cell carcinoma, melanoma, breast cancer *IFN beta-1a*: Basal cell carcinoma

IFN = interferon; mcg = microgram; mg = milligram; MS = multiple sclerosis; No. = number; NR = not reported; SAEs = serious adverse events.
[a]Some treatment-specific serious adverse events were observed:

- Natalizumab had more infections (3.2% versus 2.6%) and less MS relapse (6% versus 13%) compared with placebo.
- Alemtuzumab had more infusion reaction (2.6% versus 0%), infection (3.1% versus 1.3%), thyroid disorders (1% versus 0%), and blood and lymphatic system disorders (1.5% versus 0%) compared with interferon beta-1a 44 mcg.
- Fingolimod had more bradycardia and atrioventricular block (1.2% versus 0.1%) compared with placebo or interferon beta-1a 30 mcg.
- There were no apparent specific serious adverse events associated with teriflunomide, dimethyl fumarate, interferons, and glatiramer acetate

APPENDIX 15: SUMMARY RESULTS OF STUDIES REPORTING SUBGROUP ANALYSES AND COMBINATION THERAPY

Table A15.1: Clinical Outcomes of Subgroups

Study	Summary of Results		
CAMMS223 (2008) (2011) (2013)[13,93,128] **Alemtuzumab 12 mg** (n = 113) **Alemtuzumab 24 mg** (n = 110) **Interferon beta-1a 44 mcg** (n = 111)		**Annualized relapse rate**	**Disability progression (%)**
		(12 mg versus 24 mg versus IFNB-1a SC)	
	ITT population	0.12 vs. 0.08 vs. 0.35	8 vs. 10 vs. 26
	EDSS		
	< 2 (n = 123)	0.12 vs. 0.05 vs. 0.31	5 vs. 12 vs. 29
	≥ 2 (n = 199)	0.12 vs. 0.10 vs. 0.38	10 vs. 8 vs. 25
	P value for interaction	0.69 0.42	0.26 0.77
	Age		
	< 31 years (n = 147)	0.14 vs. 0.13 vs. 0.47	6 vs. 4 vs. 27
	≥ 31 years (n = 175)	0.10 vs. 0.05 vs. 0.25	9 vs. 14 vs. 25
	P value for interaction	0.52 0.56	0.58 0.14
	Gender		
	Female (n = 208)	0.11 vs. 0.09 vs. 0.36	9 vs. 9 vs. 20
	Male (n = 114)	0.13 vs. 0.08 vs. 0.35	6 vs. 10 vs. 36
	P value for interaction	0.70 0.92	0.22 0.59
	No of prior relapses		
	≤ 2 (n = 216)	0.10 vs. 0.09 vs. 0.29	5 vs. 9 vs. 25
	> 2 (n = 564)	0.14 vs. 0.08 vs. 0.53	12 vs. 10 vs. 29
	P value for interaction	0.60 0.27	0.39 0.86
FREEDOMS (2010) (2012)[22,94] **Fingolimod 0.5 mg** (n = 425) **Placebo** (n = 418)		**ARR (RR [95% CI]) relative to placebo**	
		Dimethyl fumarate	**Glatiramer acetate**
	ITT population	0.56 (0.42, 0.74)	0.71 (0.55, 0.93)
	EDSS		
	≤ 2 (n = 477)	0.48 (0.30, 0.78)	0.62 (0.39, 0.97)
	> 2 (n = 595)	0.63 (0.45, 0.89)	0.79 (0.57, 1.08)
	Gd+ lesions		
	0 (n = 270)	0.51 (0.29, 0.92)	0.70 (0.42, 1.19)
	≥ 1 (n = 239)	0.49 (0.28, 0.87)	0.76 (0.45, 1.30)
	Age		
	< 40 years (n = 636)	0.53 (0.38, 0.74)	0.58 (0.42, 0.81)
	≥ 40 years (n = 436)	0.64 (0.39, 1.04)	1.03 (0.66, 1.61)
	Gender		
	Female (n = 743)	0.56 (0.40, 0.78)	0.78 (0.57, 1.07)
	Male (n = 329)	0.57 (0.34, 0.95)	0.60 (0.36, 0.99)
	Relapses in the prior year		
	≤ 1 (n = 743)	0.52 (0.36, 0.73)	0.67 (0.48, 0.94)
	≥2 (n = 328)	0.66 (0.42, 1.04)	0.80 (0.53, 1.22)
	Prior MS treatment		
	No (n = 638)	0.64 (0.44, 0.95)	0.78 (0.54, 1.12)
	Yes (n = 434)	0.47 (0.31, 0.69)	0.65 (0.44, 0.94)

TEMSO (2011) (2012)[32,95]

Teriflunomide 7 mg (n = 365)
Teriflunomide 14 mg (n = 358)
Placebo (n = 363)

	Annualized relapse rate	Disability progression (%)
	(7 mg versus 14 mg versus placebo)	
ITT population	0.37 vs. 0.37 vs. 0.54	22 vs. 20 vs. 27
EDSS		
≤ 3.5 (n = 837)	0.35 vs. 0.30 vs. 0.50	23 vs. 22 vs. 26
> 3.5 (n = 249)	0.31 vs. 0.43 vs. 0.47	16 vs. 14 vs. 34
P value for interaction	0.81 0.07	0.09 0.07
Gd+ lesions		
0 (n = 684)	0.31 vs. 0.28 vs. 0.39	23 vs. 20 vs. 26
≥ 1 (n = 389)	0.48 vs. 0.53 vs. 0.79	20 vs. 20 vs. 29
P value for interaction	0.17 0.71	0.34 0.50
Age		
< 38 years (n = 499)	0.45 vs. 0.47 vs. 0.73	22 vs. 18 vs. 28
≥ 38 years (n = 587)	0.31 vs. 0.31 vs. 0.43	21 vs. 22 vs. 27
P value for interaction	0.42 0.55	0.82 0.33
Gender		
Female (n = 783)	0.35 vs. 0.36 vs. 0.54	21 vs. 19 vs. 25
Male (n = 303)	0.37 vs. 0.36 vs. 0.45	23 vs. 23 vs. 35
P value for interaction	0.40 0.62	0.26 0.51
No of prior relapses		
≤ 1 (n = 216)	0.26 vs. 0.17 vs. 0.38	16 vs. 18 vs. 23
2 (n = 564)	0.31 vs. 0.31 vs. 0.44	23 vs. 22 vs. 28
3 (n = 210)	0.46 vs. 0.41 vs. 0.66	21 vs. 15 vs. 26
≥ 4 (n = 96)	0.64 vs. 1.01 vs. 1.12	27 vs. 26 vs. 36
P value for interaction	0.88 0.39	0.95 0.80
Previous MS treatment		
No (n = 792)	0.31 vs. 0.31 vs. 0.45	18 vs. 20 vs. 25
Yes (n = 294)	0.50 vs. 0.47 vs. 0.78	33 vs. 20 vs. 36
P value for interaction	0.85 0.53	0.55 0.15

CONFIRM (2012) (2013)[18,96]

	ARR (RR [95% CI]) relative to placebo	
	Dimethyl fumarate	**Glatiramer acetate**
ITT population	0.56 (0.42, 0.74)	0.71 (0.55, 0.93)
EDSS		
≤ 2 (n = 477)	0.48 (0.30, 0.78)	0.62 (0.39, 0.97)
> 2 (n = 595)	0.63 (0.45, 0.89)	0.79 (0.57, 1.08)
Gd+ lesions		
0 (n = 270)	0.51 (0.29, 0.92)	0.70 (0.42, 1.19)
≥ 1 (n = 239)	0.49 (0.28, 0.87)	0.76 (0.45, 1.30)
Age		
< 40 years (n = 636)	0.53 (0.38, 0.74)	0.58 (0.42, 0.81)
≥ 40 years (n = 436)	0.64 (0.39, 1.04)	1.03 (0.66, 1.61)
Gender		
Female (n = 743)	0.56 (0.40, 0.78)	0.78 (0.57, 1.07)
Male (n = 329)	0.57 (0.34, 0.95)	0.60 (0.36, 0.99)
Relapses in the prior year		
≤ 1 (n = 743)	0.52 (0.36, 0.73)	0.67 (0.48, 0.94)
≥2 (n = 328)	0.66 (0.42, 1.04)	0.80 (0.53, 1.22)
Prior MS treatment		
No (n = 638)	0.64 (0.44, 0.95)	0.78 (0.54, 1.12)
Yes (n = 434)	0.47 (0.31, 0.69)	0.65 (0.44, 0.94)

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; Gd = gadolinium; IFNB = interferon beta; ITT = intention to treat; mcg = microgram; mg = milligram; MS = multiple sclerosis; RR = relative risk; SC = subcutaneous; vs. = versus.

Table A15.2: Summary of Findings in Combination Therapy Studies

Study	Summary of Results

CombiRx (2013)[35]

Interferon beta-1a 30 mcg + glatiramer acetate (n = 499)
Interferon beta-1a 30 mcg (n = 250)
Glatiramer acetate (n = 259)

Outcomes	Results (IFN + GA versus IFN versus GA)	*P* value
Annualized relapse rate	0.12 versus 0.16 versus 0.11 IFN + GA versus GA : no difference IFN + GA versus IFN: ↓25%	 0.27 0.022
Patients relapse-free (%)	77 versus 74 versus 79.5	NS
Sustained disability progression (%)	23.9 versus 21.6 versus 24.8	NS
MSFC change (mean (SD))	0.1 (0.5) versus 0.1 (0.5) versus 0.2 (0.5)	NS
Patients free of enhanced T2 lesions (%)	89.8 versus 83.2 versus 85.5	NR
Death (%)	0.2 versus 0.4 versus 0.4	NR
Serious AEs (%)	14.0 versus 15.2 versus 11.6	NR
Discontinuation because of AE (%)	1.6 versus 1.6 versus 2.3	NR

Authors' conclusion: "Combining the two most commonly prescribed therapies for MS did not produce a significant clinical benefit over three years."

Freedman 2012 et al. (2012)[36]

Teriflunomide 7 mg + interferon beta (n = 37)
Teriflunomide 14 mg + interferon beta (n = 38)
Placebo + interferon beta (n = 41)

Outcomes	Results	*P* value
Annualized relapse rate (mean ± SD)	7 mg versus placebo: 0.28 ± 0.10 versus 0.26 ± 0.29 14 mg versus placebo: 0.11 ± 0.48 versus 0.26 ± 0.29 (Risk reduction: 58%; *P* = 0.2852)	NS NS
Patients with GdE lesions (%)	7 mg versus placebo: 30.6 versus 44.7 14 mg versus placebo: 23.7% versus 44.7%	NR NR
Number of GdE lesions (mean ± SD)	7 mg versus placebo: 0.099 ± 0.60 versus 0.570 ± 0.60 Risk reduction: 82.6%	0.0009
	14 mg versus placebo: 0.024 ± 0.59 versus 0.570 ± 0.60 Risk reduction: 84.4%	0.0001
Death	none	
Serious AEs (%)	7 mg versus placebo: 5.4 versus 2.4 14 mg versus placebo: 0 versus 2.4	NR NR
Discontinuation because of AE (%)	7 mg versus placebo: 2.7 versus 2.4 14 mg versus placebo: 2.6 versus 2.4	NR NR

Authors' conclusion: "Teriflunomide as add-on therapy to interferon-beta had acceptable safety and tolerability and reduced MRI disease activity compared with interferon beta alone."

GLANCE (2009)[37]

Natalizumab + glatiramer acetate (n = 55)
Placebo + glatiramer acetate (n = 55)

Outcomes	Results (Natalizumab versus placebo)	*P* value
Annualized relapse rate (mean ± SD)	0.40 ± 1.19 versus 0.67 ± 1.19	0.237
Patients relapse-free (%)	78 versus 73	0.658
Patients with GdE lesions (%)	31 versus 45	NR
Number of GdE lesions (mean ± SD)	0.6 ± 1.8 versus 2.3 ± 5.3	0.020
Patients with new or enlarged T2 lesions (%)	33 versus 49	NR
Number of new or enlarged T2 lesions (mean ± SD)	0.5 ± 1.1 versus 1.3 ± 2.1	0.029
Death	none	
Serious AEs (%)	1.8 versus 3.6	NR
Discontinuation because of AE (%)	1.8 versus 1.8	NR

Authors' conclusion: "The combination of natalizumab and glatiramer acetate seemed safe and well-tolerated during 6 months' therapy."

SENTINEL (2006)[38]

Natalizumab + interferon beta-1a (n = 589)
Placebo + interferon beta-1a (n = 582)

Outcomes	Results (natalizumab versus placebo)	*P* value
Annualized relapse rate (mean ± SD)	0.34 ± 0.62 versus 0.75 ± 1.04	0.001
Patients relapse-free (%)	54 versus 32 HR 0.50; 95% CI 0.43 – 0.59	<0.001
Sustained disability progression (%)	23 versus 29 HR 0.76, 95% CI 0.61 – 0.96	0.02
Patients with GdE lesions (%)	3.5 versus 25.3	0.001
Number of GdE lesions (mean ± SD)	0.1 ± 0.6 versus 0.9 ± 3.2	NR
Patients with new or enlarged T2 lesions (%)	33 versus 70	0.001
Number of new or enlarged T2 lesions (mean ± SD)	0.9 ± 2.1 versus 5.4 ± 8.7	NR
Death (%)	0 versus 0.3	NR
Serious AEs (%)	18 versus 21	0.23
Discontinuation because of AE (%)	8 versus 7	NR
Mean change of PCS	1.03 versus -0.93	<0.001
Mean change of MCS	0.18 versus -0.96	NS
PCS improvement (%)	23.3% versus 17.4%	NR
PCS worsening (%)	16.5% versus 21.6%	NR
MCS improvement (%)	17.1% versus 21.0%	NR
MCS worsening (%)	17.1% versus 21.0%	NR

Authors' conclusion: "Natalizumab added to interferon beta-1a was significantly more effective than interferon beta-1a alone in patients with relapsing multiple sclerosis. Additional research is needed to elucidate the benefits and risks of this combination treatment."

AE = adverse event; GA = glatiramer; GdE = gadolinium-enhancing; HR = hazard ratio; IFN = interferon; MCS = Mental Component Summary; mcg = microgram; mg = milligram; MSFC = Multiple Sclerosis Functional Composite; n = number of patients in each arm; NR = not reported; NS = not statistically significant; PCS = Physical Component Summary; SD = standard deviation.