ORAL PHARMACOTHERAPY FOR MULTIPLE SCLEROSIS

ORAL PHARMACOTHERAPY FOR RELAPSING-REMITTING MULTIPLE SCLEROSIS: SYSTEMATIC REVIEW AND INDIRECT TREATMENT COMPARISON

By

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ABSTRACT

Background

Oral pharmacotherapy has the potential to offer multiple sclerosis patients improved clinical outcomes compared to traditional therapies.

Objectives

This review assesses the effects of oral therapies compared to placebo and interferon beta-1a in adults with relapsing-remitting multiple sclerosis (RRMS).

Search methods

We searched the MEDLINE, EMBASE, Cochrane Library, Web of Science (January 1980 to April 2011) and clinincaltrials.gov (April 2011) databases and reference lists of articles. The FDA website was also searched.

Selection criteria

Double-blind, placebo-controlled, randomized trials of RRMS patients who were treated with fingolimod, cladribine, laquinimod or interferon beta-1a.

Data collection and analysis

Two reviewers independently assessed articles for inclusion. Data extraction and quality assessment was completed by one reviewer and verified for accuracy. Meta-analysis and indirect treatment comparison methods were used to estimate relative measures of efficacy.

Results

Although 11 trials involving 7,127 participants were included in this review, only 2,109 (30%) and 1,738 (24%) participants contributed to the direct and indirect estimates respectively, for the primary outcome, annualized relapse rate. Oral therapy and interferon beta-1a had a significantly different rate of relapse compared to placebo (Mean difference [MD] -0.21, 95% confidence interval [CI] -0.27 to -0.16 , $p < 0.00001$ and MD -0.33 95% CI -0.65 to -0.01). There was a significant risk reduction of 37% and 19% in the number of patients with at least one relapse for oral therapy and interferon beta-1a compared to placebo respectively. Safety analysis favoured placebo for both sets of trials ($p=0.002$ and $p=0.04$). Indirect estimates were not significant for all three outcomes however; comparability between direct evidence was noted.

Conclusions

Oral pharmacotherapy and interferon beta-1a are effective compared to placebo in controlling relapse rate in patients with RRMS. The indirect measures of effect provide initial estimates of comparative efficacy and incorporation of future evidence will be necessary.

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ACRONYMS AND ABBREVIATIONS

MS	multiple sclerosis
CNS	central nervous system
RR	relapsing-remitting
PP	primary progressive
SP	secondary progressive
DMT	disease modifying therapy
MRI	magnetic resonance imaging
US	United States
FDA	Food and Drug Administration
RCT	randomized controlled trial
ITC	indirect treatment comparison
MTC	mixed treatment comparison
EDSS	Kurtzke Expanded Disability Status Scale
q.w	once weekly
t.i.w.	three times a week
ARR	annualized relapse rate
Gd+	gadolinium-enhancing
AE	adverse event
ITT	intention-to-treat
RR	relative risk
MD	mean difference
CI	confidence interval
NHS	National Health Service
MTC	mixed treatment comparison
OR	odds ratio
RD	risk difference
HR	hazard ratio
MCMC	markov chain monte carlo
MSE	mean squared error
CADTH	Canadian Agency for Drugs and Technologies in Health
SE	standard error
SD	standard deviation
CV	coefficient of variation

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, neurodegenerative disease of the central nervous system (CNS).[1] Auto-reactive lymphocytes, infiltrating the CNS leads to the neuronal injury and associated inflammation seen in the early stages of the disease.[2] Disability progression in MS patients is dependent on the degeneration of axons and the loss of neurons as a result of the chronic neuroinflamation.[2] These events result in clinical manifestations of motor weakness, sensory disturbances, visual loss, gait ataxia, sphincter dysfunction and cognitive changes.[1]

Approximately 1,000 new cases of MS are diagnosed each year in Canada resulting in a national prevalence among the highest in the world of at least 100 per 100,000.[3,4] MS also has a significant economic impact, not only in terms of consumption of healthcare resources but also largely in the form of indirect costs such as productivity losses.[5] Despite its devastating clinical and economic impact, MS continues to challenge investigators trying to understand both the pathogenesis of the disease and preventing further disease progression in patients.

MS is known to affect young adults and then progress with a variable prognosis.[6] The initial clinical course of MS can be broadly subdivided into two major groups, relapsing-remitting (RRMS) and primary progressive (PPMS). Approximately 80-85% of patients develop RRMS in which symptoms and signs typically evolve over a period of several days, stabilize, and then often improve. CNS dysfunction may develop after a relapse, and the disease may progress between relapses (secondary progressive multiple

sclerosis (SPMS)).[6,7] The other 15-20% of affected patients have PPMS, which is characterized by a gradually progressive clinical course.[6,8]

RRMS is most often treated with immune modulating medications; Avonex (interferon beta-1a), Rebif (interferon beta-1a), Betaseron (interferon beta-1b), and Copaxone (glatiramer acetate). Tysabri (natalizumab), a selective adhesion molecule inhibitor is also used as a second line therapy for RRMS. These five therapies are collectively known as disease-modifying-therapies (DMTs).[9] DMTs have demonstrated their clinical efficacy in large clinical trials, with an ability to control disease progression and reduce relapse rates in the short-term.[10,11] However, the long-term impact of these therapies on disease progression is modest [12,13] and patients are at risk of developing neutralizing antibodies resulting in partial efficacy.[14] In addition, these established therapies use unfavouarble routes of administration, resulting in treatment adherence and convenience issues.[15]

Three new pharmaceuticals, fingolimod, cladribine and laquinimod have the potential to offer patients with RRMS improved clinical outcomes and the ease of use associated with oral formulations. Fingolimod, a sphingosine-1-phosphate-receptor modulator that prevents lymphocyte egress from lymph nodes has shown clinical efficacy with respect to relapse rates and magnetic resonance imaging (MRI) outcomes compared to placebo and interferon beta-1a (Avonex).[16,17] Fingolimod was granted market approval by the United States (US) Food and Drug Administration (FDA) in September 2010 and is currently the only oral therapy for RRMS available on the market. Cladribine, an immunomodulator that selectively targets lymphocyte subtypes has also shown clinical

efficacy compared to placebo in reducing relapse rates.[18] In March 2011 the FDA issued a decision not to grant market approval for cladribine, which lead the manufacturer to end marketing and development plans worldwide. Laquinimod, is a novel immunomodular, still in clinical development, that has shown promising efficacy with respect to MRI outcomes compared to placebo.[19] Laquinimod was granted fast-track review in 2009 by the FDA, however the pivotal trial (BRAVO) required for approval is still ongoing. These new oral therapies have the potential to become first-line treatment options for RRMS and possibly replace more traditional treatments such as DMTs. It will therefore be important to determine not only the relative efficacy of these oral treatment options in relation to placebo but also in relation to each other and standard treatment options like interferon beta-1a.

Ideally, comparisons between two therapies should be made under the scrutiny of a randomized controlled trial (RCT). However, evidence comparing competing therapies is usually limited or insufficient. This has lead to the development of indirect treatment comparison (ITC) methods to estimate measures of effect between therapies not directly compared in an RCT setting. ITC methods range from a simple pair-wise comparison of direct evidence of A versus C and B versus C, using the common comparator C to estimate an indirect measure of association of A versus B to more complex methods that combined direct and indirect evidence as well as allow for ranking of the efficacy of all competing treatments.[20,21] ITCs are also useful to make pair-wise comparisons between two different drug classes, when evidence from a class of drugs has been grouped together by a meta-analysis.[21] ITCs have the potential to provide high-value information

on comparative efficacy, however these methods present several limitations and the results of these analyses should be interpreted with caution. The three most commonly used methodologies for conducting an ITC; anchored ITC method, network meta-analyses and mixed-treatment-comparisons (MTCs) will be outlined in detail.

The primary objective of this study was to systematically review all evidence from randomized controlled trials (RCTs) for the 3 oral treatment options; fingolimod, cladribine, and laquinimod in comparison to placebo or interferon beta-1a for the treatment of RRMS. The RCTs comparing interferon beta-1a (Avonex or Rebif) to placebo for the treatment of RRMS were reviewed to provide the data for an indirect comparison. The primary analysis of this study was to estimate cumulative measures of effect, when possible, through the use of meta-analytic techniques for each individual drug compared to placebo. The secondary analysis was to estimate cumulative measures of effect for two classes of drugs compared to placebo (i.e. oral therapies and interferon beta-1a therapies) using meta-analytic techniques. These two measures of effect with placebo as a common comparator were used to generate an indirect effect estimate of MS oral pharmacotherapy versus interferon beta-1a using the anchored ITC method.

ETHICAL CONSIDERATIONS

All health research, whether using primary or secondary data deserves careful examination for potential ethical issues that could arise over the course of the study. Since this study used secondary data (i.e. summary measures of effect obtained from the published literature) many of the ethical concerns associated with the collection and analysis of patient-level data such as confidentiality and privacy were not applicable.

The main ethical concern with this study came with the interpretation of the indirect measures of effect generated in the analysis. Since these estimates were generated from summary measures of effect from a meta-analysis grouping together all treatments within the same class it is possible to make erroneous conclusions. In addition, indirect comparisons are not considered to be fully randomized comparisons and should not be confused with direct evidence generated from a head-to-head RCT. Indirect estimates are similar to observational findings, in that indirect estimates can suffer from confounding and other biases seen in observational studies. When both direct and indirect estimates are available for a specific comparison, the direct evidence should always take precedence for decision-making purposes. However, indirect evidence can provide an initial understanding of the comparative efficacy of two treatments or two classes of drugs before investing in large, active comparator trials.

METHODS

Overview

A systematic literature review was designed to identify all relevant studies for the therapies of interest. Meta-analysis was used, when appropriate, to pool outcomes for both individual and classes of drugs compared to placebo. Comparative efficacy and safety of orally administered MS therapies compared to interferon beta-1a was also estimated using the anchored ITC method.

Criteria for considering studies for this review

Design

Included studies were randomized controlled trials (RCTs) that prospectively evaluated both a treatment group and a control group. RCTs having an oral therapy (fingolimod, cladribine, laquinimod) as a treatment group could be compared to placebo or interferon beta-1a. RCTs evaluating an interferon beta-1a as the treatment group could be only compared to placebo. Studies that compared two interferon beta-1a therapies (e.g. Avonex versus Rebif) were excluded. Uncontrolled and non-randomized trials were also excluded.

Studies comparing interferon beta-1a versus placebo with concurrent corticosteroids (e.g. methylprednisolone), immunosuppressant (e.g. methotrexate) or other concomitant therapies were excluded from the review, as this would confound the measured effect of any treatment co-administered with these drugs.

RCTs that addressed the efficacy of any of the 5 (3 oral and 2 interferon beta-1a) therapies in PPMS or SPMS were excluded from the review. Also excluded were studies

randomizing patients that have not converted to clinically definite MS (i.e. patients having only a first event suggestive of MS, an event involving the optic nerve, brain stem/cerebellum, or spinal cord).

Extension studies of the included RCTs, in which patients originally randomized to placebo were re-randomized to a specific dose of study drug or patients continued with their assigned study drug were included in the review for qualitative analysis. These extension studies might provide any long-term evidence available for the treatment options. This evidence, however, were excluded from the meta-analysis due to the dissimilar/nonrandomized patient population.

Participants

The diagnosis of MS used for the review was based on clinical guidelines.[22,23] Patients included in the review also had a diagnosis of RRMS.[24] Other diagnostic criteria were also commonly applied; at least one or two documented relapses in the last year or two, or a score of no more than 7 on the Kurtzke Expanded Disability Status Scale (EDSS).

Interventions

RCTs of the following 3 oral treatment options; Fingolimod (0.5 mg, 1.25 mg or 5.0 mg per day), Cladribine (3.5 mg or 5.25 mg per kilogram, 8 to 20 days per year), Laquinimod (0.1 mg, 0.3 mg or 0.6 mg per day) compared to placebo or interferon beta-1a were considered. RCTs comparing interferon beta 1-a; Avonex (30 μg intramuscular injection weekly (q.w.)) or Rebif (22 μg or 44 μg subcutaneous injection three times per week (t.i.w.) or weekly (q.w.)) to placebo were also included.

The RCTs assessing the use of parenteral cladribine of any dose were excluded as this review aimed to evaluate the efficacy and safety of oral cladribine specifically.

Outcome measures

Primary outcomes

The primary outcome measure of this review was annualized relapse rate (ARR) defined by the total number of relapses divided by the total number of person-years exposure. A relapse or an exacerbation was defined as: new, worsening, or recurrent neurological symptoms that last at least 24 hours, preceded by a stable or improving neurological state. The event could be recorded with or without objective confirmation of a treating neurologist.

ARR was chosen as the primary outcome due to both its clinical importance and the consistency in reporting as the primary outcome across both oral therapy and interferon beta-1a trials. Ideally, the patient important outcome, disability progression would be most appropriate for analysis. However, a large proportion of the included trials were dose-finding, Phase II trials in which clinical outcomes such as disability progression were rarely reported and when reported, these trials were not powered to obtain reliable estimates for this outcome. In addition, the definition of disability progression varied across the included trials which could lead to difficulties in pooling the outcome and using these summary measures in an indirect comparison.

Secondary outcomes

The secondary outcomes included the number of patients without a relapse; the number of patients without disability progression; the number of gadolinium-enhancing

(Gd+) lesions on T_1-weighted images (mean per patient per scan); the number of patients with no Gd+ lesions on T_1-weighted images, number of new or enlarged lesions on T_2-weighted images (mean); the number of patients without new or enlarged lesions on T_2-weighted images; the number of combined unique lesions; the number of patients with an adverse event (AE) leading to study drug discontinuation; and the number of patients with any adverse event.

Literature search strategies

This reviewed adopted two different search strategies to identify all published and unpublished RCTs for the 5 therapies of interest.

Electronic searches

The detailed search strategy is outlined in Appendix I. The search was conducted on April 26, 2011. The Ovid interface was used to search the MEDLINE and EMBASE databases from 1980-Present. The following key words and Medical Subject Heading terms were employed in the search strategies: "Avonex" "Rebif," "cinnovex," "beta1a interferon," "interferon beta-1a," "interferon beta," "FTY720," "Gilenya," "fingolimod," "Movectro," "cladribine," "laquinimod," "multiple sclerosis" and "relapsing-remitting multiple sclerosis." Limits used included; "humans" and a pre-designed RCT filter (Appendix I). The search strategy employed for the MEDLINE and EMBASE databases was modified to also search the Cochrane Library, clinincaltrials.gov and Web of Science for relevant studies. No restrictions were initially placed on the language of the articles.

Searching other resources

The US FDA website was searched to locate any additional studies or information relevant for this review. Specifically, a search for each drug was conducted using the DRUGS@FDA public database as well as a general search of the FDA website (www.fda.gov) using the following terms: "fingolimod," "cladribine," "laquinimod" and "interferon beta-1a".

In addition, hand searching of the quoted references from included articles was conducted to identify any additional studies.

Literature selection and analysis

Selection of articles

The author and another reviewer independently reviewed the title and abstract of all the studies identified from the search strategies. Based on the screening form presented in Appendix II, a Microsoft Excel 2010 (Microsoft, Redmond, WA) template was developed to record the screening information. The two reviewers individually indicated whether to include or exclude each study for full-text review. If either reviewer was unsure of study inclusion, the article was by default included in the full-text review.

Full-text of the articles identified in the initial screening were independently review by the two reviewers. Studies meeting the inclusion criteria (Appendix III) were included in the final review and the data were extracted. The reviewer agreement was measured using the Cohen's kappa [25] and interpreted as described by Landis JR, et al.[26] Discrepancies were resolved by discussion until a consensus between the reviewers was reached.

Data extraction and management

The author independently extracted data from all included articles using the pre-developed data extraction form and instructions (Appendices IV and V). Approximately 25% of the included articles were also reviewed by a second reviewer to ensure accuracy in the data extraction. Disagreement about data was resolved by discussion among the reviewers.

Data was extracted for characteristics of participants, interventions (type/route of administration, dose, duration of treatment), length of follow-up, frequency and type of clinical assessments and outcome measures. Also extracted were sources of funding, study enrollment initiation and termination dates, location of trial and number of clinical centres.

Assessment of risk of bias

An assessment of each of the included studies was based on the following characteristics: sequence generation, allocation concealment, adequacy of blinding, incomplete outcome data addressed, free of selective reporting and free of other bias. These criteria were judged as "low risk", "unclear risk" or "high risk" according to the Cochrane Handbook.[27] The use of an intention-to-treat (ITT) analysis was also noted. When available, published protocols were included for data extraction. Deviations in the protocol including outcomes reported were noted for each study. However, the majority of trials did not publish the protocols making it difficult to determine any reporting biases in outcome measures.

Measures of treatment effect

Continuous outcomes, including the primary outcome, ARR, were analyzed according to the mean difference (MD). All secondary outcomes were binary, except the mean number of MRI lesions (continuous outcomes) and were analyzed for each trial using relative risk (RR) as a measure of association. Uncertainty was measured using 95% confidence intervals (CI).

The weighted treatment effect was calculated across trials for each outcome. Combined results were expressed as weighted (Mantel-Hazel method) estimates of relative risks with their 95% CI when binary variables were considered. Continuous outcomes were combined using weighted (inverse variance method) mean differences and their 95% CI. CIs and standard error values obtained in data extraction were converted to a SD, when necessary. When median values or unique units of measurement were obtained from data extraction, they were excluded from the meta-analysis, but reported qualitatively, when applicable.

Missing data

When only mean values were reported and no measures of variance were available from the published trial a standard deviation was assigned based on the average proportion of each reported SD respective to its mean value for each specific outcome measure included in the meta-analysis. Since this method is analogous to single imputation it may result in an over estimation in the precision in the summary measures of effect and therefore important to consider when interpreting the pooled results.

Assessment of heterogeneity

Heterogeneity of the pooled outcomes was assessed using the I^2 statistic. I^2 was interpreted as follows: 0.25 as small heterogeneity, 0.25–0.50 as moderate, and >0.50 as large heterogeneity. These cut points have been indiscriminately chosen and represent a limitation of the I^2 statistic. In addition, 95% confidence intervals have not been reported for the I^2 statistic making it difficult to quantify the uncertainty in these estimates of heterogeneity. Potential sources of heterogeneity identified a priori included: 1) definitions used to identify patient populations; 2) method of outcome measurement; 3) different drug formulations; 4) route of administration; 5) drug dosing schedules; and 6) length of follow up.

Data synthesis

Data was analyzed, when possible according to the ITT principle. Data on the number of participants in the treatment groups and numbers with each outcome was used in an analysis regardless of follow-up and compliance issues. It is also common for MRI outcomes to be reported for only a certain proportion of the study participants; therefore under these circumstances analyses were not according to the ITT principle.

When two doses of a study drug were reported, the higher dose was chosen for analysis. The exception was for fingolimod, where the dose of 1.25 mg/day was chosen for analysis based on the consistency of reporting in the three trials. (FTY720/D2201[28], FREEDOMS[17] and TRANSFORMS[16]).

The primary analysis pooled data, when possible, for each individual drug compared to placebo. Since, the oral therapies are relatively new compounds, few studies

are available for each therapy. Individual pooled estimates were therefore not available for both cladribine and laquinimod.

The secondary analysis was used to pooled outcome data for all oral therapies together as a class compared to placebo. Outcome data was also pooled for interferon beta-1a therapies as a class compared to placebo.

Random effects models were used to pool binary outcomes using the Mantel-Hazel method as a weighted average of each trial estimate. Continuous outcomes were pooled using random effects models and the inverse variance statistical method. Statistical analyses were conducted in Review Manager 5 software developed by the Cochrane Collaboration.

Methodological quality of study outcomes

A secondary quality assessment was also conducted using the GRADEprofiler software for each pooled outcome in the primary analysis. The outcomes were graded based on the definitions of each of the 5 GRADEprofiler characteristics: limitations, inconsistency, indirectness, imprecision, and other considerations.[29] The National Health Service (NHS) clinical guideline for the treatment of MS [30] was used, when possible to determine baseline risks, however risks were usually assumed for each outcome based on the included trials.

Sensitivity analyses

Sensitivity analysis was used to observe the effect of removing any data for the oral therapy, cladribine from any summary measures of effect. This drug has been voluntarily removed from the market in Australia and Russia and development of the

drug by the manufacturer has ceased in other markets such as the US and Canada. Since, this drug will no longer be available to patients it may be more appropriate to exclude cladribine from the oral therapy class meta-analyses.

Sensitivity analysis also included removing the PRISMS [31] study from various meta-analyses as this trial had a t.i.w. dosing schedule compared to other interferon beta-1a trials (q.w.).

Indirect treatment comparison methods

There are three commonly used methods for conducting ITCs: anchored ITC, Lumley network meta-analysis and mixed treatment comparisons (MTCs). The basic theoretical framework and underlying assumptions for each method were described. Strengths of the 3 methods were contrasted with their limitations. A description and justification of the ITC methods used in this study were also presented.

Anchored indirect treatment comparison

The simplest of the 3 methods is that developed by Bucher et al.[20] The classic example used a meta-analysis of RCTs that compares 2 prophylactic regimens versus standard prophylaxis for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection.[20] This method was developed to ensure that the randomization of the originally assigned patients groups included in the ITC would be preserved when estimating the indirect measures of treatment effect. Thereby avoiding the bias of naïve ITCs, where only data from the treatment arms of interest are used to draw comparisons.[32]

The odds ratio (OR) was originally used by Bucher et al. as the method's measure of association, however the method has since been applied to estimates of effect such as relative risk (RR), mean difference (MD), risk difference (RD) and hazard ratio (HR).[21] The method uses direct evidence (meta-analysis of RCTs) of *g* studies comparing A versus C and *h* studies comparing B versus C anchored on the common comparator C to determine an indirect measure of association of A versus B. The summary ORs (logarithmic transformation) of the two paired-comparisons (A vs. C and B vs. C) are used to calculate the summary OR of the indirect comparison using the following association: $\ln(OR_{AB}) = \ln(OR_{AC}) - \ln(OR_{BC})$, with the variance of the indirect estimate being the sum of the variance of the two direct measures of association ($Var(\ln OR_{AC}) + Var(\ln OR_{BC})$). An overall measure of variation between the two paired-comparisons (A vs. C and B vs. C) can also be calculated as the sum of their respective total chi-squared values, with $g + h$ degrees of freedom.

The anchored ITC method has also been expanded to incorporate analysis of direct evidence in a "ladder design" (i.e. trials are available for A vs. B, B vs. C, C vs. F and F vs. G). Multiple common comparators (B, C and F) are used to generate indirect estimates for A vs. G, however the number of comparators should be limited to avoid reducing precision in the indirect estimates.[21] It is also important to note that the anchored ITC method can only be used to make pair-wise comparisons when there is a closed-loop evidence network (i.e. both placebo controlled and active comparator evidence is available, A vs. C, B vs. C and A vs. C) and therefore may not incorporate all existing evidence concerning the treatments of interest.

The underlying assumption of the anchored ITC method is that the effects of A and C, observed in the A versus B and B versus C trials respectively, are expected to remain constant had they been administered instead of B in the respective trials. This assumption can only be fulfilled when the two sets of trials are comparable in terms of the linking treatment, patient population/heterogeneity and methodological quality. Differences in these criteria may lead to incorrect estimates of effect.

Bucher et al. [20] also cited that the estimated indirect values were often different (more pronounced) than direct evidence already available for the comparison of interest. This might be attributed to a number of factors including; differences in the efficiency of indirect and direct estimates as a result of larger variance in indirect estimates (Var(ln OR_{AC}) + Var(ln OR_{BC})), methodological differences in trial design, differences in the measurement of outcomes and over representation of different sub-groups in the included trials.

Overall, the anchored ITC method presents a fairly straightforward analysis that allows for pair-wise contrasts to be made to generate indirect measures of effect. Randomization between treatments is partially maintained, reducing confounding unrelated to treatment effect. However, more complex networks of evidence cannot be considered with this method, as analysis is limited to simple pair-wise comparisons and small ladder designs.

Lumley network meta-analysis

Network meta-analysis as termed by Lumley et al. [33] allows for evidence networks with multiple common comparators to be used to determine an indirect estimate

of two treatments. The simplest example is that of using 4 treatment options with direct evidence of A vs. C, A vs. D, C vs. B and D vs. B and using the two common comparators C and D to obtain an indirect estimate of A vs. B. Two separate paths can be used to calculate two indirect estimates. These paths are components of a larger network, in which each pathway can be assigned weights to determine an overall indirect measure of effect.[32] Lumley et al. [33] also developed a measure of the agreement between indirect estimates obtained through different evidence pathways termed "incoherence" that can be incorporated into measures of uncertainty such as 95% CIs.[21,33]

A linear mixed model containing components for sampling variability, true average effects of the treatments *i* and *j* (μ_i and μ_j), treatment heterogeneity (difference between average effects of *i* and *j* and their effects in study (η_{ik} and η_{jk})) and inconsistency (change in effect of treatment *i* when compared to treatment *j* (ζ_{ij})) was developed. Incoherence of the network was defined as the variance of ζ_{ij}, represented as ω. The model used the maximum likelihood estimation which can be formally define as follows[33]:

$$Y_{ijk} \sim N(\mu_i - \mu_j + \eta_{ik} + \eta_{jk} + \zeta_{ij}, \sigma^2_{ijk})$$
$$\eta_{ij} \sim N(0, \tau^2)$$
$$\zeta_{ij} \sim N(0, \omega^2)$$

Network meta-analysis provides the ideal framework for an analysis when at least one closed looped structure is present and a large number of different treatment comparisons are available in the evidence network. Network meta-analysis can, however, be limited especially when incorporating multi-armed trials as well as other complex data structures into an analysis.

Mixed treatment comparisons

Mixed treatment comparisons (MTCs) allow for the simultaneous comparison of multiple treatments using both direct and indirect evidence. A combination of both direct and indirect evidence strengthens estimates of the relative efficacy of two treatments by incorporating the total body of evidence available (direct and indirect). In addition, simultaneous comparisons allow treatments to be ranked based on their efficacy to select the best treatment available.[21]

The most common methodological framework for MTCs is a Bayesian approach described by Lu and Ades.[34] Bayesian methods make use of a likelihood function and prior distributions to form a joint posterior probability density function.[35] WinBUGS software uses simulation methods such as Markov Chain Monte Carlo (MCMC) to summarize the posterior distribution.[36,37]

A simple example can be used to explain the model. If there are 4 treatments available; A, B, C, D, then there are a possible 6 corresponding ln(ORs); A vs. B, A vs. C, A vs. D, B vs. C, B vs. D, C vs. D. If Treatment A is the reference treatment and the true treatment effects (ln(OR)) of B, C and D relative to A are expressed as "basic parameters", d_{AB}, d_{AC}, d_{AD}, where d=(ln(OR)). The remaining 3 contrasts can then be expressed as functions of the basic parameters: $d_{BC} = d_{AB} - d_{AC}$, $d_{BD} = d_{AB} - d_{AD}$, $d_{CD} = d_{AC} - d_{AD}$. Therefore, evidence from comparisons; B vs. C, B vs. D, C vs. D contributes to the estimates of d_{AB}, d_{AC}, d_{AD}.[21,34,38]

Through the use of a random effects model on the logit scale, measures of association for each treatment compared to a reference treatment (A) can be derived. The likelihood of an observed number of events for treatment *k* in study *j* can be expressed as

the distribution: r_{jk}~binomial(p_{jk}, n_{jk}). The probability of the event of interest, p_{jk} , can then be described by the random effect model[34]:

logit (p_{jk}) =

μ_{jb}	b = A, B, C,	if k = b
$\mu_{jb} + \delta_{jbk}$	k = B, C, D,	if k is "after" b

Where, μ_{jb} is the outcome for treatment *b* in study *j* and δ_{jbk} is the random effects (trial-specific effect of treatment *k* relative to *b*) described by the normal distribution, $N(d_{bk} = d_{Ak} - d_{Ab}, \sigma^2)$. The variance for this normal distribution is suitable for analysis of single armed trials, however the correlation between treatment groups in multi-armed trials can be accounted for through use of the parameter Σ, the variance-covariance matrix.[21,34]

Lu and Ads [39] also described a method (inconsistency factor, *w*) for assessing the consistency between direct and indirect evidence from a closed looped structure (e.g. A vs. C, B vs. C and A vs. B).

MTCs are powerful methodologies for comparing and ranking multiple treatments. The incorporation of the total body of evidence (direct and indirect treatment effects) allows for an increase in precision in estimating the true relative measure of effect.[34] However, MTC are quite complex and require Bayesian priors to be estimated, further increasing computational complexity.

Summary of methods

Indirect treatment comparisons (ITCs) rely on one common assumption. The trials included in an ITC have to be "sufficiently similar". Any effect modifiers should be equally distributed across the trials and in cases where both direct and indirect evidence is

used consistency must be observed. Heterogeneity between sets of direct evidence used to determine indirect measures effect can also not be present. These assumptions inevitably drive the selection of an appropriate evidence network for analysis and require the careful consideration of all clinical, statistical and methodological aspects of the included trials.

The methodological aspects of three common ITC methods have been presented; anchored ITC, Lumley network meta-analysis and mixed treatment comparisons. The anchored ITC method is an attractive option due to its ease of calculation and limited data requirements. This method also allows for the calculation of statistical bias and the mean squared error (MSE) of the analysis to determine the precision and accuracy of the indirect estimators. Network meta-analysis and mixed treatment comparisons provide frameworks for analysis of more complex evidence networks, with multiple comparisons and in the case of MTCs, incorporation of both direct and indirect evidence into estimated measures of effect. However, both these methods can be quite computationally complex and have increased data requirements compared to the anchored ITC method. Overall, these three methods provide unique approaches to synthesizing evidence and increasing the understanding of comparative efficacy of treatments of interest.

Justification for choice of method

ITC were made, when possible for groups of pooled outcomes from the secondary analysis using the Canadian Agency for Drugs and Technologies in Health (CADTH) ITC Application.[40] This software has been developed to facilitate the estimation of indirect measures of effect based on the methodology outlined by Bucher H, et al. Since,

the oral therapies of interest are all new chemical entities, the only RCTs available are those used for regulatory approval. This evidence base consisted of one closed loop (fingolimod vs. placebo, Avonex (interferon beta-1a) vs. placebo and fingolimod vs Avonex (interferon beta-1a) opening the possibility to use a network meta-analysis or MTC approach, however only a single or a maximum of 2 studies were available for each pair-wise comparison in the network. Therefore, in order to have an appropriate number of studies for meta-analysis outcomes had to be pooled for classes of drugs (secondary analysis). After grouping the drugs by class, the evidence network became smaller and lacked a closed looped structure, as only two pair-wise comparisons were available (oral therapy vs. placebo and interferon beta-1a vs. placebo). The anchored ITC method was then chosen to be the most appropriate based on the available evidence network. The bias (expected difference between the estimator and the parameter to be estimated) and mean squared error (expected squared deviation between the estimator and this parameter) was also estimated for each indirect estimator using the simulation results presented by Wells G, et al.[21]

RESULTS

Search results

After searching the MEDLINE, EMBASE, Web of Science, Cochrane Clinical Trials Library and clinicaltrials.gov databases, a total of 2,072 citations were collected. After removing duplicates (n=225), 1,847 unique titles and abstracts were screened for inclusion. A total of 1,699 citations were excluded from the review with 148 titles and abstracts eligible for full-text review. The independent full-text review of 148 articles by the two reviewers had substantial agreement (Cohen's kappa = 0.645 standard error 0.0656) and identified 27 articles for data extraction. The secondary search strategy resulted in a total of 88 additional citations (78 citations identified from fda.gov and 10 identified through hand searching of included articles) for review, 2 of which were unique articles identified for data extraction. In total, 29 articles were identified for data extraction. Fifteen articles described the results of RCTs for one of the 5 therapies of interest compared to placebo or interferon beta-1a. A total of 14 articles presented the results of extension trials of the included RCTs. Nine articles (for 7 RCTs)[16-19,28,41-44] comparing an oral therapy to placebo or interferon beta-1a were identified. Six additional articles (4 RCTs)[11,31,45-48] were identified comparing interferon beta-1a to placebo. The remaining 14 articles were the extension studies of 7 RCTs (1 RCT had two different extension trials).[49-62] Figures 1 and 2 provide a detailed flow chart of the study selection process and a network of evidence diagram for the included RCTs, respectively.

Description of studies

<u>Excluded studies</u>

A total of 121 articles were excluded based on various reasons: 38 were duplicate publications of included RCTs in abstract or conference proceeding form.[63-88]; 10 were not RCTs and were either controlled and un-randomized or uncontrolled, open-label trials.[89-98]; 13 were reviews or correspondence associated with RCTs.[99-111]; 15 where post-hoc, retrospective, secondary or sub-group analyses of RCT data.[112-126]; 9 examined the use of parenteral administration of cladribine; including RCTs, post-hoc analyses and conference abstracts.[127-135]; 5 assessed the effects of a treatment or comparator group not of interest.[136-140]; 7 directly compared two doses or two different interferons.[141-147]; 5 were not available in English for screening.[148-152]; 6 reported outcomes not of interest.[153-158]; 4 were still recruiting patients.[159-162]; 5 had concomitant therapy [163-167]; 2 were in patients with a diagnosis other than RRMS. [168,169]; 2 citations from the initial search could not be located.[170,171]

Included studies – Original RCTs

Overview

A total of 11 RCTs were included in the review. These RCTs had comparable participants. The study and baseline participant characteristics are presented in Tables 1 and 2, respectively. The mean age for each treatment group was quite similar across all RCTs ranging from 34 to 42 years. Females accounted for roughly 70% of all trial participants in each individual study. The EDSS score were also similar for all included trials ranging from 2.2 to 3.2. The mean number of relapses experienced in the previous year was also fairly consistent across trials at an approximate mean value of 1.5 relapses/year. Studies only reporting the number of relapses within the previous 2 years

had mean values approximately double the one year mean value.[31,45] MRI baseline characteristics such as the number of Gd+ lesions on a T_1-weighted MRI scan as well as the volume of T_2-weighted images were collected for the majority of RCTs. Two of the older trials for interferon beta-1a [31,45] did not report baseline MRI values. When reported, baseline MRI characteristics were fairly consistent across the remaining trials.
The study characteristics of individual RCT are shown in Tables 3-13 and summarized below.

Fingolimod vs placebo

The safety and efficacy of fingolimod compared to placebo have been assessed in two RCTs. These trials included a 6-month proof-of-concept core study with a 6-month extension (i.e. the patients receiving placebo re-randomized to one of the two doses of fingolimod),[28] and a 24-month, phase III, double-blind, placebo-controlled, multicentre trial.[17] Trial participants were similar across both trials with ages ranging from 18 to 60 years, a diagnosis of MS [22] and the EDSS scores ranging from 0 to 6. The trials included 1,553 participants randomized to either oral fingolimod or matching placebo. Of the 1,553 participants only 1,518 had a diagnosis of RRMS, the remaining 35 participants (from the FTY720 D2201 trial) [28] had a diagnosis of SPMS. The 1.25 mg/day was used in both trials. The primary outcome measure was ARR for the FREEDOMS[17] study. In contrast, the surrogate outcome total number of Gd+ lesions per patient recorded on a T_1-weighted MRI scan was the primary outcome in the FTY720 D2201 trial[28] used, while ARR was one of the secondary outcomes which also included time to first relapse, changes in EDSS score, number of Gd+ lesions, and number of new or enlarged lesions on a T_2-weighted MRI scan.

Cladribine vs placebo

Oral cladribine has only been assessed in one 96-week phase III double-blind, placebo-controlled multicentre trial.[18,42] A total of 1,326 participants were randomized to one of two doses (3.5 mg/kg or 5.0 mg/kg) or matching placebo. Participants were 18 to 65 years and had diagnosis of RRMS [22] and a score of no more than 5.5 on the EDSS scale. The primary outcome reported was the rate of relapses at 96 weeks; also reported was the ARR. An array of secondary outcomes were also reported including; proportion of patients relapse free, time to the first relapse, mean number of lesions per patient scan at 96 weeks for Gd+ T_1-weighted lesions, active T_2-weighted lesions and combined unique lesions (new Gd+ T_1-weighted lesions or new non-enhancing or enlarging T_2-weighted lesions).

Laquinimod vs placebo

Laquinimod has been studied in 3 RCTs. However, outcome data are only available for 2 trials: a proof-of-concept[43] and a phase IIb[19] study which evaluated the safety and efficacy of oral laquinimod compared to placebo for 24 and 36-weeks, respectively. The participants of the proof-of-concept study were followed for an additional 8-week study drug-free period. The results of the 24-month randomized, double-blind, placebo-controlled, phase III study termed ALLEGRO are currently unpublished and only general study and baseline participant characteristics are available.[41] The participants across the trials were 18 to 65 years, with a diagnosis of MS [22] and at least one relapse or exacerbation within the year before study entry. The three studies combined to randomize a total of 1,622 participants to one of three doses of oral laquinimod or a matching placebo. Only 1,590 of the participants had a diagnosis of

RRMS, with the remaining 32 participants from the LAQ in Relapsing MS trial [43] having a diagnosis of SPMS. Doses of laquinimod varied across the three trials ranging from 0.1 mg to 0.6 mg/day. The reported primary outcome was different for each trial. The LAQ in Relapsing MS trial [43] reported the number of cumulative active lesions over 24 weeks (sum of new Gd+ lesions on T_1-weighted images, new lesions appearing on T_2 weighted images but non-enhancing on T_1 weighted images and new enlargement of lesions on T_2-weighted images but non-enhancing on T1 weighted images). The LAQ/5062 trial [19] reported the cumulative number of Gd+ lesions on week 24, 28, 32 and 36 scans. Whereas, the ALLEGRO trial [41] uses the relapse rate at 24 months as the primary outcome measure. Secondary outcomes reported varied for the three trials and included; number of exacerbations (relapses), proportion of patients relapse free, time to first confirmed relapse and other surrogate MRI outcome measures.

Interferon beta-1a vs placebo

Four RCTs comparing an interferon beta-1a therapy with placebo were identified with participants ranging in age from 18 to 60 years, a diagnosis of clinically definite or laboratory supported definite MS [22,23], and an EDSS score ranging from 0 to 5.5. A total of 1,334 participants were randomized to one of 5 doses of interferon beta-1a or placebo. A variety of different doses were used for each trial. The PRISMS[31,48] and IMPROVE[46] trials reported Rebif doses of 22 or 44 μg t.i.w, whereas the OWIMS[45] trial used Rebif doses of 22 or 44 μg q.w. The sole Avonex trial reported a dose of 30 μg q.w.[11,47] Primary outcomes differed across the 4 trials. The IMPROVE[46] and OWIMS[45] trials reported the number of combined unique lesions detected by MRI scanning as the primary outcome measure. Primary outcomes measures for the PRISMS[31] and MSRCG[11]

trials were relapse count over the course of the study and time to onset of sustained worsening in disability, defined as deterioration from baseline by at least 1.0 point on the EDSS persisting for 6 months. Other reported secondary outcomes included; number of exacerbations and annualized rate, times to first and second relapse, proportion of patients relapse free, progression in disability (increase in EDDS of at least 1.0 point sustained over at least 3 months) as well as the number and volume of Gd+ T_1-weighted lesions.

Oral drugs vs interferon beta-1a

The active comparator trial, TRANSFORMS[16] included a total of 1,292 participants originally randomized to a treatment group (0.5 mg/day, 1.25 mg/day fingolimod or 30 μg q.w.), however a modified ITT population of 1,280 participants was also reported as 12 participants were not treated with any study drug. Trial participants had a diagnosis of MS, [22] ranged in age from 18 to 60 years and had EDSS scores ranging from 0 to 5.5. The primary outcome was ARR (number of confirmed relapses during a 12-month period). Secondary outcomes included; the number of new or enlarged hyperintense lesions on T_2 weighted MRI scans at 12 months and time to confirmed disability progression.

In addition, 0.6 mg/day laquinimod is being evaluated in a randomized, placebo-controlled, parallel-reference active treatment arm (Avonex) trial, BRAVO. This study aims to enroll 1331 participants to determine the primary outcome measure; relapse rate at 24 months. However, additional study details are limited as the trial is currently ongoing.

Included studies – RCT extension studies

A summary of the 8 included extension studies is presented in Table 14. Outcomes of interest for the extension studies were concerned mainly with safety, tolerability and the presence of neutralizing anti-bodies. When reported, relapse rates remained favourable for participants on a continuous dose of oral therapy[51,59,62] and in some instances greatly improved after participants had switched from placebo to active study drug.[62]

Risk of bias

Tables 3 to 13 outline the details of the risk of bias assessment of the included RCTs. Assessments were made for 10 of the include trials. Data analysis for the ALLEGRO trial is ongoing and no full publication of trial results is available, therefore a quality assessment was not conducted for that trial.

Allocation (selection bias)

Random sequence generation was clearly reported for all included RCTs except the IMPROVE[46] trial. The majority of trials used computer generated sequences, stratified by site. [16-18,28,31,45,64] A coin-based method of sequence generation was used by one study.[11] Allocation concealment was adequate in three studies, as a result of using coded medication containers, envelopes and other appropriate packaging to ensure concealment.[11,31,43,45] Methods of concealment were not reported in seven studies [11,16-19,28,46] and were therefore labeled with an "unclear risk" of bias.

Blinding (performance bias and detection bias)

Blinding of participants, study personnel and outcome assessments were consistently reported for all the included RCTs. All trials were double-blind in design. However, side effects of interferon beta-1a (e.g. injection site reactions) might compromise the masking of treatment assignment. To reduce this event, the studies using interferon beta-1a required patients to cover injection sites and/or avoid discussion of AEs during neurological examinations.[11,16,31,45] A blinded neurologist or other qualified evaluator preformed neurological examinations and MRI evaluations for all included studies.[11,16-18,28,31,43,45,46,64] All included studies were therefore assigned a "low risk" of performance and detection bias.

Incomplete outcome data (attrition bias)

An ITT analysis was mentioned in 10 trials.[11,16-18,28,31,43,45,46,64] Efficacy and safety outcomes were measured using ITT analysis in 9 trials [11,17,18,28,31,43,45,46,64] whereas two trials, [28,43] reported MRI outcomes using a modified ITT population. Modified ITT populations were also used in 3 trials for safety analyses [16,18,28] and one trial for efficacy analysis.[16] Missing data was imputed in 6 trials [11,16,18,28,31,45,46] using various methods, excluded from analyses in one trial [17] and not reported in 3 trials.[16,19,43]

Selective reporting (reporting bias)

A study protocol was available for review for only one study.[11] All outcomes listed in the protocol were consistently reported in the published paper of the trial. The reporting bias of the remaining 9 trials [16-19,28,31,43,45,46] was defined as "unclear risk", as

uncertainty exists, to the number of other outcomes measured and not reported in the papers.

Other potential sources of bias

All the included trials were fully [16-19,28,31,43,45,46] or partially [11] funded by the pharmaceutical industry. There existed a large potential for publication bias of only favourable outcomes. In spite of this, all financial disclosures and study funding sources were provided for each trial. However, all trials were still labeled with a "high risk" of bias.

Effects of intervention

Primary analysis

Outcome measures were pooled, when possible for each drug compared to placebo. Fingolimod was the only oral therapy with multiple trials reporting the primary outcome of interest as well as various secondary outcomes.[17,28] When pooling outcomes for fingolimod, the common dose reported in both trials (1.25 mg/day) was used for analysis. The ARR was presented in both trials, however, no measure of variance was reported for the relapse rate in the FTY720/D2201 trial.[28] Therefore the SD was estimated to be the same proportion of its mean value as observed for the mean and SD for ARR in the FREEDOMS trial.[17] The pooled analysis involved 1,032 participants receiving either placebo or 1.25 mg/day fingolimod in a random effects model using inverse variance for weighting. The effect of fingolimod on the ARR was statistically significant (weighted mean difference = -0.27, 95% CI -0.40 to -0.14, $p < 0.0001$). There was small heterogeneity between the two studies for this outcome ($I^2 = 23\%$). Possible

sources include; difference in follow-up (6 months[28] versus 24 months[17]) and/or inclusion of 11 participants from the FTY70/D2201 trial[28] with a diagnosis of SPMS. Figure 5 outlines the comparison in more detail. Pooled estimates for 4 secondary outcomes (number of Gd+ lesions on T_1-weighted images (mean), presence of Gd+ lesions on T_1-weighted images, number of patients experiencing an AE leading to study drug discontinuation, number of patients with at least one adverse event) were also derived and are presented in Figures 6-9, respectively. MRI outcomes were pooled using 839 participants receiving 1.25 mg/day fingolimod or placebo. There was no statistically significant difference in the pooled mean number of Gd+ lesions on T_1-weighted images between the two groups (weighted mean difference = -2.47, 95% CI -7.34 to 2.40, p = 0.32). In contrast, the pooled relative risk (RR) (0.3, 95% CI 0.24, 0.51, p<0.00001) for the presence of Gd+ lesions on T_1-weighted images was statistical significant resulting in a 70% risk reduction when the participants were treated with fingolimod. Large (I^2 = 57%) and moderate (I^2 = 47%) heterogeneity were present for both pooled MRI outcomes respectively. As previously mentioned, sources of heterogeneity could include differences in length of follow-up and patient populations. However, increased heterogeneity was seen for both pooled MRI outcomes despite both trials using the same MRI evaluation centre in Switzerland. The heterogeneity might be accounted for due to the differences in included participants as modified ITT populations were used for both trials and therefore exact randomization was not maintained. The safety outcomes were pooled using 1,034 participants receiving 1.25 mg/day fingolimod or placebo. The pooled RR (1.79, 95% CI 1.22 to 2.64, p = 0.003) for the secondary outcome “number of

patients experiencing an AE leading to study drug discontinuation" was statistically significant and favoured placebo with a 79% risk increase for the event in 1.25 mg/day fingolimod treated patients. The pooled RR for the secondary outcome, "number of patients with a least one AE" was not statistically significant (1.20, 95% CI 0.98 to 1.05, p = 0.87). Both analyses had no significant heterogeneity.

Rebif (interferon beta-1a) was compared to placebo in 3 trials.[31,45,46] Two secondary outcomes from the trials were pooled: number of combined unique lesions (mean) and number of patients with at least one relapse. The mean number of combined unique lesions was reported in 2 trials with 569 participants receiving one of the two doses of Rebif (44µg t.i.w or 44µg q.w.) or placebo.[45,46] There was a statistically significant difference in the two pooled means (weighted mean difference = -1.41, 95% CI -2.58 to -0.25, p = 0.02), however large heterogeneity was present (I^2 = 73%). Thought to be attributed to the differences in the dosing schedule for each trial (44µg t.i.w [46] versus 44µg q.w. [45]). Two trials [31,45] reported the outcome "number of patients with at least one relapse", with a pooled analysis of 569 participants. The analysis was not statistically significant (RR = 0.79, 95% CI 0.55 to 1.12, p-0.19) and a large heterogeneity was present (I^2 = 81%). Again the heterogeneity can be largely attributed to the difference in the dosing schedule for each trial (44µg t.i.w [31] versus 44µg q.w. [45]).

Secondary analysis

All oral therapies compared to placebo were grouped as a class and various outcomes were pooled for analysis. Interferon beta-1a therapies were also grouped as a class and compared to placebo.

The ARR was reported in 4 oral therapy trials for a total of 2,132 participants treated with either 5.25 mg/kg cladribine, 1.25 mg/day fingolimod, 0.6 mg/day laquinimod or placebo.[17-19,28] The effect of oral therapy on relapse rate was statistically significant (weighted mean difference = -0.21, 95% CI -0.27 to -0.16) and only small heterogeneity was present (I^2 = 22%). Figure 12 outlines the comparison in more detail. Secondary outcomes including; number of patients with at least one relapse, number of Gd+ lesions on T_1-weighted images (mean), presence of Gd+ lesions on T_1-weighted images, number of patients experiencing an AE leading to study drug discontinuation and number of patients with at least one AE were also pooled and are presented in Figures 13-17 respectively. The number of patients with at least one relapse was reported in 2 oral therapy trials.[18,19] The pooled RR (0.63, 95% CI 0.44 to 0.9, p = 0.01) was statistically significant, resulting in a 37% risk reduction in the patients treated with oral therapy compared to placebo. Large heterogeneity was present (I^2 = 64%) and thought to be attributed to the differences in length of follow-up and treatments in general.

Two different MRI outcomes were consistently reported across the oral therapy trials. The mean number of Gd+ lesions on T_1-weighted images was reported in 4 trials.[17-19,28] The CLARITY trial, however, only reported a mean value.[18] The SD was estimated using the average proportion of the mean respective to its SD reported in the other three other trials.[17,19,28] The pooled effect included 1,940 participants in a random effect model resulting in a statistically significant difference in the two mean values (weighted mean difference = -0.84, 95% CI -1.02 to -0.66, p < 0.00001) with small heterogeneity. The secondary outcome, presence of GD+ lesions on T_1-weighted images was reported in 3

oral therapy trials. [17,19,28] The pooled RR (0.49, 95% CI 0.18 to 1.31, p = 0.16) was not significant and had large heterogeneity. (I^2 = 97%) Since there was already large heterogeneity for this outcome when pooling the two-fingolimod trials it follows logically that addition of laquinimod to the pooled estimate increased the heterogeneity.

Two safety outcomes were also consistently reported across the oral therapy trials. Four trials reported the number of patients experiencing an adverse event leading to study drug discontinuation for a total of 2,064 participants.[17,18,28,43] The pooled RR (2.15, 95% CI 1.32 to 3.50, p = 0.002) favoured placebo with moderate heterogeneity (I^2 = 27%). The number of patients with at least one adverse event was reported in 4 trials, [17-19,28] totaling 2,131 participants. The pooled RR (1.04, 95% CI 0.96 to 1.13, p = 0.36) was not significant and large heterogeneity was also present.

Three different outcomes were pooled for the interferon beta-1a trials: ARR, number of patients with at least one relapse, and number of patients experiencing an AE leading to study drug discontinuation.

The ARR was reported in 3 trials [11,31,45] combining for a total of 870 participants treated with one of three doses of interferon beta-1a (Avonex 30 μg q.w., Rebif 44 μg q.w. and Rebif 44 μg t.i.w.) or placebo. However, only the mean value was reported for 2 trials.[11,31] Therefore the SD for the 2 trials' mean values were estimated using the proportion of the mean respective to its SD reported in the OWIMS[45] trial for the ARR. The effect of interferon beta-1a on relapse rate was significantly different than placebo (weighted mean difference = -0.33, 95% CI -0.65, -0.01, p = 0.04), however large heterogeneity was present (I^2 = 71%) (Figure 18). The 3 trials were very different in

terms of their dosing schedule as previously describe, which may account for the large heterogeneity.

The number of patients with at least one relapse was reported in 3 trials[11,31,45], however data for this outcome from the MSCRG[11] trials was calculated using the first 104 weeks of data for patients accrued early enough to complete >104 weeks of follow up. Therefore, only 741 participants were included in the analysis. The pooled RR (0.81, 95% CI 0.66 to 0.99, p = 0.04) was significant with a 19% risk reduction for interferon beta-1a treated patients compared to placebo. Large heterogeneity was present as an I^2 value of 65% was reported. (Figure 19) Two trials [11,45] reported the number of patients experiencing an AE leading to study drug discontinuation. Combining a total of 499 participants, resulted in a statistically significant pooled RR (4.21, 95% CI 1.07 to 16.56, p = 0.04), favouring placebo. Heterogeneity was not significant. (Figure 20)

Sensitivity analyses

A sensitivity analysis of removing the data from the CLARITY[18,42] trials was used for the three pooled outcomes of interest: ARR, number of patients experiencing an AE leading to study drug discontinuation, and number of patients with at least one AE. Overall, the pooled measures of effect remained largely unchanged, however heterogeneity greatly decreased and was not significant for all three outcomes (I^2 = 0%). The CLARITY trials used a very unique dosing schedule as well as longer follow-up than two of the other 3 trials, which may help to explain the heterogeneity, observed. Figures 21-23 present the detailed results for each outcome.

Large heterogeneity was present for two of the pooled outcomes for interferon beta-1a compared to placebo. A sensitivity analysis was used to explain the heterogeneity by only including the trials with weekly dosing of interferon beta-1a therapy.[11,45] The pooled effect on the ARR in the sensitivity analysis slightly decreased but still remained statistically significant (weighted mean difference = -0.17, 95% CI -0.32 to -0.01). Heterogeneity was not significant ($I^2 = 0\%$). (Figure 24) This sensitivity analysis was also used for the number of patients with at least one relapse. The pooled RR (0.89, 95% CI 0.77 to 1.04, p = 0.13) became non-significant when the PRISMS trial[31] was excluded, however, heterogeneity was greatly reduced ($I^2 = 0\%$). Based on the sensitivity analyses, the heterogeneity observed in the original analyses were caused by the PRISMS trial and most likely attributed to the t.i.w. dosing used in the trial.

Methodological quality of study outcomes

The quality of evidence at the outcome level for the comparison of fingolimod and placebo was assessed using GRADEprofiler software.[29] Table 15 outlines the details of the assessment. Three of the pooled outcomes (ARR, number of patients with at least one AE and number of patients experiencing an AE leading to study drug discontinuation) were assessed to be of moderate quality. Whereas, the two pooled MRI outcomes were defined as low quality evidence due to variations in the ITT populations used in each study as well as the presence of large unexplained heterogeneity. Table 15 outlines the assessment in more detail.

Indirect treatment comparison

Indirect measures of effect

ITCs were conducted for three different outcome measures: ARR, number of patients with at least one relapse, and number of patients experiencing an AE leading to study drug discontinuation. Pair-wise comparisons were made using summary measures of effect for oral therapy (A) versus placebo (C) and interferon beta-1a (B) versus placebo (C), using placebo as the common comparator to obtain an indirect measure of effect of oral therapy (A) versus interferon beta-1a (B). All estimated indirect measures of association were not statistical significant and the details of the comparisons are outlined in Table 16.

Comparison of direct and indirect evidence

Bias and mean squared error

To measure the accuracy and precision of the indirect estimates, the bias and MSE was estimated using the simulation methods by Wells et al.[21] To estimate the bias and MSE the following parameters setting were estimated for the continuous outcome, ARR: coefficient of variation, $CV_C = SD_C/M_C = 0.3$, where SD_C is the SD of the outcome in the placebo group and M_C is the mean of the outcome of interest in the placebo group. In addition, effect sizes (ES) for A vs. C and B vs. C were both estimated to be ≈0.2. Based on these parameters settings the bias was -0.159 and the MSE 0.342. To estimate the bias and MSE of the indirect estimates for the two dichotomous outcomes, the average probability of the event of interest across all included trials in the placebo groups and the respective pooled direct estimates for the relative effect of each pair-wise comparison (A vs. B, B vs. C) was required. The bias and MSE (0.668 and 6.115, respectively) were

relatively high for the indirect estimator for the outcome; number of patients with an AE leading to study drug discontinuation. In contrast, the bias and MSE values (0.024 and 0.027, respectively) for the outcome, number of patients with at least one relapse were relatively small. The details are provided in Table 16.

Internal validity

The comparability between the set of trials that estimated the effect of oral therapy compared to placebo and those that estimated the effect of interferon beta-1a therapy compared to placebo was considerable. The baseline characteristics of study participants were fairly consistent across all trials (Table 2) The length of follow-up was variable for each set of trials, ranging from 6 to 24 months. One difference however, is the study enrollment dates. The interferon beta-1a therapies were mainly assessed in the early 1990's, whereas the oral therapies have just recently been developed. An approximately difference of 10 years in evidence collection could result in heterogeneity between the two sets of trials, leading to potentially biased indirect estimates.

External validity

The only direct evidence available comparing an oral therapy to interferon beta1-a therapy is the TRANSFORMS trial.[16] All three outcomes, for which the indirect estimates were generated, were reported in the TRANSFORMS trial.[16] The ARR was statistically significant in the direct trial (MD=-0.13, 95% CI -0.22 to -0.04). Although, not statistically significant the indirect point estimate was found within the CI of the direct evidence (MD=-0.08, 95% CI -0.25 to 0.09). The direct evidence was also statistically significant for the number of patients with at least one relapse (RR=0.65, 95%CI 0.51 to 0.83). The corresponding indirect point estimate was 0.71 (95% CI 0.48 to

1.044). The indirect and direct estimates for the number of patients with an AE leading to study drug discontinuation were in favour of the opposite treatment group (oral therapy and interferon beta-1a therapy respectively). However, statistical significance was only observed for the in the direct evidence trial.

DISCUSSION

This review identified 11 RCTs assessing efficacy and safety of 3 oral therapies (i.e. fingolimod, cladribine, and laquinimod) and 2 interferon beta-1a therapies (i.e. Avonex and Rebif) compared to placebo for patients with RRMS. Due to the limited number of RCTs and difference in outcome measures, the meta-analysis for individual drugs was conducted for fingolimod only where fingolimod was associated with lower ARR but higher severe adverse events. The finding was consistent if the estimates were pooled for the oral therapies as a class compared to placebo. Pooled measures of the effect of individual interferon beta-1a therapies compared to placebo were limited by significant heterogeneity, attributable to different dosing schedules. The indirect evidence comparing oral therapies with interferon beta-1a was consistent with direct evidence for efficacy outcomes, although not statistical significant. In contrast, indirect estimates favoured oral therapies in the safety analysis despite direct evidence to the contrary, leading to an increase in uncertainty in the comparable safety profile of the two drug classes.

The results of this study support the clinical use of oral therapies in patients with RRMS compared to the interferon beta-1a, Avonex. Clinical guidelines currently recommend first-line treatment with beta interferons or glatiramer acetate and in cases of highly reactive RRMS, natalizumab.[172,173] Avonex is one of the most commonly prescribed beta interferons and has shown broadly comparable effectiveness to other first-line therapies, making it a suitable comparator in this study. However, in some jurisdictions such as Canada and the United Kingdom, the oral therapy fingolimod has

been approved as a second line therapy, only after patients have failed on an interferon. Under these circumstances Avonex no longer becomes a logical comparator and the evidence network presented in this study needs to be modify. Natalizumab, a commonly used second line therapy would be a more appropriate comparator when analyzing oral therapies in this particular sequence of treatments. However, this approach may be difficult as the majority of clinical evidence has been generated in a first line therapy patient population, which may vary greatly from patients who have already failed on Avonex treatment. In addition, the applicability of the evidence generated in this study to patients with more severe forms of RRMS may be limited due to the exclusion of natalizumab from the evidence network.

Since, indirect estimates were derived for classes of drugs, recommendation of a specific oral therapy is not possible. However, the indirect efficacy estimates have confirmed the available head-to-head evidence and shown oral therapies to be more effective in controlling relapses. The discrepancy between the estimated indirect effect measures and the trial-based estimates of effect can be accounted for a number of reasons. CI for indirect estimates should be larger than direct estimates based on the equation for variance of an indirect estimate: (Var(ln ORAC) + Var(ln ORBC)). Since, the CIs of the direct estimates for two efficacy outcomes (ARR and number of patients with at least one relapse) were fairly close to non-significance and point estimates were similar to the indirect values, confidence in the reliability of the indirect estimates can be increased. The indirect estimates for the safety analysis reported conflicting results compared to the available direct evidence, favouring oral therapies. The difference in the

respective values for the outcome, number of patients experiencing an AE leading to study drug discontinuation can most likely be explained by a larger proportion of patients experiencing this event in the early trials than in the recent active comparator trial TRANSFORMS. At the time of the initial interferon beta-1a trials patients would probably be more likely to discontinue treatment simply due to interferon beta-1a being an experimental therapy. Whereas, in the TRANSFORMS trial participants were probably more familiar with interferon beta-1a and its benefit/risk profile thereby making discontinuation less likely.

Discrepancies in the direct and indirect estimates may be further explained by heterogeneity in dosing schedules and trial dates as well as a relatively small number of included trials. However, in general the indirect estimates were based on a fairly comparable, homogenous patient population and should accurately reflect true measures of efficacy and safety.

There are a number of strengths to this study. A comprehensive systematic review, according to the Cochrane methodology [27] was used to capture all relevant data sources. Grey literature from the FDA was also evaluated to increase breadth of the review. Methodological quality of the included trials was assessed by means of two different approaches. Individual trial risk of bias was determined according to 6 criteria outlined in the Cochrane Handbook.[27] The quality of various pooled outcome measures from the primary analysis was also assessed using GRADEprofiler software,[29] allowing evidence to be downgraded in the presence of methodological flaws. In addition, an appropriate network of treatment options was selected, that included homogeneous trials

and study participants as well as included treatment options that are standard therapies or viable alternatives with the potential for widespread clinical use. Also, the use of anchored ITC methods to determine indirect estimators, allows for new information on comparative efficacy of oral therapies and interferon beta-1a for the treatment of RRMS. Since, direct evidence is available it was also possible to contrast the generated indirect estimates with trial based evidence to establish external validity of the study results. Precision and accuracy of the indirect estimates was also assessed through bias and MSE to further increase confidence in the reliability of the indirect measures of effect.

There is limited evidence from a systematic review perspective for the 5 therapies of interest, included in the review. No attempts to systematically review the RCT evidence of MS oral therapies have been published to date. Reviews and meta-analysis of the efficacy and safety of recombinant interferons [174] and interferon beta therapies [175] for the treatment of RRMS are available. However, both reviews did not specifically address the efficacy of interferon beta-1a compared to placebo as evidence was grouped into a large class of treatments. Therefore a direct comparison of study results is not appropriate.

The results of the indirect comparisons in this study, although not statistical significant, still provide a valuable contribution to the total evidence base for MS oral pharmacotherapy. Oral therapies are emerging treatments and are just beginning to change how MS patients treat and cope with their disease. Since, these treatments have the potential to drastically change the burden of disease treatment, it can be expected that uptake of these drugs will be both large and fairly rapid. Therefore, it will be important to

confirm RCT evidence of direct trials through the use of indirect comparisons. ITCs are iterative processes and as new evidence is generated for these novel oral therapies it should be incorporated into the network to determine any resulting changes in relative efficacy. Since, evidence is currently limited more complex ITC methods that are more amendable for inferring relative effect of treatments for either clinical or reimbursement decisions, such as MTCs were not appropriate. This is mainly due to the inclusion of dose-finding, Phase II trials which have relatively small sample sizes and have a limited number of reported clinical outcomes. Also, the ongoing trials ALLEGRO and BRAVO will produce important information on the proposed dose of laquinimod to be marketed that is currently not available. In addition, the BRAVO trial will provide active comparator evidence which will further strength the network and allow for an increase in the incorporation of both direct and indirect evidence.

The indirect estimates from this study should not be used to infer treatment decisions but to provide a general sense of the relative treatment effects and information of how they relate to the direct evidence. Individual judgments can be made, concerning if the new indirect estimates increase, decrease or result in indifference in one's confidence in the trial-based direct evidence. From there decisions can be made regarding further data collection to verify the direct and indirect estimators. In addition, the ITCs presented here can provide some initial evidence as to what results can be expected from the ongoing trial of laquinimod and interferon beta-1a (BRAVO). It is not to be said that laquinimod, based on the results of this study, will not be significantly better at controlling relapses than interferon beta-1a in the BRAVO trial but that the difference in

treatment effect should be close or within the 95% CI of the indirect point estimate in this study. Once more trial data becomes available (ALLERGO and BRAVO) the evidence network can be strengthened and will allow for the use of more complex ITC methods to obtain more reliable indirect estimates of effect of MS oral therapies.

Nevertheless, this study has provided additional evidence concerning the comparative safety and efficacy of oral pharmacotherapy compared to interferon beta-1a. It will be important however, to update this network as new evidence becomes available and incorporate more complex methods to ensure clinical and treatment decisions are based on evidence from all potential sources, both direct and indirect.

CONCLUSIONS

Both oral therapies and interferon beta-1a are effective compared to placebo in controlling relapses in patients with RRMS. Indirect measures of efficacy estimated are consistent with direct evidence, however uncertainty in safety outcomes has been noted. Re-analysis of relative indirect estimates should be made using mixed treatment comparison methods when the ALLERGO and BRAVO trial data become available to obtain more reliable indirect estimators and increase the precision in our understanding of the comparative efficacy and safety of MS oral pharmacotherapy and interferon beta-1a.

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TABLES

Table 1. Study Characteristics - Randomized Controlled Trials

Study (No. of centres/countries)	Accrual period (years)	Follow-up	Interventions	Rescue therapy	No. of patients randomized	Patient Characteristics
Oral therapies compared to placebo						
FREEDOMS (138 centres in 22 countries)	January 2006 to August 2007	24 months	1:1:1 randomization ratio; Oral fingolimod (capsules); 0.5 mg/day or 1.25 mg/day or matching Plb	NR	1272	18 to 55 yrs; diagnosis of MS (revised McDonald criteria); RR course (Lublin FD et al.); one/two or more documented relapses in the previous yr/2 yrs; EDSS 0 to 5.5
FTY720/D2201 (32 centres in 11 countries)	May 2003 to April 2004	6 mths - core study 6 mths - extension study	1:1:1 randomization ratio; Oral fingolimod (capsules); 1.25 mg/day or 5.0 mg/day or matching Plb	Relapse treatment: up to 1000 mg of methylprednisolone per day given i.v. for 3 to 5 days	281 246 (88%) had diagnosis of RRMS; remaining had diagnosis of SPMS	18 to 60 yrs; diagnosis of relapsing MS; at least one of the following: one/two or more documented relapses during the previous yr/ 2 yrs; one or more Gd+ lesion; EDSS 0 to 6; no relapses 30 days before study entry.
CLARITY (155 centres in 32 countries)	April 20, 2005, to January 18, 2007	96 weeks	1:1:1 randomization ratio; Oral Cladribine (tablets); 3.5 mg/kg over 96 weeks or 5.25 mg/kg over 96 weeks or matching Plb	Relapse treatment: s.c. IFN beta-1a 44 ug (tiw) available after wk 24, if a patient experienced more than one relapse and/or a sustained increase in EDSS score	1326	18-65 yrs; diagnosis of RRMS (McDonald criteria); lesions consistent with MS on MRI (Fazekas criteria); at least one relapse within 12 months before study entry; score of no more than 5.5 on EDSS scale
LAQ/5062 (51 centres in 9 countries)	March, 2005 to October 2005	36 weeks	1:1:1 randomization ratio; Oral laquinimod; 0.3 mg/day (2 tablets, one 0.3 mg laquinimod and one Plb) or 0.6 mg/day (2 tablets, two 0.3 mg laquinimod) or matching Plb (two Plb tablets)	Relapse treatment: 1000 mg dose of i.v. methylprednisolone for 3 consecutive days without an oral taper	306	18 to 50 yrs; diagnosis of MS (McDonald criteria); RRMS (Lublin FD et al.); ambulatory with EDSS between 1 and 5; at least 1 Gd+ lesion on MRI scan; at least one documented relapse within the year before study entry
LAQ in Relapsing MS (20 centres in 4 countries)	April 6 to October 3, 2002 Last follow-up on June 17, 2003	24 weeks	1:1:1 randomization ratio; Oral laquinimod; 0.1 mg (3 tablets/day) or 0.3 mg (3 tablets/day) or Plb (3 tablets/day)	NR	209 177 (85%) had diagnosis of RRMS; remaining had diagnosis of SPMS	18 to 65 yrs; diagnosis of MS (McDonald criteria); EDSS score 0 to 5.5; RRMS or SPMS (Lublin and Reingold criteria); active disease (presence of at least one/two documented clinical or sub-clinical exacerbations in the last yr/2 yrs); presence of Gd+ lesions on the screening MRI; at least nine T2 lesions; combination of at least three T2 lesions and at least one Gd+ lesion on a T1 weighted scan at screening
ALLEGRO (Not reported, ongoing trial)	NR	24 months	1:1 randomization ratio; Oral laquinimod once-daily (capsule); 0.6 mg or matching Plb	NR	1107	18 to 55 yrs; diagnosis of MS (McDonald criteria); at least one/two relapses in the last 12/24 months; or 1 relapse between years 1-2 prior to screening combined with at least one Gd+ lesion on MRI observed within 1 year prior to screening

Study (No. of centres/countries)	Accrual period (years)	Follow-up	Interventions	Rescue therapy	No. of patients randomized	Patient Characteristics
Parenteral therapies compared to placebo						
IMPROVE (10 countries)	NR	16 wk - core study; 24 wk -active extension; 4 wk - safety extension	2:1 randomization ratio (weeks 0 to 16); s.c. IFN beta-1a (Rebif) - 44 ug (tiw) or Plb (weeks 17 to 40); all patients receive Rebif - 44 ug (tiw)	Consitiutional symptoms: ibuprofen or acetaminophen were used before each injection during the initial 16 wks	180	18 to 60 yrs; diagnosis of RRMS (McDonald criteria); EDSS score ≤5.5; active disease (≥1 clinical event and ≥1 Gd+ MRI lesion
OWIMS (11 centres in 5 countries)	March 1995 to Nov 1995 Last study visit Nov 1996	24 wk; additional 24 wk; re-randomization to one dose of Rebif	1:1:1 randomization ratio; s.c. IFN beta-1a (Rebif) 22 ug (qw) or 44 ug (qw) or Plb; administered as ready-to-use solutions in a volume of 0.5 mL	Relapse treatment: 1.0 g/day methylprednisolone for 3 consecutive days at physician's discretion; Consitiutional symptoms: acetaminophen	293	18 to 50 yrs; diagnosis of clinical definite or laboratory supported definite RRMS of at least 1 year's duration (Poser CM, et al.); EDSS 0 to 5.0; at least one relapse in the prior 24 months but not in the 8 weeks before entry and at least 3 lesions consistent with MS on MRI
PRISMS (22 centres, 9 countries)	May, 1994, and February, 1995	2 years	1:1:1 randomization ratio; self-administered s.c. IFN beta-1a (Rebif) 22 ug (tiw) or 44 ug (tiw) or Plb; dose was gradually increased over 4-8 weeks with 20% of the dose given for 2-4 weeks and 50% for another 2-4 weeks before full dose was given	Relapse treatment: 1.0 g i.v. methylprednisolone for 3 consecutive days	560	Median age 34.9; diagnosis of clinically definite or laboratory supported definite MS of at least 1 year's duration (Poser CM, et al.); EDSS 0 to 5.0; at least two relapses in the preceding 2 yrs
MSCRG (4 centres in 1 country)	Nov 1990 to early 1993 (trial ended 1 yr early; sample size reduced)	2 years	1:1 randomization ratio; i.m. IFN beta-1a (Avonex) 30 ug (qw) or Plb; injections were performed by study nurses or by local health professionals under the supervision of study personnel	Relapse treatment: i.m. adrenocorticotropic hormone gel, 80 units/day for 10 days or i.v. methylprednisolone 1000 mg/day for 4 days followed by a brief course of oral prednisone; Consitiutional symptoms: acetaminophen 650 mg was given prior to and for 24 hours after each injection	301	18 to 55 yrs; complete remissions (returned to baseline pre-exacerbation disability status); incomplete remissions (did not return to their baseline pre-exacerbation disability status because of new residua); EDSS 1.0 to 3.5; clinical definite MS for at least 1 year (Poser CM, et al.); at least two documented exacerbations in the prior 3 years and no exacerbations for at least 2 months at study entry

Study (No. of centres/countries)	Accrual period (years)	Follow-up	Interventions	Rescue therapy	No. of patients randomized	Patient Characteristics
Oral therapy compared to parenteral therapy						
TRANSFORMS (172 centres in 18 countries)	May 2006 to September 2007	12 months	1:1:1 randomization ratio; Oral fingolimod 1.25 mg/day or 0.5 mg/day or i.m. IFN beta-1a (Avonex) 30 ug (qw)	NR	1292	18 to 55 yrs; diagnosis of MS (revised McDonald criteria); RR course (Lublin FD et al.); EDSS 0 to 5.5; at least one/two documented relapses in the last yr/2yrs

Table 2. Baseline characteristics of patients from included studies

Trial (Ref. #)	Mean Age			No. of (%) females randomized			EDSS score (mean)			No. of relapses in previous yr (mean)			No. of Gd+ T1 lesions (mean)			Mean volume of T2 images (mm^3)		
Oral therapies compared to placebo																		
	Plb	**0.5 mg**	**1.25 mg**	**Plb**	**0.5 mg**	**1.25 mg**	**Plb**	**0.5 mg**	**1.25 mg**	**Plb**	**0.5 mg**	**1.25 mg**	**Plb**	**0.5 mg**	**1.25 mg**	**Plb**	**0.5 mg**	**1.25 mg**
FREEDOMS	37.2 ±8.6	36.6 ±8.8	37.4 ±8.9	298 (71.3)	296 (69.6)	295 (68.8)	2.5 ±1.3	2.3 ±1.3	2.4 ±1.4	1.4 ±0.7	1.5 ±0.8	1.5 ±0.8	1.3 ±2.9	1.6 ±5.6	1.8 ±4.7	6162 ±7085	6128 ±7623	6829 ±8491
	Plb	**1.25 mg**	**5.0 mg**	**Plb**	**1.25 mg**	**5.0 mg**	**Plb**	**1.25 mg**	**5.0 mg**	**Plb**	**1.25 mg**	**5.0 mg**	**Plb**	**1.25 mg**	**5.0 mg**	**Plb**	**1.25 mg**	**5.0 mg**
FTY720/D2201	37.1	38.0	38.3	61 (66)	70 (75)	65 (71)	2.6	2.7	2.5	1.2	1.3	1.3	2.8	3.4	2.8	8805	10,219	8722
	Plb	**3.5 mg/kg**	**5.25 mg/kg**	**Plb**	**3.5 mg/kg**	**5.25 mg/kg**	**Plb**	**3.5 mg/kg**	**5.25 mg/kg**	**Plb**	**3.5 mg/kg**	**5.25 mg/kg**	**Plb**	**3.5 mg/kg**	**5.25 mg/kg**	**Plb**	**3.5 mg/kg**	**5.25 mg/kg**
CLARITY	38.7 ±9.9	37.9 ±10.3	39.1 ±9.9	288 (65.9)	298 (68.8)	312 (68.4)	2.9 ±1.3	2.8 ±1.2	3.0 ±1.4	NR	NR	NR	0.8 ±2.1	1.0 ±2.7	1.0 ±2.3	14,287.6 ± 13,104.8	14,828.0 ± 16,266.8	17,202.1 ± 17,467.7
	Plb	**0.3 mg**	**0.6 mg**	**Plb**	**0.3 mg**	**0.6 mg**	**Plb**	**0.3 mg**	**0.6 mg**	**Plb**	**0.3 mg**	**0.6 mg**	**Plb**	**0.3 mg**	**0.6 mg**	**Plb**	**0.3 mg**	**0.6 mg**
LAQ/5062	NR	NR	NR	NR	NR	NR	2.5 ±1.1	2.3 ±1.1	2.3 ±1.0	1.37 ±0.56	1.46 ±0.69	1.51 ±0.78	4.8 ±9.0	5.6 ±8.7	4.2 ±8.0	15.4 ±16.4*	15.1 ±12.4*	14.9 ±13.5*
	Plb	**0.1 mg**	**0.3 mg**	**Plb**	**0.1 mg**	**0.3 mg**	**Plb**	**0.1 mg**	**0.3 mg**	**Plb**	**0.1 mg**	**0.3 mg**	**Plb**	**0.1 mg**	**0.3 mg**	**Plb**	**0.1 mg**	**0.3 mg**
LAQ in Relapsing MS	38.7	42.4	39.6	49 (73.1)	54 (79.4)	52 (70.3)	2.96	3.23	3.15	NR	NR	NR	2.25 ±5.00	1.48 ±2.10	1.65 ±2.52	8.79 ±12.39	10.8 ±9.8	12.0 ±12.8
	Total (Plb and 0.6 mg)			**Total (Plb and 0.6 mg)**			**Total (Plb and 0.6 mg)**			**Total (Plb and 0.6 mg)**			**Total (Plb and 0.6 mg)**			**Total (Plb and 0.6 mg)**		
ALLEGRO	38.7			68.6%			2.6			1.2 ±0.7			NR			NR		

Parenteral therapies compared to placebo																		
	Total (Plb and 44 µg tiw)			**Total (Plb and 44 µg tiw)**			**Total (Plb and 44 µg tiw)**			**Total (Plb and 44 µg tiw)**			**Total (Plb and 44 µg tiw)**			**Total (Plb and 44 µg tiw)**		
IMPROVE	NR			NR			NR			NR			NR			NR		
	Plb	**22 µg qw**	**44 µg qw**	**Plb**	**22 µg qw**	**44 µg qw**	**Plb**	**22 µg qw**	**44 µg qw**	**Plb**	**22 µg qw**	**44 µg qw**	**Plb**	**22 µg qw**	**44 µg qw**	**Plb**	**22 µg qw**	**44 µg qw**
OWIMS	34.9 ±7.8	35.4 ±7.3	35.5 ±7.4	100 (74)	95 (73)	98 (71)	2.6 ±1.3	2.7 ±1.2	2.6 ±1.4	2.4 ±1.2†	2.3 ±1.3†	2.4 ±1.1†	NR	NR	NR	NR	NR	NR
	Total (Plb, 22, 44 µg tiw)			**Plb**	**22 µg tiw**	**44 µg tiw**	**Plb**	**22 µg tiw**	**44 µg tiw**	**Plb**	**22 µg tiw**	**44 µg tiw**	**Plb**	**22 µg tiw**	**44 µg tiw**	**Plb**	**22 µg tiw**	**44 µg tiw**
PRISMS	34.9 ±7.5			(75)	(67)	(66)	2.4 ±1.2	2.5 ±1.2	2.5 ±1.3	3.0 ±1.3†	3.0 ±1.1†	3.0 ±1.1†	NR	NR	NR	NR	NR	NR
	Plb		**30 µg qw**	**Plb**		**30 µg qw**	**Plb**		**30 µg qw**	**Plb**		**30 µg qw**	**Plb**		**30 µg qw**	**Plb**		**30 µg qw**
MSCRG	39.9 (SEM 0.64)		36.7 (SEM 0.57)	103 (72)		118 (75)	2.3 (SEM 0.07)		2.4 (SEM 0.06)	1.2 (SEM 0.05)‡		1.2 (SEM 0.05)‡	2.32 (SE 0.37)		3.17 (SE 0.62)	219.0 (SE 36.2)		255.0 (SE 45.1)
Oral therapy compared to parenteral therapy																		
	30 µg qw	**0.5 mg**	**1.25 mg**	**30 µg qw**	**0.5 mg**	**1.25 mg**	**30 µg qw**	**0.5 mg**	**1.25 mg**	**30 µg qw**	**0.5 mg**	**1.25 mg**	**30 µg qw**	**0.5 mg**	**1.25 mg**	**30 µg qw**	**0.5 mg**	**1.25 mg**
TRANSFORMS	36.0 ±8.3	35.8 ±8.4	36.7 ±8.8	295 (67.8)	293 (68.8)	282 (65.4)	2.19 ±1.26	2.21 ±1.31	2.24 ±1.33	1.5 ±0.8	1.5 ±0.9	1.5 ±1.2	1.06 ±2.80	1.49 ±4.77	0.98 ±2.81	4924 ±5711	5085 ±5962	5170 ±6642

*Values reported in mL, not in mm^3
†Mean number of relapses within the previous 2 years
‡Pre-study exacerbation rate
SEM = standard error of the mean
SE = standard error

Table 3. Study characteristics (FTY720 D2201 Trial)

Methods	6-month, double-blind, placebo-controlled, proof-of-concept, core study to evaluate the efficacy and safety of oral fingolimod and a 6-month extension study where patients initially receiving placebo are randomized in a blinded fashion to one of the two doses of fingolimod. Patients initially receiving one of the two doses of study drug were able to continue treatment in the 6-month extension study.
Participants	Patients (18 to 60 years old) had a diagnosis of relapsing multiple sclerosis, and at least one of the following: two or more documented relapses during the previous 2 years, one or more documented relapses in the year before enrollment, one or more gadolinium-enhanced lesion detected by MRI, EDSS score of 0 to 6 and neurologically stable condition (no relapses for at least 30 days before study entry). Only 83 patients (90%) from the placebo group, 83 patients (89%) from the 1.25 mg group and 80 patients (87%) from the 5.0 mg group had a diagnosis of relapsing-remitting MS. All remaining patients had a diagnosis of secondary progressive multiple sclerosis.
Interventions	1:1:1 randomization ratio Oral fingolimod (capsules) - 1.25 mg/day Oral fingolimod (capsules) - 5.0 mg/day Matching placebo Relapses were managed by the treating physician according to a standardized scheme, with up to 1000 mg of methylprednisolone per day given intravenously for 3 to 5 days.
Outcomes	Primary - total number of gadolinium-enhanced lesions per patient recorded on T1-weighted MRI, Secondary - total volume of gadolinium-enhanced lesions per patient, the porportion of patients with gadolinium-enhanced lesions, total number of new lesions per patient on T2-weighted images, change in lesion volume on T2-weighted images, change in brain volume, number of patients remaining free of relapse, annualized relapse rate, time to first relapse, change in EDSS score, adverse events and laboratory evaluations.
Notes	(ClinicalTrials.gov number, NCT00333138 [CORE STUDY]), (ClinicalTrials.gov number, NCT00235430 [EXTENSION])

Risk of bias

Bias	Author's judgment	Support for judgment
Random sequence generation (selection bias)	**Low risk**	Core study - Stratified according to disease course (RRMS or SPMS) with the use of a centralized automated system that provided randomization packages of the study drug to each center. The medication was prepackaged on the basis of a block size of 3 (1.25 mg, 5.0 mg and placebo)

Allocation concealment (selection bias)	**Unclear risk**	Not reported.
Blinding of participants and personnel (performance bias)	**Low risk**	"The study included a 6-month double-blind core study (0 to 6 months) and a 6-month extension study during which the investigators and patients were unaware of treatment assignments (0 to 7 months)." "Participating patients received a new set of medications and were unaware of the treatment assignments."
Blinding of outcome assessment (detection bias)	**Low risk**	"MRI scans were assessed for quality and compliance at the MS-MRI Evaluation Center in Basel without the evaluators' knowledge of treatment assignments or clinical results." "Neurologic assessments were performed by specially trained, independent neurologists who were unaware of the treatment assignments."
Incomplete outcome data (attrition bias)	**Low risk**	MRI analyses were primarily performed in a population of patients who underwent randomization and who completed 6 months of treatment had no major protocol violations and for whom MRI scans were available at baseline and on three or more visits. Use of per-protocol-like population for MRI analyses is appropriate for a proof of concept study.Modified ITT - all patients randomized to receive at least one dose of study medication and had at least one post-baseline MRI.Clinical outcomes were evaluated in the ITT population.Safety outcomes - all patients randomized to receive at least one dose of study medication and had at least one post-baseline safety assessment. "When scans were missing patients discontinued treatment or MRI was performed within 14 days after corticosteroid treatment and the results were therefore considered invalid, the median of number and volume of gadolinium enhancing lesions and the number of new lesions on monthly T2-weighted scans avilable post-base-line was imputed."
Selective reporting (reporting bias)	**Unclear risk**	This is difficult to tell as the study protocol is not available for review. All outcomes listed in the manuscript are reported but there is uncertainty as to the number of other outcomes measured and not reported in the manuscript.
Other bias	**High risk**	The study was supported by Novartis Pharma. As this entity has a finacial stake in the compound under investigation there is the potential for publication bias of only favourable outcomes. However, all finacial disclosures and study funding sources have been listed.

Table 4. Study characteristics (FREEDOMS)

Methods	24-month, phase III, double-blind, placebo-controlled, multicentre trial to investigate the effects of daily oral fingolimod on various clinical outcomes measures.
Participants	Patients (18 to 55 years old) had a diagnosis of multiple sclerosis, according to the revised McDonald criteria, a relapsing-remitting course (Lublin FD et al.), one or more documented relapses in the previous year or two or more in the previous 2 years, EDSS score of 0 to 5.5.
Interventions	1:1:1 randomization ratio Oral fingolimod (capsules) - 0.5 mg/day Oral fingolimod (capsules) - 1.25 mg/day Matching placebo
Outcomes	Primary - Annualized relapse rate, Secondary - time to confirmed disability progression, time to first relapse, time to disability progression (confirmed after 6 months), changes in EDSS score, number of gadolinium-enhancing lesions, number of new or enlarged lesions on T2-weighted MRI scans, proportion of patients free from new or enlarged lesions on T2-weighted MRI scans, volumes of hypointense lesions on T2-weighted scans and hypointense lesions on T1-weighted scans, change in brain volume and safety and tolerability measures.
Notes	FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS). (ClinicalTrials.gov number, NCT00289978)

Risk of bias

Bias	Author's judgment	Support for judgment
Random sequence generation (selection bias)	**Low risk**	"Centrally, with the use of a validated system and stratification according to site, with a block size of six within each site."
Allocation concealment (selection bias)	**Unclear risk**	Not reported.
Blinding of participants and personnel (performance bias)	**Low risk**	Participants are likely to be blinded due to the double-blinded nature of the study and the use of a matching placebo.
Blinding of outcome assessment (detection bias)	**Low risk**	"To ensure that all assessments remained unbiased regarding the study-group assignments (i.e., uneffected by awareness of them) an independent, specially trained and certified examining neurologist determined all EDSS scores." "MRI scans were analyzed at a central MRI evaluation centre by radiologists who were unaware of the study group assignments."
Incomplete outcome data (attrition bias)	**Low risk**	Both the ITT and safety populations included all patients who had undergone randomization. "Missing data were not imputed."

Selective reporting (reporting bias)	**Unclear**	This is difficult to tell as the study protocol is not available for review. All outcomes listed in the manuscript are reported but there is uncertainty as to the number of other outcomes measured and not reported in the manuscript.
Other bias	**High risk**	The study was supported by Novartis Pharma. As this entity has a finacial stake in the compound under investigation there is the potential for publication bias of only favourable outcomes. However, all finacial disclosures and study funding sources have been listed.

Table 5. Study characteristics (TRANSFORMS)

Methods	12-month, parallel-group, double-blind, double-dummy, phase III, multicentre randomized trial comparing oral fingolimod and interferon beta-1a.
Participants	Patients (18 to 55 years old) had a diagnosis of multiple sclerosis according to the revised McDonald Criteria and relapsing-remitting course according to Lublin FD et al., EDSS 0 to 5.5 and had at least 1 documented relapse in the last year or at least 2 documented relapses in the previous 2 years.
Interventions	Oral fingolimod once daily - 1.25 mg Oral fingolimod once daily - 0.5 mg Intramuscular interferon beat-1a (Avonex) weekly dose of 30 μg.
Outcomes	Primary - annualized relapse rate (number of confirmed relapses during a 12-month period), Secondary - number of new or enlarged hyperintense lesions on T2 weighted MRI scans at 12 months and time to confirmed disability progression.
Notes	Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS). (ClinicalTrials.gov number, NCT00340834)

Risk of bias

Bias	Author's judgment	Support for judgment
Random sequence generation (selection bias)	**Low risk**	"Centrally in blocks of six within each site and was stratified according to site. Study group assignments were preformed with the use of an interactive voice -response system."
Allocation concealment (selection bias)	**Unclear risk**	Not reported.
Blinding of participants and personnel (performance bias)	**Low risk**	"During the trial, patients, study personnel, MRI evaluators, steering-committee members and the study statistician were unaware of study group assignments and leukocyte counts. Capsules, syringes and packaging materials for active and placebo treatments were indistinguishable."
Blinding of outcome assessment (detection bias)	**Low risk**	"During the trial, patients, study personnel, MRI evaluators, steering-committee members and the study statistician were unaware of study group assignments and leukocyte counts." Patients were instructed to cover injection sites at visits and not discuss adverse events with clinical evaluators."
Incomplete outcome data (attrition bias)	**Unclear risk**	The efficacy and safety analyses used a "Modified ITT" population (all patients who underwent randomization and received at least one dose of study drug). Methods for dealing with missing data were not provided in detail.

Selective reporting (reporting bias)	**Unclear risk**	This is difficult to tell as the study protocol is not available for review. All outcomes listed in the manuscript are reported but there is uncertainty as to the number of other outcomes measured and not reported in the manuscript.
Other bias	**High risk**	The study was supported by Novartis Pharma. As this entity has a financial stake in the compound under investigation there is the potential for publication bias of only favourable outcomes. However, all financial disclosures and study funding sources have been listed.

Table 6. Study characteristics (CLARITY)

Methods	96-week phase III double-blind, placebo-controlled multicentre trial to investigate the efficacy and safety of oral cladribine tablets.
Participants	Patients (18-65 years old) had diagnosis of relapsing-remitting multiple sclerosis according to the McDonald criteria, lesions consistent with multiple sclerosis on MRI according to the Fazekas criteria, had at least one relapse within 12 months before study entry and had a score of no more than 5.5 on the EDSS scale.
Interventions	1:1:1 randomization ratio Oral Cladribine (tablets) - 3.5 mg/kg over 96 weeks Oral Cladribine (tablets) - 5.25 mg/kg over 96 weeks Matching placebo Rescue therapy with subcutaneous interferon beta-1a 44 μg (3x per week) was available after week 24, if a patient experienced more than one relapse and/or a sustained increase in EDSS score.
Outcomes	Primary - Rate of relapse at 96 weeks, Secondary - proportion of patients who were relapse free and the time to sustained progression of disability, time to the first relapse, proportion of patients receiving INF beta-1a rescue therapy, mean number of lesions per patient scan at 96 weeks for gadolinium-enhancing T1-weighted lesions, active T2-weighted lesion, combined unique lesions (new gadolinium-enhancing T1-weighted lesions or new non-enhancing or enlarging T2-weighted lesions), adverse events and laboratory measurements.
Notes	Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY). (ClinicalTrials.gov number, NCT00213135)

Risk of bias

Bias	Author's judgment	Support for judgment
Random sequence generation (selection bias)	**Low risk**	"Randomization was performed with the use of a central system and a computer-generated treatment randomization code with dynamic allocation by site in permuted blocks of six."
Allocation concealment (selection bias)	**Unclear risk**	Not reported.
Blinding of participants and personnel (performance bias)	**Low risk**	"To maintained the double-blind nature of the study, all patients within a weight range received the same number of tablets (cladribine or matched placebo)."

Blinding of outcome assessment (detection bias)	**Low risk**	"An independent evaluating physician, who was unaware of study-group assignments, performed neurological exams and determined whether a clinical event fulfilled criteria consistent with a relapse." "Evaluators at a central neuroradiology centre assessed MRI evaluations in a blinded fashion." "For suspected relapses occurring between study visits, patients were required to attend the study site within 7 days after onset of neurological symptoms for objective assessment by the evaluating physician in a blinded fashion."
Incomplete outcome data (attrition bias)	**Low risk**	ITT analysis was used for efficacy outcomes (all patients randomized) and the , safety population include all patients who received at least one dose of study drug and follow up was available "For the primary end point, imputed data were derived only from patients in the placebo group." "For patients who received rescue therapy, the primary and secondary efficacy analyses included the pre-rescue data and imputed data from the time of rescue onward, according to methods in the statistical analysis plan."
Selective reporting (reporting bias)	**Unclear risk**	This is difficult to tell as the study protocol is not available for review. All outcomes listed in the manuscript are reported but there is uncertainty as to the number of other outcomes measured and not reported in the manuscript.
Other bias	**High risk**	The study was supported by Merck Serono. As this entity has a financial stake in the compound under investigation there is the potential for publication bias of only favourable outcomes. However, all financial disclosures and study funding sources have been listed.

Table 7. Study characteristics (LAQ in Relapsing MS Trial)

Methods	24-week multicentre, double-blined, randomized, placebo-controlled, proof-of-concept study to evaluate the safety and efficacy of laquinimod administered orally. Followed by a 8-week drug free period after completion of intial 24 weeks).
Participants	Patients (18 to 65 years old) had a diagnosis of MS according to the McDonald critera, EDSS score 0 to 5.5, Lublin and Reingold criteria for relapsing-remitting or secondary progressive multiple sclerosis, active disease (presence of at least one documented clinical or subclinical exacerbation in the last year or two documented exacerbations in the last 2 years or the presence of gadolinium enhancement on the screening MRI scan, at least nine T2 lesions or a combination of at least three T2 lesions and at least one gadolinium-enhancing lesion on a T1 weighted scan at screening. Only 61/67 patients from the placebo group, 54/68 patients from the 0.1 mg group and 62/74 patients from the 0.3 mg group had a diagnosis of relapsing-remitting MS (total 177/209). All remaining patients had a diagnosis of secondary progressive multiple sclerosis.
Interventions	Oral laquinimod (3 tablets/day) 0.1 mg Oral laquinimod (3 tablets/day) 0.3 mg Placebo (3 tablets/day)
Outcomes	Primary - number of cumulative active lesions over 24 weeks (sum of new gadolinium-enhanced T1 weighted images, new appearance on T2 weighted images but nonenhancing on T1 weighted images and new enlargement on T2-weighted images but nonenhancing on T1 weighted images), Secondary - gadolinium-enhancing lesion volume on T1 weighted MRI scans, lesion volume on T2 weighted MRI scans and number of exacerbations over the 24 week treatment period and safety measures.
Notes	None.

Risk of bias

Bias	Author's judgment	Support for judgment
Random sequence generation (selection bias)	**Low risk**	"Individual centers were issued with blocks of randomization numbers and corresponding tablet blisters with randomization numbers to balance the treatment allocation within each center."
Allocation concealment (selection bias)	**Low risk**	Coded medication containers were used for allocation concealment.
Blinding of participants and personnel (performance bias)	**Low risk**	Participants and personnel are probably blinded due to the double-blinded nature of the study.
Blinding of outcome assessment (detection bias)	**Low risk**	"The image analysis centre as well as investigators and sponsor personnel remained blinded throughout the study."

Incomplete outcome data (attrition bias)	**Low risk**	Two main populations were used in the analysis of the study, ITT (all patients randomized) and PP (all patient eligible for study inclusion and have MRI assessments up to 24 weeks per protocol).
Selective reporting (reporting bias)	**Unclear risk**	This is difficult to tell as the study protocol is not available for review. All outcomes listed in the manuscript are reported but there is uncertainty as to the number of other outcomes measured and not reported in the manuscript.
Other bias	**High risk**	The study was supported by Active Biotech. As this entity has a financial stake in the compound under investigation there is the potential for publication bias of only favourable outcomes. However, all financial disclosures and study funding sources have been listed.

Table 8. Study characteristics (LAQ/5062 Trial)

Methods	36-week multicentre parallel-group, double-blind, placebo-controlled phase IIb study to evaluate the effect of oral daily laquinimod.
Participants	Patients (18 to 50 years old) had diagnosis of multiple sclerosis according to the McDonald criteria and relapsing-remitting according to Lublin FD et al., ambulatory with EDSS score between 1 and 5, had at least 1 gadolinium-enhancing lesion on MRI scan and at least one documented relapse within the year before study entry.
Interventions	Oral laquinimod (received 2 tablets, one 0.3 mg laquinimod and one placebo) - 0.3 mg/day Oral laquinimod (received 2 tablets, two 0.3 mg laquinimod) -0.6 mg/day Matching placebo (two placebo tablets) Relapses could be treated with a standard 1000 mg dose of intravenous methylprednisolone for 3 consecutive days without an oral taper.
Outcomes	Primary - cumulative number of gadolinium-enhanced lesions on week 24, 28, 32 and 36 scans, Secondary - cumulative number of new T2 lesions, total number of confirmed relapses, Exploratory - cumulative number of new T1-hypointense lesions and proportion of patients with no gadolinium-enhancing lesions, proportion of relapse-free patients, time to first confirmed relapse as well as tolerability and safety assessments.
Notes	(ClinicalTrials.gov number, NCT00349193)

Risk of bias

Bias	Author's judgment	Support for judgment
Random sequence generation (selection bias)	**Low risk**	"Stratified by study centre and was computer generated by the Teva Statistical Data Management Department."
Allocation concealment (selection bias)	**Unclear risk**	Not reported.
Blinding of participants and personnel (performance bias)	**Low risk**	"Patients and all personnel were blinded to treatment assignment. Patient and investigator blinding were not formally assessed."
Blinding of outcome assessment (detection bias)	**Low risk**	"Treating and examining neurologists at the sites were blinded to MRI results during the study."
Incomplete outcome data (attrition bias)	**Unclear risk**	An interim analysis was done when 75% of MRI information was obtained. Significance level for principal analysis was adjusted to 0.0442. Principal analysis was done on ITT cohort.
Selective reporting (reporting bias)	**Unclear risk**	This is difficult to tell as the study protocol is not available for review. All outcomes listed in the manuscript are reported but there is uncertainty as to the number of other outcomes measured and not reported in the manuscript.

Other bias	**High risk**	The study was supported by Teva Pharmaceutical Industries. As this entity has a financial stake in the compound under investigation there is the potential for publication bias of only favourable outcomes. However, all financial disclosures and study funding sources have been listed.

Table 9. Study characteristics (ALLERGO)

Methods	24-month randomized, double-blind, placebo-controlled, phase III study to evaluate safety and efficacy of oral laquinimod.
Participants	Patients (18 to 55 years old) had a diagnosis of multiple sclerosis according to the McDonald criteria, at least one relapse in the last 12 months or two relapses in the last 24 months or 1 relapse between years 1-2 prior to screening combined with at least one gadolinium-enhanced lesion on MRI observed within 1 year prior to screening.
Interventions	Oral laquinimod once-daily (capsule) - 0.6 mg Matching placebo
Outcomes	Primary - number of confirmed relapses during the double-blind study period (relapse rate at 24 months), Secondary - time to confirmed progression of EDSS, MRI outcomes (not specified).
Notes	Safety and Efficacy of Orally Administered Laquinimod Versus Placebo for Treatment of Relapsing Remitting Multiple Sclerosis (ALLEGRO) (ClinicalTrials.gov number, NCT00509145) Study Start Date: December 2007 Study Completion Date: December 2010 Primary Completion Date: November 2010 (Final data collection date for primary outcome measure) Data Analysis: Ongoing

Risk of bias – Not applicable as data analysis is ongoing and no full publication is available.

Table 10. Study characteristics (PRISMS)

Methods	2-year double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy an safety of subcutaneous 3x weekly interferon beta-1a.
Participants	Patients (median age 34.9) had a diagnosis of clinically definite or laboratory supported definite MS of at least 1 year's duration according to Poser CM, et al., EDSS score 0 to 5.0, at least 2 relapses in the preceding 2 years.
Interventions	Subcutaneous interferon beta-1a (Rebif) 3x weekly (tiw) - 22 ug (6 million IU) (66 ug per week) Subcutaneous interferon beta-1a (Rebif) 3x weekly (tiw) -44 ug (12 million IU) (132 ug per week) Placebo The total volume of the subcutaneous injected dose was 0.5 mL and study medication was usually self-administered. The dose was gradually increased over 4-8 weeks with 20% of the dose given for 2-4 weeks and 50% for another 2-4 weeks before full dose was given. Relapses could be treated with a standard regimen of 1.0 g intravenous methylprednisolone for 3 consecutive days.
Outcomes	Primary - relapse count over the course of the study, Secondary - times to first and second relapse, proportion of relapse free patients, progression in disability (increase in EDDS of at least 1.0 point sustained over at least 3 months, disease activity under MRI and physiological status.
Notes	Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis (PRISMS).

Risk of bias

Bias	Author's judgment	Support for judgment
Random sequence generation (selection bias)	**Low risk**	"Computer generated by Serono Biometrics and stratified by centre. Equal allocation of the three treatment groups was used with a block size of six."
Allocation concealment (selection bias)	**Low risk**	"The study drug was packed accordingly and delivered to the centres so that treatment allocation remained concealed."
Blinding of participants and personnel (performance bias)	**Low risk**	"All personnel involved in the study were unaware of treatment allocation."

Blinding of outcome assessment (detection bias)	**Low risk**	"All injection sites were covered up at neurological examinations to ensure that masking was not compromised because of local reactions." "Scans were analyzed centrally by the University of British Columbia MS/MRI Analysis Research Group and treatment allocation was concealed from these researchers."
Incomplete outcome data (attrition bias)	**Low risk**	Analysis was by ITT and all outcome data were included. "The data from the few patients who withdrew from the study early were retained in the statistical analyses, if relevant, by use of a censoring mechanism an offset for the time spent in the study or calculation of a rate that was standardized for the time spent in the study."
Selective reporting (reporting bias)	**Unclear risk**	This is difficult to tell as the study protocol is not available for review. All outcomes listed in the manuscript are reported but there is uncertainty as to the number of other outcomes measured and not reported in the manuscript.
Other bias	**High risk**	The study was supported by Ares-Serono International SA (Geneva, Switzerland). As this entity has a financial stake in the compound under investigation there is the potential for publication bias of only favourable outcomes. However, all financial disclosures and study funding sources have been listed.

Table 11. Study characteristics (MSCRG)

Methods	104-week randomized, double-blinded, placebo-controlled, multicentre, phase III, to evaluated the efficacy of weekly intramuscular interferon beta-1a (Avonex).
Participants	Patients (18 to 55 years old) with complete remissions (returned to baseline pre-exacerbation disability status) and patients with incomplete remissions (did not return to their baseline pre-exacerbation disability status because of new residua), EDSS 1.0 to 3.5, clinical definite MS for at least 1 year according to Poser CM, et al., at least 2 documented exacerbations in the prior 3 years and no exacerbations for at least 2 months at study entry.
Interventions	Intramuscular interferon beta-1a (Avonex) weekly doses - 6.0 million units (30 ug) Placebo Injections were performed by study nurses or by local health professionals under the supervision of study personnel. Acetaminophen 650 mg was given prior to and for 24 hours after each injectionAt the discretion of the treating physician patients in exacerbation recieved im adrenocorticotropic hormone gel, 80 units daily for 10 days or iv methylprednisolone 1000 mg daily for 4 days followed by a brief course of oral prednisone.
Outcomes	Primary - time to onset of sustained worsening in disability, defined as deterioration from baseline by at least 1.0 point on the EDSS persisting for 6 months, Secondary - number of exacerbations and annualized rate, number and volume of gadolinium-enhancing T1 weighted lesions, T2 lesion volume, number of exacerbation free patients and saftey and tolerability measures.
Notes	The Multiple Sclerosis Collaborative Research Group (MSCRG).

Risk of bias

Bias	Author's judgment	Support for judgment
Random sequence generation (selection bias)	**Low risk**	"Efron's biased coin method was used for randomization."
Allocation concealment (selection bias)	**Unclear risk**	Not reported.
Blinding of participants and personnel (performance bias)	**Low risk**	"All personnel and patients were blinded to treatment status."
Blinding of outcome assessment (detection bias)	**Low risk**	"MRIs were analyzed by one neuroradiologist and one technician (both blinded to treatment." "Patients did not discuss medical issues with the examining physician."

Incomplete outcome data (attrition bias)	**Low risk**	Study initiated in Nov 1990 and in early 1993 it was determined that patient drop out rate was over estimated in sample size calculation therefore it could be reduced and the study could be ended earlier without sacrificing power. It was determined that enrollment could be stopped at 288 patients and study would end 1 year early. At this time 301 patients were enrolled (therefore ITT population is 301, number of patients randomized). The decision to end early was made without the knowledge of interim efficacy results. "Patients who discontinued treatment continued to be followed until the end of the study whenever possible and were included in the analyses." In accordance with the study design, these 5 patients were included in the failure-time analysis for the duration of their observation periods."
Selective reporting (reporting bias)	**Low risk**	All outcomes listed in the protocol are reported in the manuscript.
Other bias	**High risk**	The study was supported by a National Institutes of Health, National Institute of Neurological Disorders and Stroke (NINDS) grant and Biogen Inc. The latter has a financial stake in the compound under investigation therefore leading to the potential for publication bias of only favourable outcomes. However, all financial disclosures and study funding sources have been listed.

Table 12. Study characteristics (OWIMS)

Methods	24-week multicentre, randomized, double-blind, placebo-controlled, parallel-group study. If desired patients could remain on blinded study medication for another 24 weeks until week 48. After 48 weeks patients receiving placebo were re-randomized in 1:1 ratio to receive one of the two doses of interferon beta-1a.
Participants	Patients (18 to 50 years old) had a diagnosis of clinical definite or laboratory supported definite RRMS of at least 1 year's duration according to Poser CM, et al., EDSS score 0 to 5.0, had experienced at least one relapse in the prior 24 months but not in the 8 weeks before entry and at least 3 lesions consistent with MS were required on screening MRI.
Interventions	Subcutaneous interferon beta-1a (Rebif) weely (qw) - 22 ug or 6MIU Subcutaneous interferon beta-1a (Rebif) weely (qw) - 44 ug or 12 MIU Placebo Both active treatment and placebo were administered as ready-to-use solutions in a volume of 0.5 mL. Patients experiencing an exacerbation during study could be given IV methylprednisolone at a dose of 1.0 g/day for 3 consecutive days at physician's discretion. Acetaminophen was for prophylactic use and to ameliorate constitutional symptoms throughout study
Outcomes	Primary - number of combined unique lesions at 24 weeks detected by MRI scanning (those showing PD/T2 or T1-Gd activity), Secondary - proportion of scans showing combined active lesions, percentage change in burden of disease, T2 lesion activity, Clinical - exacerbation count per patient, time to first exacerbaton, proportion of patients remaining exacerbation free, number of active lesions on PD/T2 and T1-Gd scans (Active lesions on PD/T2 were identified as new, enlarging or recurrent, enhancing lesions on T1-Gd scans were identified as new or persistent). Cumulative active lesions were those showing PD/T2 or T1-Gd activity or both and adjusted for to avoid double counting.
Notes	Once Weekly Interferon for MS (OWIMS).

Risk of bias

Bias	Author's judgment	Support for judgment
Random sequence generation (selection bias)	**Low risk**	Computer generated randomization list. Randomized in a 1:1:1 ratio, stratified by study center.
Allocation concealment (selection bias)	**Low risk**	"Sealed envelopes to be opened in emergency situations requiring knowledge of treatment assignment. Envelopes were returned at the end of treatment."
Blinding of participants and personnel (performance bias)	**Low risk**	"If desired patients could remain on blinded study medication for another 24 weeks."

Blinding of outcome assessment (detection bias)	**Low risk**	"Throughout the study, the evaluating physician remained unaware of adverse event profiles and any changes in safety assessments. To preserve blinding, patients were instructed to cover injection sites and to refrain from discussing any symptoms that might be in any way related to treatment when visiting the evaluating physician."
Incomplete outcome data (attrition bias)	**Low risk**	"In keeping with an ITT analysis, all patients were analyzed as randomized with inclusion of all outcome data." "The data from the few patients who withdrew early from the study were retained in the statistical analyses through the use of a censoring mechanism and their time on study accounted for by different means, depending on which statistical method was used."
Selective reporting (reporting bias)	**Unclear risk**	This is difficult to tell as the study protocol is not available for review. All outcomes listed in the manuscript are reported but there is uncertainty as to the number of other outcomes measured and not reported in the manuscript.
Other bias	**High risk**	The study was supported by Ares-Serono International SA (Geneva, Switzerland). As this entity has a financial stake in the compound under investigation there is the potential for publication bias of only favourable outcomes. However, all financial disclosures and study funding sources have been listed.

Table 13. Study characteristics (IMPROVE)

Methods	16-week, multicentre phase IIIb double-blind, placebo-controlled study to evaluate the short term efficacy of a new formulation of subcutaneous interferon beta-1a (Rebif) and 24-week rater blinded extension where all patients are assigned interferon beta-1a.
Participants	Patients (18-60) had a diagnosis of relapsing-remitting multiple sclerosis (McDonald criteria, EDSS score <=5.5 and active disease (>=1 clinical event and >= 1 gadolinium-enhancing MRI lesion.
Interventions	2:1 radomization ratio (weeks 0 to 16) New subcutaneous formulation of interferon beta-1a (Rebif) - 44 ug 3x weekly (tiw) Placebo (weeks 17 to 40) All patients receive new subcutaneous formulation of interferon beta-1a (Rebif) - 44 ug 3x weekly (tiw). Standard doses of ibuprofen or acetaminophen (for patients intolerant to ibuprofen) were used before each injection for prophylaxis against "flu-like" symptoms during the initial 16 weeks and at the physician's discretion thereafter.
Outcomes	Primary - combined unique active (CUA) MRI brain lesions (defined in PRISMS) at week 16, Secondary - number of CUA lesions/patient/scan during double-blind phase (weeks 1 to 16) vs rater blinded (weeks 17 to 40) and safety measures.
Notes	Investigating MRI Parameters with Rebif imprOVEd formulation (IMPROVE). (ClinicalTrials.gov number, NCT00441103)

Risk of bias

Bias	Author's judgment	Support for judgment
Random sequence generation (selection bias)	**Unclear risk**	"patients were randomized centrally in 2:1 ratio."
Allocation concealment (selection bias)	**Unclear risk**	Not reported.
Blinding of participants and personnel (performance bias)	**Low risk**	Participants and study personnel are probably blinded for the core study as it was "double-blinded" (weeks 0 to 16) and probably not blinded for the extension (weeks 17 to 40) as this portion of the study is only "rater blinded"
Blinding of outcome assessment (detection bias)	**Low risk**	MRI outcomes assessments are "rater blinded" for the extension study (weeks 17 to 40) and are probably blinded for the core study as well. It was unclear if safety assessments were also blinded.

Incomplete outcome data (attrition bias)	**Low risk**	ITT analysis was used for the Core study and safety populations. The rater blind study analysis used the population comprised of patients who completed treatment during the double-blind period. Missing data were imputed using the median number of lesions across both treatment groups, using data from all patients with week 16 scans. Nine missing values were imputed for placebo and 12 for interferon beta-1a (primary outcome).
Selective reporting (reporting bias)	**Unclear risk**	This is difficult to tell as the study protocol is not available for review. All outcomes listed in the manuscript are reported but there is uncertainty as to the number of other outcomes measured and not reported in the manuscript.
Other bias	**High risk**	The study was supported by Merck Serono S.A. - Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany. As this entity has a financial stake in the compound under investigation there is the potential for publication bias of only favourable outcomes. However, all financial disclosures and study funding sources have been listed.

Table 14. Study characteristics of extension trials

Publication (first author, year, trial acronym)	Treatments/ pathways used for analysis	Follow-up	No. of patients enrolled/completed extension	Outcomes	Results of interest
Clinicaltrials.gov, 2008, FREEDOMS (Heidelberg, Australia)	fingolimod 0.5 mg/day or 1.25 mg/day	estimated date of study completion August 2011	estimated enrollment 1250	safety analyses: based mainly on the frequency of adverse events and on the incidence of notable clinical laboratory abnormalities	enrolling participants by invitation only
Clinicaltrials.gov, 2010, FREEDOMS II	fingolimod 0.5 mg/day	estimated date of study completion April 2013 (collection of primary outcome)	estimated enrollment 1080	vital signs, bradycardia events, dermatologic and ophthalmic exams and ECG data; relapse rate, EDSS and MSFC scores and number of Gd+ lesions	enrolling participants by invitation only
O'Connor P, 2009, FTY720/D2201	1. fingolimod 1.25mg/day (24 mths) 2. fingolimod 5.0mg/day (24 mths) 3. placebo (6 mths) then fingolimod 1.25mg/day (18 mths) 4. placebo (6 mths) then fingolimod 5.0mg/day (18 mths) During the 15 to 24 month study visits, patients receiving 5.0mg were switched to 1.25mg due to an unfavourable risk benefit profile	24 months total (6 month core and 18 month extension study)	250 enrolled from core study (225 with RRMS and 25 with SPMS) 189 completed 24 months	relapses, EDSS and MSFC score; Gd+ lesions, new T2 lesions, T2 burden of disease, change in brain volume from baseline; adverse events; laboratory evaluation (hematology, clinical chemistry, urinalysis) pulmonary function testing	ARR remained low during extension for patients initially receiving fingolimod (0.14 to 0.17); ARR decreased markedly during first 6 months of extension (0.7 for FTY720 1.25 mg and 0.69 for 5.0 mg for months 0 to 6 vs 0.21 for 1.25 mg and 0.10 for 5.0 mg for months 7 to 12) and was low throughout the extension (ARR for months 7 to 24: 0.12 to 0.26)
Comi G, 2010, FTY720/D2201	1. fingolimod 1.25mg/day 2. fingolimod 5.0mg/day then 1.25mg/day 3. placebo then fingolimod 1.25mg/day or placebo then fingolimod 0.5mg/day then 1.25mg/day	36 months total (6 month core and 30 month extension)	173 of 250 (69%) patients entering the extension completed 36 months	relapses, EDSS and MSFC score; Gd+ lesions, new T2 lesions, proportions of patients free of Gd+ lesions or new T2 lesions; adverse events; laboratory evaluation (hematology, clinical chemistry, urinalysis) pulmonary function testing	66% of placebo receiptients were relapse free at month 6; at 36 months 51% of patients in the placebo/fingolimod group were relapse free (n=93); 68% of patients receiving fingolimod 1.25mg/day and 73% receiving fingolimod 5.0mg/day then 1.25mg/day were relapse free at 36 mths

Publication (first author, year, trial acronym)	Treatments/ pathways used for analysis	Follow-up	No. of patients enrolled/completed extension	Outcomes	Results of interest
Montalban X, 2009 (abstract), FTY720/D2201	all patients by month 36 had been receiving fingolimod 1.25mg/day for at least 12 months	48 months total (6 month core and 42 month extension)	155 of 250 (62%) patients entering the extension completed 48 months	relapse rate, proportion of patients relapse free; proportion of patients free of Gd+ lesions, proportion of patients free of new T2 lesions; adverse events and proportion of patients experiencing an AE leading to study drug discontinuation	sustained low ARR in patients treated continuously with fingolimod (M48, 0.21; M36, 0.24; M24, 0.25)"; 63-70% of continuously treated patients and 51% of patients initially receiving placebo were relapse free at month 48
Clinicaltrials.gov, 2010, (ongoing study), CLARITY	placebo patients re-randomized to low dose cladribine; patients on low dose or high dose re-randomized in a 2:1 ratio to receive either low dose cladribine or placebo	2 years extension	883 enrolled	safety evaluations including clinical laboratory testing, ECGs and AEs); MRI outcomes, progression of disease and time to disability	study ongoing but not recruiting participants
Comi G, 2010, LAQ/5062	actively treated patients continued their original treatment and placebo patients were randomly switched to either 0.3mg/day or 0.6mg/day laqunimod	36 week core study with 36 week extension	239 of 257 enrolled in the extension completing 36 weeks	number of Gd+ lesions, number of new T2 lesions, volume of T2 lesions and number of new hypointense T1 lesions on enhanced scans; relapse rate, EDSS and MSFC scores	patients treated with 0.6mg/day sustained a low relapse rate (0.35 in both placebo controlled and extension phases;
Freedman M, 2055, OWIMS	patients remained on their initially assigned study drug or if they initially received placebo re randomized to 22 µg qw or 44 µg qw Rebif (interferon beta-1a)	48 weeks core study with two 48 week extensions; total 144 weeks	293 patients enrolled 261 (89%) completed 2 years 246 (84%) completed 3 years on study	MRI activity based on semi-annual T2 scans, T2 lesion burden, exacerbation count per patient, proportion remaining relapse free, time to first exacerbation, number of EDSS progressions, proportion remaining free of EDSS progression; physical exams, clinical laboratory assessment and AEs	mean relapse rate was 0.83 and 0.77 at 3 years for continuously treated patients with 22 µg qw or 44 µg qw respectively

Publication (first author, year, trial acronym)	Treatments/ pathways used for analysis	Follow-up	No. of patients enrolled/completed extension	Outcomes	Results of interest
PRISMS Study Group, 2001 and Gold R, 2004, PRISMS	patients continued in extension on originally assigned dose 22 µg or 44 µg tiw or patients initially receiving placebo were randomized to blinded Rebif (interferon beta-1a) 22 µg or 44 µg tiw	2 years core study with 2 year extension	506 of 560 (90%) remained in the study after 2 years. Of these, 172 had received placebo, 167 had received IFN Beta-1a, 22 ug tiw and 167 had received IFN Beta-1a 44 ug tiw 445 of 506 who entered year 3, (79% of the original 560) completed 4 years on study drug. A total of 429 remained on study drug to the end of year 4 (77% of the original 560). During 4 years of study 544 patients received at least one dose of active therapy.""""	relapse count per patient, time to second relapse, proportion of patients free of relapses, duration and severity of relapses, time to first confirmed disability progression, number of new T2 lesions, proportion of scans showing lesions, burden of disease; AEs, neutralizing anti-bodies to interferon beta-1a	over 4 years the smaller number of relapses per patient per year in the 44 µg tiw group compared with the 22 µg tiw group approached significance (p=0.069)
Kappos L, 2006, PRISMS	patients who completed 4 year study could continue on blinded or open label treatment (22 or 44 ug) for the following two years (i.e. up to 6 years); between withdrawal from or completion of 6 years on study and up to and including the LTFU, treatment was open label such that patients could take any or no MS DMT."	2 years with core study, 4 years with extension study and LTFU within 7 to 8 years of baseline visit"	382 of 560 patients originally randomized (68.2%) returned for LTFU, if the 3 centres who did not participant in LTFU are excluded 77.5% (382/493) of those who could return for the LTFU assessment did so	relapses, EDSS score, development of SPMS; incidence of neutralizing anti-bodies, AEs, blood chemistry, haematology and urine testing	original PRISMS cohort had ARR of 0.67 relapses per patient per year for the period from baseline to LTFU; the equivalent ARR for the PRISMS LTFU cohort was slightly lower at 0.61 relapses per patient per year
Herndon R, 1999, MSCRG	all patients received Avonex 30 ug q.w.	mean time on study was 60 weeks (including time in core study)	301 enrolled in core study, with 382 enrolled in the extension (218 from core study and 164 new participants)	incidence of neutralizing anti-bodies, AEs; number of intravenous (IV) steroid courses required per patient per year was determined as a surrogate measure of clinical relapses	47% reduction in IV steroid use in the extension study in those who had previously received placebo in the phase III trial (core study)

Publication (first author, year, trial acronym)	Treatments/ pathways used for analysis	Follow-up	No. of patients enrolled/completed extension	Outcomes	Results of interest
Herndon R, 2005, MSCRG	all patients received Avonex 30 ug q.w.	2 year core study with 6 year extension	382 enrolled in the extension; of these 218 were from the core study (103 placebo, 115 Avonex); an additional 164 not from the core study enrolled in the extension (140 previous treated with Betaseron and 24 IFN Beta naive)	incidence of neutralizing anti-bodies, AEs, blood chemistry, haematology and urine testing	favourable immunogenicity, safety and tolerability; majority of patients who entered extension study with netralizing anti-bodies from previous Betaseron therapy converted to neutralizing antibody negative status when switched to interferon beta-1a (Avonex).
Bermel R, 2010, MSCRG	46% (n=56) of the patients remained on intramuscular interferon beta-1a (Avonex) at follow-up, 54% (n=66) were on another DMT or other appropriate therapy	patients were evaluated an average of 15 years after randomization in the MSCRG trial	172 completed the 2 year core study, 122 living patients (71%) were enrolled in the follow-up, the remaining patients were either deceased or unascertained	patient-reported EDSS, the Short Form-36, a visual analog scale of self-care independence, and a living situation questionnaire were administered	patients currently using intramuscular interferon beta-1a had a significantly lower mean EDSS score ($p = 0.011$), less progression to EDSS milestones, significantly better scores on the physical component of the Short Form-36 ($p < 0.0001$), and reported better general health and greater independence.

Table 15. GRADE evidence profile for the comparison fingolimod vs. placebo

Question: Should Fingolimod be used for relapsing-remitting multiple sclerosis?
Bibliography:

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%) With Control	Study event rates (%) With Fingolimod	Relative effect (95% CI)	Anticipated absolute effects Risk with Control	Anticipated absolute effects Risk difference with Fingolimod (95% CI)
Annualized relapse rate (CRITICAL OUTCOME[1])											
1032 (2 studies) 6 to 24 months	serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	undetected[4]	See comment	0/510 (0%)	0/522 (0%)	**MD -0.27** (0.4 to 0.14)	**Low**[5]	
										250 ARR per 1000	**317 fewer ARR per 1000** (from 150 fewer to 215 fewer)
										Moderate[5]	
										500 ARR per 1000	**635 fewer ARR per 1000** (from 300 fewer to 430 fewer)
										High[5]	
										750 ARR per 1000	**952 fewer ARR per 1000** (from 450 fewer to 645 fewer)
Number of patients experiencing at least one adverse event (CRITICAL OUTCOME[6])											
1034 (2 studies) 6 to 24 months	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[4]	⨁⨁⨁◯ **MODERATE**[4,7] due to risk of bias	463/511 (90.6%)	483/523 (92.4%)	**RR 1.02** (0.98 to 1.05)	**906 per 1000**	**18 more per 1000** (from 18 fewer to 45 more)
Number of patients experiencing an adverse event leading to study drug discontinuation (CRITICAL OUTCOME[6])											
1034 (2 studies) 6 to 24 months	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[4]	⨁⨁⨁◯ **MODERATE**[4,7] due to risk of bias	36/511 (7%)	66/523 (12.6%)	**RR 1.79** (1.22 to 2.64)	**70 per 1000**	**56 more per 1000** (from 15 more to 116 more)
Number of gadolinium-enhancing lesions on T1-weighted images (mean) (IMPORTANT OUTCOME[8])											
839 (2 studies) 6 to 24 months	serious[9]	serious[10]	no serious indirectness	no serious imprecision	undetected[4]	See comment	0/413 (0%)	0/426 (0%)	**MD -2.47** (7.34 to 0)	**Low**[5]	
										250 per 1000	**868 fewer per 1000** (from 250 more to 1000 fewer)
										Moderate[5]	
										500 per 1000	**1000 fewer per 1000** (from 500 more to 1000 fewer)
										High[5]	
										750 per 1000	**1000 fewer per 1000** (from 750 more to 1000 fewer)
Presence of gadolinium-enhancing lesions on T1-weighted images (IMPORTANT OUTCOME[8])											
839 (2 studies) 6 to 24 months	serious[9]	serious[11]	no serious indirectness	no serious imprecision	undetected[4]	⨁⨁◯◯ **LOW**[4,9,11] due to risk of bias, inconsistency	159/413 (38.5%)	54/426 (12.7%)	**RR 0.35** (0.24 to 0.51)	**385 per 1000**	**250 fewer per 1000** (from 189 fewer to 293 fewer)

[1] Primary outcome for study meta-analysis.

[2] ITT population in FTY720/D2201 trial included all patients who were randomly assigned to receive at least one dose of study medication and had at least one post-basline MRI. Whereas, FREEDOMS used all patients who were randomized for an ITT population.

[3] Heterogeneity observed in analysis most likely result of the inclusion of 11 patients with diagnosis of SPMS

[4] Included studies were industry funded, therefore unlikely to present unfavourable results.

[5] NHS guidelines do not specify an appropriate baseline risk estimate for relapses or MRI outcomes in patients with RRMS. Therefore, 3 risk levels were chosen to summarize an array of possible situations.

[6] Secondary outcome for study meta-analysis.

[7] The safety population in the FTY720/D2201 trial included all patients who were randomly assigned to receive at least one dose of study medication and completed at least one safety assessment. Whereas, FREEDOMS used all patients who were randomized for a safety population.

[8] Secondary outcome for study meta-analysis. Also, MRI outcomes are considered surogate measure of effect.

[9] In the FTY70/D2201 trial MRI analyses were primarily performed in a population of patients who underwent randomization and who completed 6 months of treatment, had no major protocol violations, and for whom MRI scans were available at baseline and on three or more visits. Although, this per protocol analysis was exceptable for the proof of concept study, the use of a selected group of patients with available data was used in the FREEDOMS trial for MRI outcomes was not justified.

[10] Large heterogeneity I2=57% despite MRI evaluations being conducted at the same MRI evaluation centre for the two trials and low heterogeneity for other pooled events (e.g. annualized relapse rate).

[11] Moderate heterogeneity I2=47% despite MRI evaluations being conducted at the same MRI evaluation centre for the two trials and low heterogeneity for other pooled events (e.g. annualized relapse rate).

Table 16. Indirect treatment comparison results

Outcome	Direct pooled estimate (A versus C)	Direct pooled estimate (B versus C)	Indirect estimate (A versus B)	(CV_C and M_C)* or Event rate P(E|C)†	Indirect estimator			Direct estimate‡ (A versus B)
					Variance	Bias	MSE	
Annualized relapse rate** (3 OT and 2 IFN trials)	-0.25 (-0.32, -0.18) ES_{AC}=0.199‡‡	-0.17 (-0.32, -0.01) ES_{BC}=0.096‡‡	-0.08 (-0.25, 0.09)	CV_C = 0.316 M_C = 0.768	0.317	-0.159	0.342	-0.13 (-0.22, -0.04)
No. of patients with at least 1 relapse†† (2 OT and 2 IFN trials)	0.63 (0.44, 0.90)	0.89 (0.77, 1.04)	0.708 (0.48, 1.044)	P(E|C) ≈ 0.5	0.027	0.024	0.027	0.65 (0.51, 0.83)
No. of patients with an AE leading to drug discontinuation†† (3 OT and 2 IFN trials)	1.77 (1.20, 2.59) d_{CA}=0.56 (0.38, 0.82)***	4.21 (1.07, 16.56) d_{CB}=0.24 (0.06, 0.93)***	0.42 (0.10, 1.744)	P(E|C) ≈ 0.1	5.668	0.668	6.115	2.69 (1.54, 4.72)

*Coefficient of variation $CV_C = SD_C/M_C$, where SD_C is the standard deviation of the outcome in the placebo group and M_C is the mean of the outcome of interest in the placebo group
†Likelihood of event in placebo group
‡TRANSFORMS (1.25 mg/day fingolimod versus 30μg q.w. Avonex)
**Mean difference (95% CI)
††Relative risk (95% CI)
‡‡Effect size $ES_{AC} = MD_{AC}/SD_{AC}$, $ES_{BC} = MD_{BC}/SD_{BC}$, where SD is the standard deviation and MD is the mean difference for the respective comparison
***Simulation results by Wells G et al only report bias and MSE for RR <1, therefore RR recalculated to have placebo in the numerator
A = oral therapy (OT)
B = interferon beta-1a therapy (IFN)
C = placebo

FIGURES

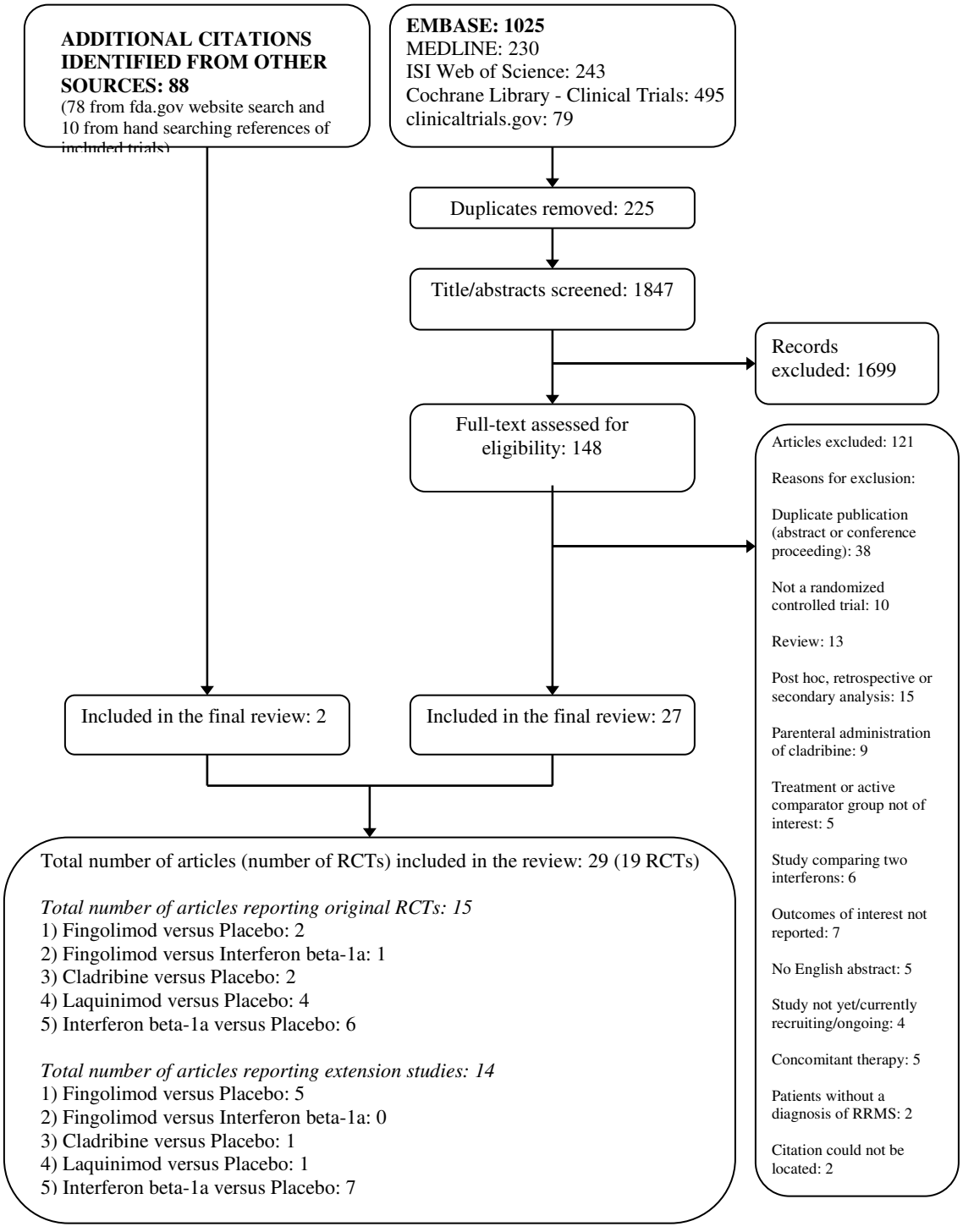

Figure 1. Flow diagram of study selection process

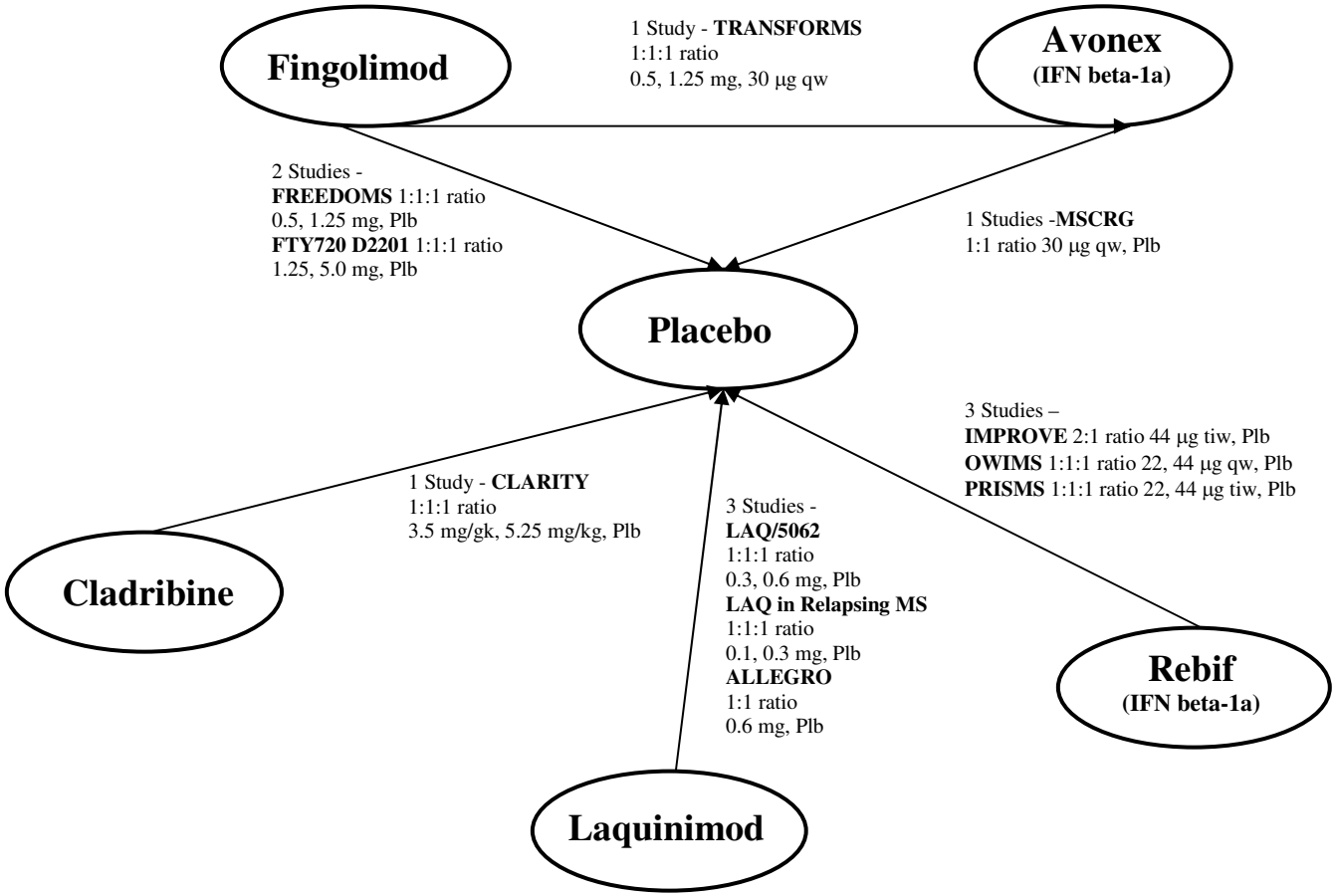

Figure 2. Network of evidence for five therapies

Plb=Placebo

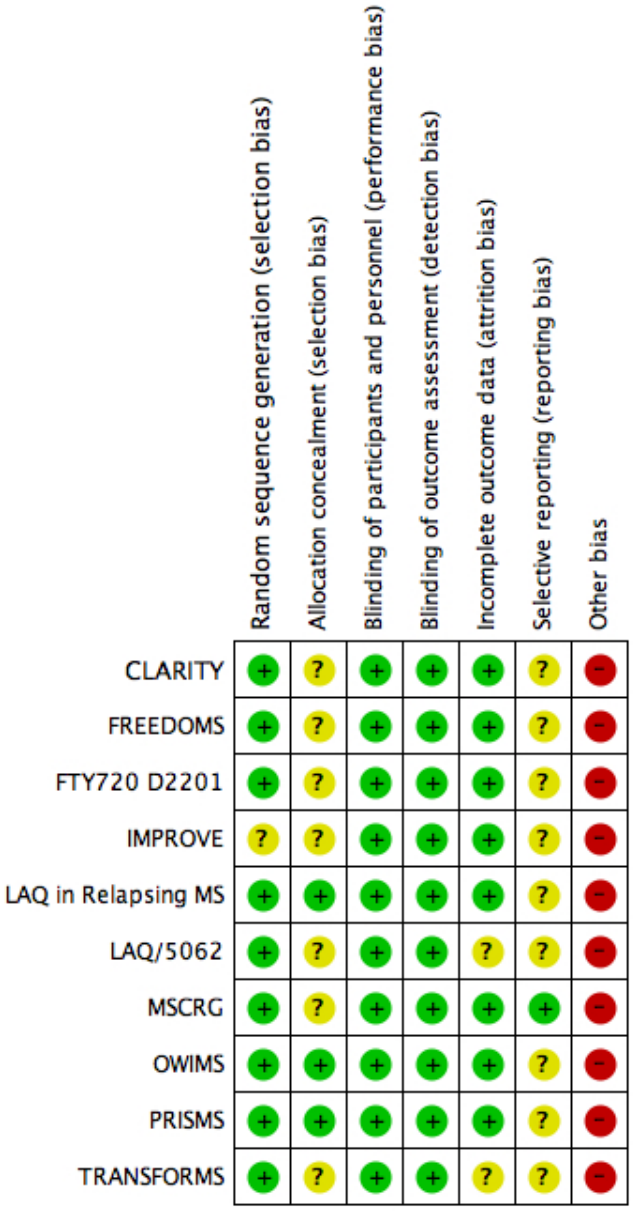

Figure 3. Methodological quality summary: review authors' judgments about each methodological quality item for each included randomized controlled trial

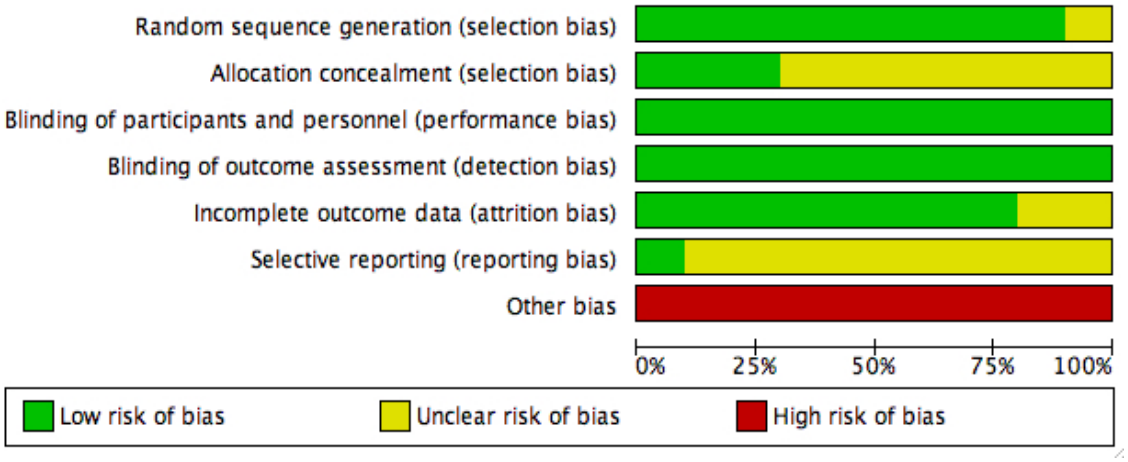

Figure 4. Methodological quality graph: authors' judgments about each methodological quality item presented as percentages across all included studies

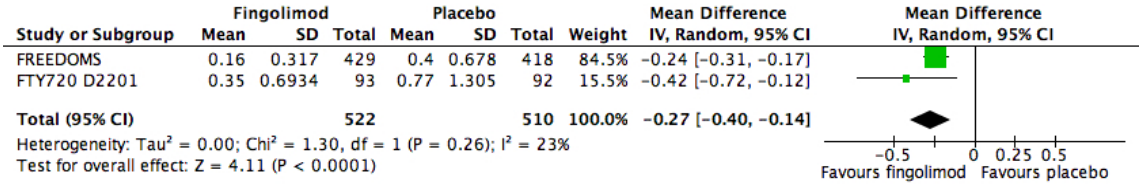

Figure 5. Forest plot of comparison: Fingolimod (1.25 mg/day) versus placebo in RRMS, primary outcome: annualized relapse rate

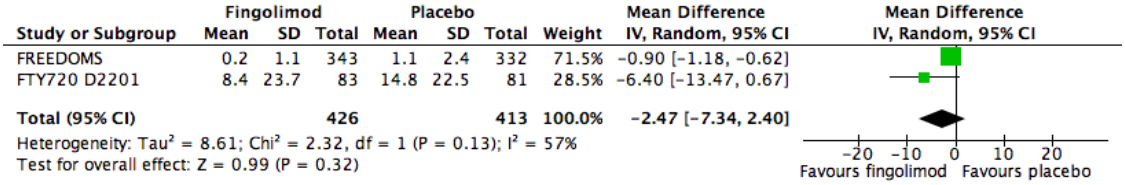

Figure 6. Forest plot of comparison: Fingolimod (1.25 mg/day) versus placebo in RRMS, secondary outcome: Number of gadolinium-enhancing lesions on T_1-weighted images (mean)

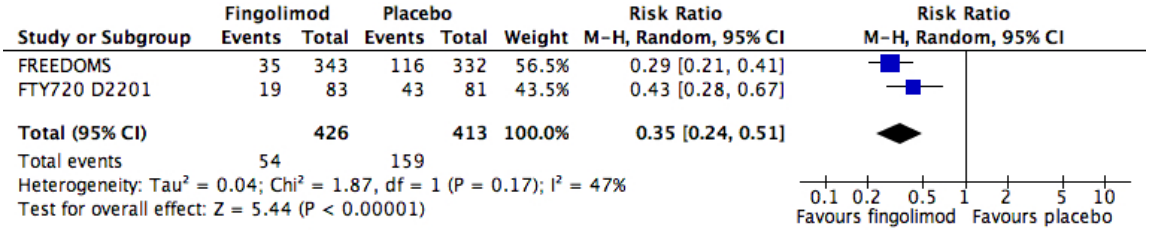

Figure 7. Forest plot of comparison: Fingolimod (1.25 mg/day) versus placebo in RRMS, secondary outcome: Presence of gadolinium-enhancing lesions on T_1-weighted images

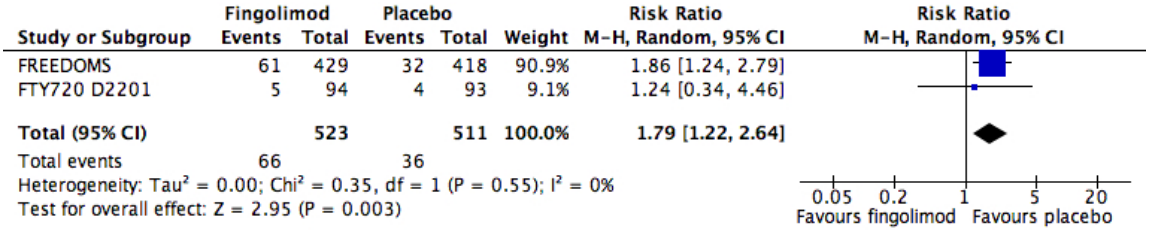

Figure 8. Forest plot of comparison: Fingolimod (1.25 mg/day) versus placebo in RRMS, secondary outcome: Number of patients experiencing an adverse event leading to study drug discontinuation

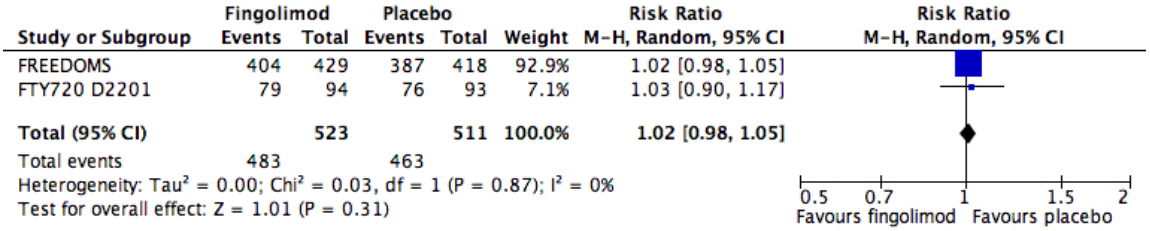

Figure 9. Forest plot of comparison: Fingolimod (1.25 mg/day) versus placebo in RRMS, secondary outcome: Number of patients with at least one adverse event

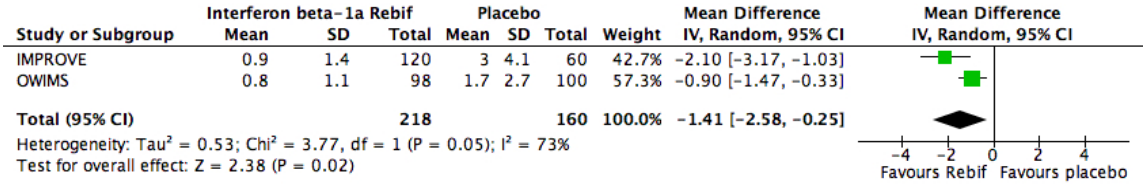

Figure 10. Forest plot of comparison: Rebif (interferon beta-1a) (44µg t.i.w and 44µg q.w.) versus placebo in RRMS, secondary outcome: Number of combined unique lesions (mean)

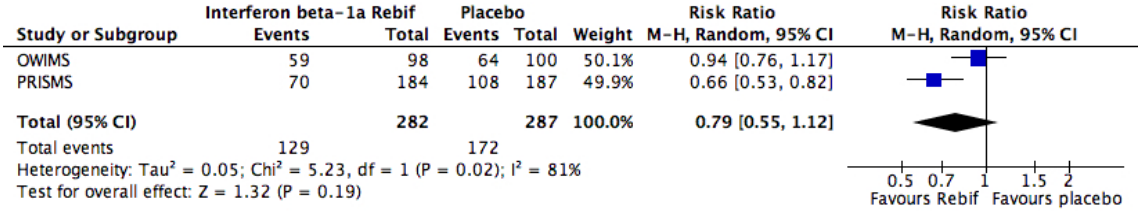

Figure 11. Forest plot of comparison: Rebif (interferon beta-1a) (44µg q.w. and 44µg t.i.w) versus placebo in RRMS, secondary outcome: Number of patients with at least one relapse

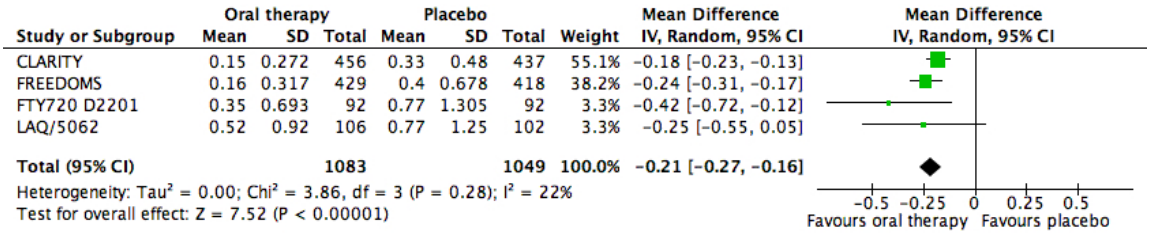

Figure 12. Forest plot of comparison: Oral therapy (5.25 mg/kg cladribine, 1.25 mg/day fingolimod and 0.6 mg/day laquinimod) versus placebo in RRMS, primary outcome: Annualized relapse rate

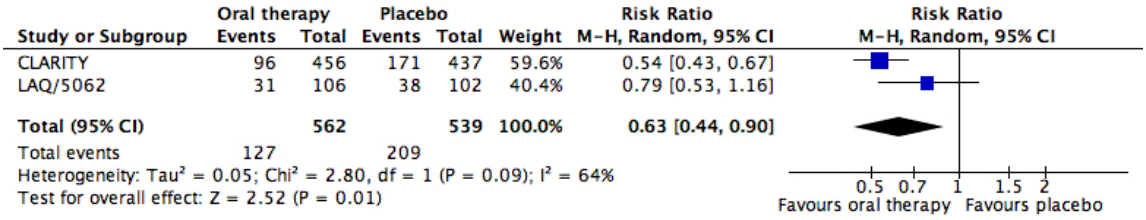

Figure 13. Forest plot of comparison: Oral therapy (5.25 mg/kg cladribine and 0.6 mg/day laquinimod) versus placebo in RRMS, secondary outcome: Number of patients with at least one relapse

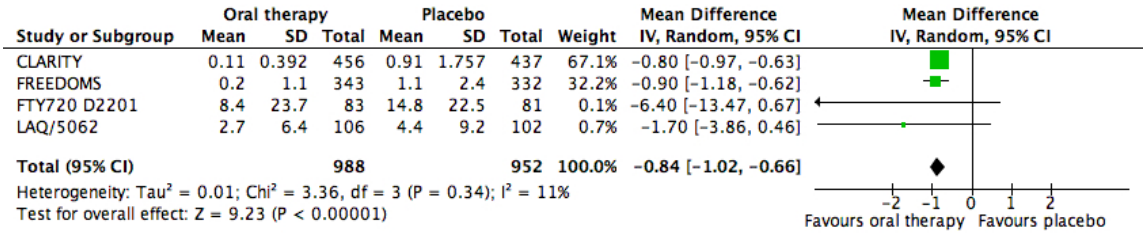

Figure 14. Forest plot of comparison: Oral therapy (5.25 mg/kg cladribine, 1.25 mg/day fingolimod and 0.6 mg/day laquinimod) versus placebo in RRMS, secondary outcome: Number of gadolinium-enhancing lesions on T_1-weighted images (mean)

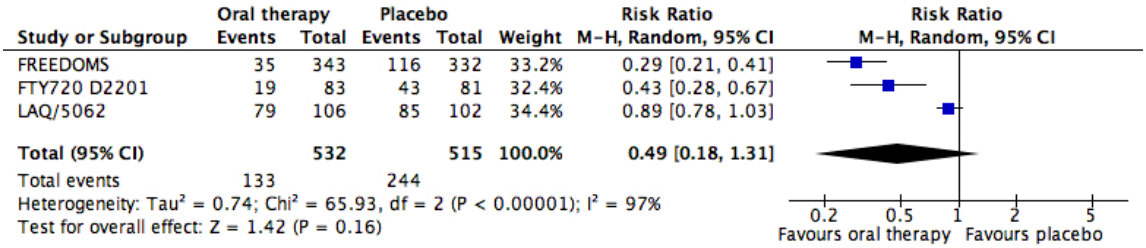

Figure 15. Forest plot of comparison: Oral therapy (1.25 mg/day fingolimod and 0.6 mg/day laquinimod) versus placebo in RRMS, secondary outcome: Presence of gadolinium-enhancing lesions on T_1-weighted images

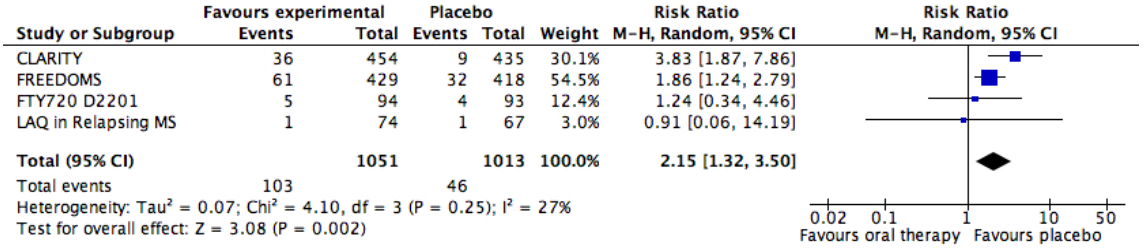

Figure 16. Forest plot of comparison: Oral therapy (5.25 mg/kg cladribine, 1.25 mg/day fingolimod and 0.3 mg/day laquinimod) versus placebo in RRMS, secondary outcome: Number of patients experiencing an adverse event leading to study drug discontinuation

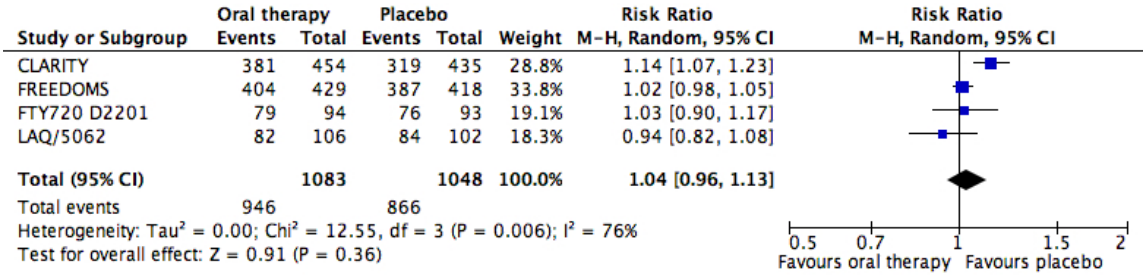

Figure 17. Forest plot of comparison: Oral therapy (5.25 mg/kg cladribine, 1.25 mg/day fingolimod and 0.6 mg/day laquinimod) versus placebo in RRMS, secondary outcome: Number of patients with at least one adverse event

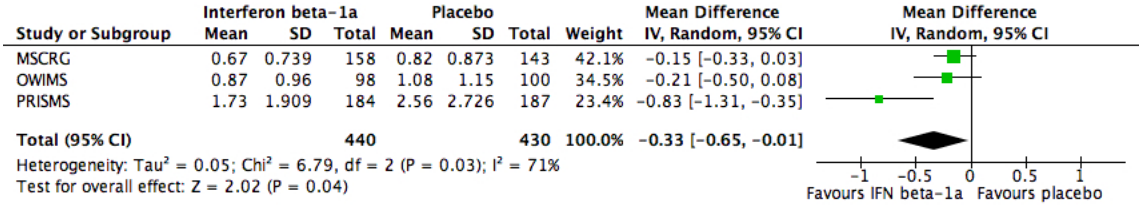

Figure 18. Forest plot of comparison: Interferon beta-1a (Avonex 30 µg q.w., Rebif 44 µg q.w. and Rebif 44 µg t.i.w.) versus placebo in RRMS, primary outcome: Annualized relapse rate

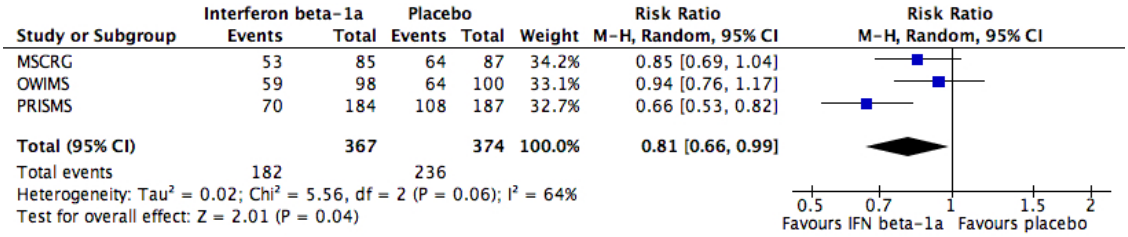

Figure 19. Forest plot of comparison: Interferon beta-1a (Avonex 30 µg q.w., Rebif 44 µg q.w. and Rebif 44 µg t.i.w.) versus placebo in RRMS, secondary outcome: Number of patients with at least one relapse

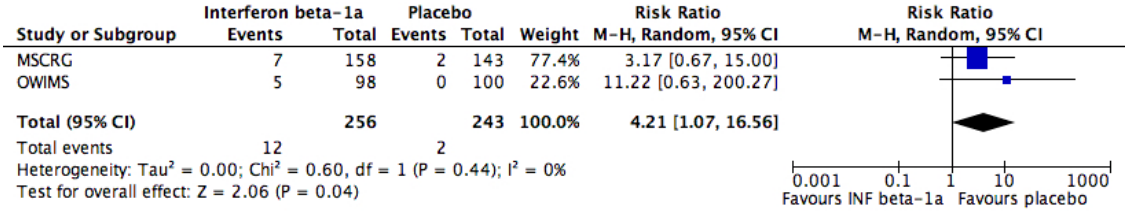

Figure 20. Forest plot of comparison: Interferon beta-1a (Avonex 30 µg q.w. and Rebif 44 µg q.w.) versus placebo in RRMS, secondary outcome: Number of patients experiencing an adverse event leading to study drug discontinuation

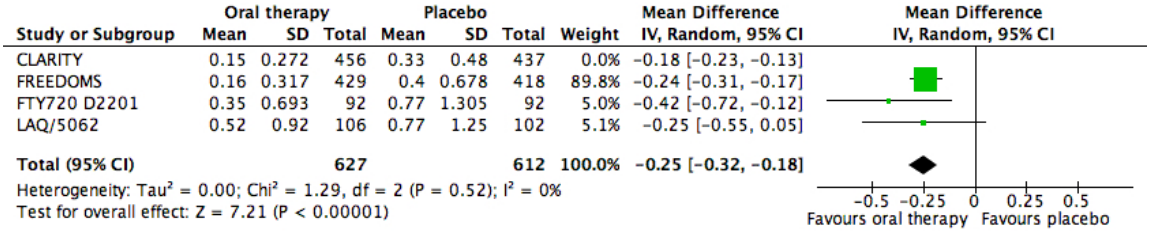

Figure 21. Sensitivity analysis: Forest plot of comparison: Oral therapy (1.25 mg/day fingolimod and 0.6 mg/day laquinimod) versus placebo in RRMS, primary outcome: Annualized relapse rate

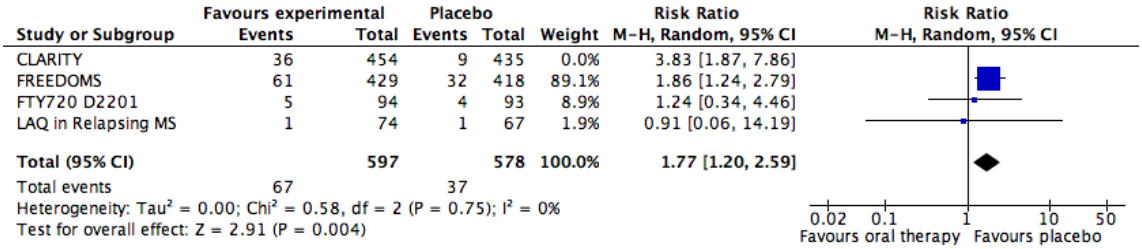

Figure 22. Sensitivity analysis: Forest plot of comparison: Oral therapy (1.25 mg/day fingolimod and 0.3 mg/day laquinimod) versus placebo in RRMS, secondary outcome: Number of patients experiencing an adverse event leading to study drug discontinuation

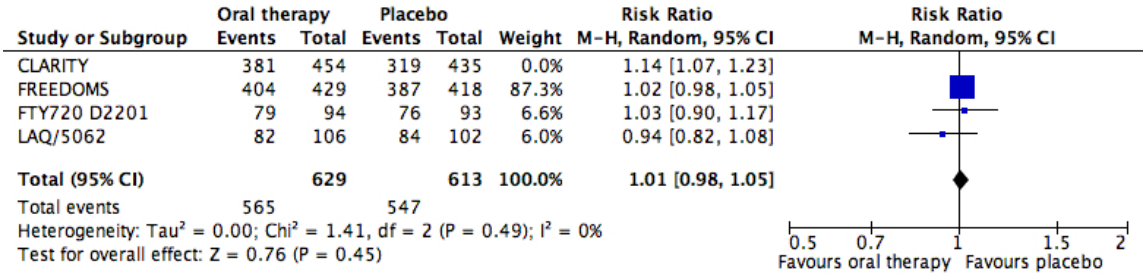

Figure 23. Sensitivity analysis: Forest plot of comparison: Oral therapy (1.25 mg/day fingolimod and 0.6 mg/day laquinimod) versus placebo in RRMS, secondary outcome: Number of patients with at least one adverse event

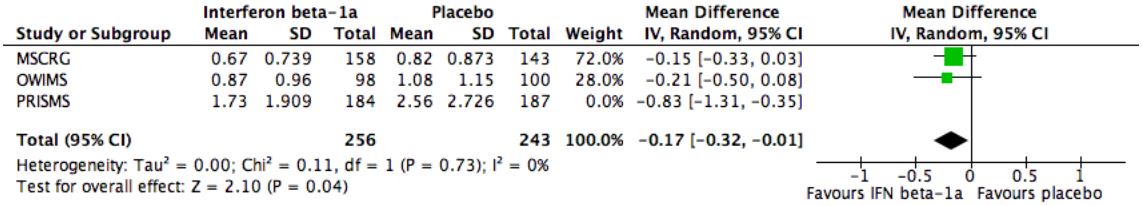

Figure 24. Sensitivity analysis: Forest plot of comparison: Interferon beta-1a (Avonex 30 µg q.w., Rebif 44 µg q.w.) versus placebo in RRMS, primary outcome: Annualized relapse rate

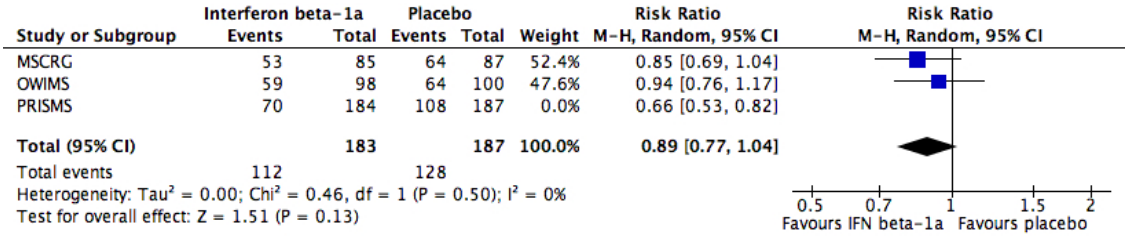

Figure 25. Sensitivity analysis: Forest plot of comparison: Interferon beta-1a (Avonex 30 µg q.w., Rebif 44 µg q.w.) versus placebo in RRMS, secondary outcome: Number of patients with at least one relapse

APPENDICES

Appendix I

Search Strategy

Database	Dates/Limits	Subject Headings/Keywords
Ovid interface of MEDLINE (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present)	**RCT Filter:** Randomized Controlled Trials as Topic.sh., Randomized Controlled Trial.pt., (Double-Blind Method OR Single-Blind Method OR Placebo Effect OR Placebos).sh., (random$ or rct$ or sham$ or placebo$).ti,ab., ((singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab., ((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab. **Other Limits:** Humans, 1980-Current	Avonex.mp., Rebif.mp., Interferon-beta/, interferon beta-1a.mp., cinnovex.mp., FTY720.mp., fingolimod.mp., Gilenya.mp., Cladribine/, cladribine.mp., laquinimod.mp., Multiple Sclerosis, Relapsing-Remitting/, relapsing-remitting multiple sclerosis.mp.
Ovid interface of EMBASE (1980 to 2011 Week 14)	**RCT Filter:** (Double-Blind Method OR Single-Blind Method OR Placebo Effect OR Placebos).sh., (random$ or rct$ or sham$ or placebo$).ti,ab., ((singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab., ((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab., Randomized Controlled Trial.sh., (Randomization OR Double Blind Procedure OR Single Blind Procedure OR Placebo).sh. **Other Limits:** Humans	Avonex.mp., Rebif.mp., beta1a interferon/, interferon beta-1a, cinnovex/, cinnovex.mp, Fingolimod/, fingolimod.mp, FTY720.mp., Gilenya.mp., cladribine/, cladribine.mp., Laquinimod/, laquinimod.mp., multiple sclerosis/, relapsing-remitting multiple sclerosis.mp.
Cochrane Library	**Restrict Search by Produc**t: All Cochrane Library **Date Range:** 1980-2011	**Title, abstract, keywords:** interferon beta OR interferon beta-1a OR avonex OR rebif OR CinnoVex OR Gilenya OR FTY720 OR fingolimod OR cladribine OR Movectro OR laquinimod AND Relapsing-Remitting Multiple Sclerosis OR multiple sclerosis
ISI Web of Knowledge	**Timespan:** 1980-2011 **Citation Databases:**	TS=(interferon beta-1a), TS=avonex, TS=rebif,

interface of Web of Science (updated 2011-04-02)	*Science Citation Index Expanded (SCI-EXPANDED)* --1976- present *Social Sciences Citation Index (SSCI*) --1976-present *Arts & Humanities Citation Index (A&HCI)* --1976-present *Conference Proceedings Citation Index- Science (CPCI-S)* --1990-present *Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)* --1990-present	TS=CinnoVex, TS=FTY720, TS=fingolimod, TS=Cladribine, TS=movectro, TS=laquinimod, TS=relapsing-remitting multiple sclerosis, TS=Randomized Controlled Trials, TS=(Double-Blind Method or Single-Blind Method or Placebo Effect or Placebo)
Clinicaltrials.gov	**Age Group:** Adult (18-65)	**Conditions:** Relapsing-Remitting Multiple Sclerosis **Interventions:** interferon beta-1a OR avonex OR rebif OR CinnoVex OR Gilenya OR FTY720 OR fingolimod OR cladribine OR Movectro OR laquinimod

Appendix II

Initial Screening Criteria

Date: _____
Reviwer: _____
Ref ID: _____

(please place check mark in appropriate column)

	Yes	No
Randomized controlled trial (RCT)*†		
Patients with a diagnosis of relapsing-remitting multiple sclerosis		
Treatment group randomized to intramuscular/subcutaneous injections of interferon beta-1a (Avonex/Rebif) or one of the following oral treatments: fingolimod (Gilenya), cladribine (Movectro), laquinimod		
To be included for full review? (Only if all questions above have been answered "yes")		

*Only RCTs in which both treatment and control groups are prospectively evaluated will be considered
†Also include extension studies of randomized trials for qualitative analysis of long-term outcomes

Appendix III

Full-text screening criteria and identification of unique studies

Date: _____
Reviwer: _____
Ref ID: _____

(please place check mark in appropriate column)

	Yes	No
Randomized controlled trial (RCT)*†		
At minimum an English abstract is available		
Patients with a diagnosis of relapsing-remitting multiple sclerosis		
Treatment group randomized to intramuscular/subcutaneous injections of interferon beta-1a (Avonex/Rebif) or one of the following oral treatments: fingolimod (Gilenya), cladribine (Movectro), laquinimod		
At least one control group received placebo for Avonex/Rebif trials or at least one control group received placebo or interferon beta-1a (Avonex/Rebif) for oral treatment trials		
The study is **NOT** a comparison of two interferon beta-1a (e.g. Avonex vs Rebif)		
The patients are **NOT** receiving concurrent corticosteroids (e.g. methylprednisolone) or immunosuppressant (e.g. methotrexate)		
The patients are **NOT** receiving parenteral cladribine		
At least one of the following outcomes was assessed: annualized relapse rate, number of patients without a relapse, number of patients without disability progression, number of gadolinium-enhancing (Gd+) lesions on T1-weighted images (mean per patient per scan), number of patients with no Gd+ lesions on T1-weighted images, number of new or enlarged lesions on T2-weighted images (mean), number of patients without new or enlarged lesions on T2-weighted images, number of combined unique lesions, number of patients with an adverse event leading to study drug discontinuation and number of patients with any adverse event		
To be included for data abstraction? (none of the above should be "no")		

*Only RCTs in which both treatment and control groups are prospectively evaluated will be considered
†Also include extension studies of randomized trials for qualitative analysis of long-term outcomes

Reason for exclusion: _____
(if applicable)

Appendix IV

Data Abstraction Form

1	Reference ID	
2	Check Your Initials	☐BD ☐JN
3	Full Journal Name	
4	Last Name of First Author or the first meaningful word in the bi-line and/or study acronym/title	
5	Publication Year	
6	Study Design of RCT	☐ Parallel ☐ Cross-Over # of phases: _____ ☐ washout between phases ☐ no washout between phases reported ☐ Other _____
7	Study Approved by an Ethics Committee	☐ Yes ☐ Not Reported ☐ No
8	Where did the Study Take Place?	
9	Was Informed Consent Obtained from Participants?	☐ Yes ☐ Not Reported ☐ No
10	Method of Randomization	☐ Random Number Table ☐ Computer Random Number Generator ☐ Coin Tossing ☐ Rolling of Die ☐ Picking Allocation from a Hat/Box ☐ Minimization/Dynamic Allocation ☐ Other Appropriate Method (Describe): _____ ☐ Other Inappropriate Method (Describe)_____ ☐ Not Reported

11	Definition of relapsing-remitting multiple sclerosis	
12	Diagnostic criteria used to determine diagnosis?	☐ McDonald Criteria ☐ Expanded Disability Status Scale Range:_____ ☐ >1 T1 gadolinium-ehancing lesion on brain MRI ☐ Other _____
13	Concealment of Allocation	☐ Sequentially numbered, opaque, sealed envelope ☐ Coded medication containers ☐ Central randomization ☐ Envelopes, other ☐ Open random allocation schedule ☐ Quasi-randomized ☐ "Concealed", no method described ☐ "Not concealed" ☐ Not reported
14	Blinding of patients	☐ Definitely Yes ☐ Probably Yes ☐ Probably Not ☐ Definitely No
15	Blinding of health care providers	☐ Definitely Yes ☐ Probably Yes ☐ Probably Not ☐ Definitely Not
16	Blinding of data collectors	☐ Definitely Yes ☐ Probably Yes ☐ Probably Not ☐ Definitely Not
17	Blinding of outcome adjudicators	☐ Definitely Yes ☐ Probably Yes ☐ Probably Not ☐ Definitely Not
18	Blinding of data analysis	☐ Definitely Yes ☐ Probably Yes ☐ Probably Not ☐ Definitely Not
19	Study stopped early for benefit	☐ Yes ☐ No
20	Authors used ITT	☐ Yes ☐ Yes, "modified ITT" ☐ No
21	Type of oral pharmacotherapy or interferon beta-1a	☐ Interferon Beta 1-a (Avonex) ☐ Interferon Beta 1-a (Rebif) ☐ Fingolimod (Gilenya) ☐ Cladribine (Movectro) ☐ Laquinimod
22	Type of comparator(s) (indicate in which arm by writing next to comparator)	☐ Placebo ☐ Interferon Beta 1-a (Avonex) ☐ Interferon Beta 1-a (Rebif)
23	Frequency of dose (indicate for all medications	☐ once daily ☐ 2x daily ☐ 3x daily ☐ every other day ☐ other_____

24	Duration of dose				
25	Dose(s) (specify for all medications)				
26	Route of administration	☐ intramuscular ☐ oral – for fingolimod and placebo ☐ intravenous ☐ subcutaneous ☐ other_____			
27	Duration of follow up after treatment randomization	☐ days_____ ☐ weeks_____ ☐ months _____ ☐ years_____			
28	Number of individuals invited to participate who chose not to	☐ Not reported ☐ Reported as _____			
Baseline Characteristics					
		Control	ARM 1	ARM 2	ARM 3
29	Mean/Median Age (circle which)				
30	# females randomized (%)				
31	Mean # of relapses within previous year				
32	Mean # of relapses within previous 2 years				
33	EDSS score (mean)				
34	Mean # of gadolinium-enhancing lesions on T_1-weighted images				
35	Mean volume of lesions on T_2-weighted images (mm^3)				
36	Total # patients randomized				
37	# not followed at all				
38	# lost part-way				
39	% compliance				
40	How was loss to follow up dealt with?	☐ Best case scenario ☐ Worst case scenario ☐ Counted as not having events and included in denominators			

		☐ exclusion from numerator and denominator ☐ included in denominator and counted as no event ☐ included in denominator and counted as event ☐ last known value carried forward ☐ other_____
41	Number of clinical assessments and specific time points?	
42	Type of clinical assessment (check all that apply)	☐ EDSS score ☐ MSFC z score ☐ MRI scans
43	If the study was a cross-over design what was the wash out period?	☐ days ☐ weeks ☐ unclear ☐ other_____ ☐ not applicable
44	Does the study declare industry funding or conflict of interest?	☐ Yes ☐ No ☐ Unclear ☐ Not reported
45	Which outcomes are reported?	☐ Annualized relapse rate ☐ Proportion of patients relapse free ☐ Absence of disability progression (3 or 6 months) ☐ Number of patients with disability progression ☐ Number of gadolinium-enhancing lesions ☐ Absence of gadolinium-enhancing lesions ☐ Number of new or enlarged lesions on T_2-weighted images ☐ Absence of new or enlarged lesions on T_2-weighted images ☐ Number cumulative unique active lesions ☐ Adverse event leading to study drug discontinuation ☐ Adverse events (headache, nausea, infections) ☐ Death ☐ Other _____

OUTCOMES TABLES

Annualized Relapse-rate

	Control	Arm I	Arm II	Arm III
N				
If raw data not provided, identify statistic				

Outcome:_____

	Control	**Arm I**	**Arm II**	**Arm III**
N				
If raw data not provided, identify statistic				

Outcome:_____

	Control	**Arm I**	**Arm II**	**Arm III**
N				
If raw data not provided, identify statistic				

Authors General Conclusions:

Appendix V

Instruction Manual for Data Extraction Form – Oral Pharmacotherapy for Relapsing-Remitting Multiple Sclerosis: A Systematic Review of Randomized Trials

***To remind you of the eligibility criteria for inclusion in the study please read the following, if you feel one of the articles sent to you do not meet the eligibility criteria, please email Brett (doblebm@mcmaster.ca).*

Inclusion Criteria

-Randomized control trial where all arms are prospectively evaluated
-At minimum, an abstract published in English
-Evaluates an oral pharmacotherapy (eg. fingolimod, cladribine, laquinimod) versus placebo or another disease-modifying-drug (eg. interferon beta-1a)
-The study evaluates pharmacotherapy for the purpose of treating patients with relapsing-remitting multiple sclerosis

Exclusion Criteria

-Studies not conducted on human subjects
-Articles where an abstract is not published in English
- Patients receiving concurrent corticosteroids (e.g. methylprednisolone) or immunosuppressant (e.g. methotrexate)
-Studies evaluating the use of parenteral cladribine, or any other route of administration other than oral for the following three treatment options: fingolimod, cladribine, laquinimod
- Studies comparing two interferons beta-1a (e.g. Avonex vs. Rebif)

Instructions

• The data extraction sheet is designed to be completed in the accompanying MS Excel file.
• If the study states the methods are described elsewhere please write in the reference on an email and send it on to me (doblebm@mcmaster.ca).

Preamble: This Procedure Manual is designed to answer most questions you may have in regards to completing the data extraction sheet. If you have any questions regarding the methodology, please contact me for clarification (doblebm@mcmaster.ca).

Q1 Reference Manager number, this number should be written on the top of the first page of all articles. There is a spot at the top of each page of the data extraction sheet to write this number in.

Q2 Check the box beside their initials.

Q3 Full name of the journal in which the article was published.

Q4 Last name of the first author. If the byline only identifies a group then use the first meaningful word on the byline – do not record the name of the corresponding author or the name of the first author in the writing committee. Also include, if applicable, the study acronym/title.

Q5 Year of publication of the study.

Q6 Note the type of RCT. All studies under review should be randomized controlled trials (RCT). If not, the article should be excluded from review.

Q7 Note if the study was approved by an ethics board (i.e. institutional review board, research ethics board).

Q8 Note in which country the study took place. More than one country may be indicated. The country where the study took place is defined as where participants were recruited and treated - not where the investigators are from.

Q9 Note if informed consent was obtained.

Q10 Note the method of trial randomization.

Q11 Provide the exact definition or source for the definition used for relapsing remitting multiple sclerosis.

Q12 Check the diagnostic criteria used to determine the presence of active disease (i.e. multiple sclerosis). More than one criterion may apply. Please specify any specific limits or ranges applicable to the diagnostic tests (e.g. EDDSS score ranges)

Q13 Concealment of allocation

- Use of telephone, web-based, independent research assistant, or pharmacy-controlled randomization → *Central randomization*
- Allocation by minimization→ *Central randomization*
- Use of envelopes but at least one of the 3 descriptors or an equivalent (sequentially numbered, opaque, sealed) missing → *Envelopes, other*
- Use of a list of random numbers, a randomization table → *Open random allocation schedule*
- Use of alternation, rotation, date of birth, day of the week, or case record number → *Quasi-randomized*
- Explicitly described as concealed but no concealment method described → *Concealed, no method described*
- Explicitly described as not concealed →*Not concealed*
- No mention of a concealment method or of concealment at all → *Not reported*
- "The randomization schedule was generated centrally by computer, distributed to the randomization centers". This is a description of the allocation sequence and does not indicate whether the allocation was concealed.

Q14-18: Blinding

Follow the following stepwise rules:

1. Explicit statement that a group of interest was blinded →*Definitely Yes* for that group
2. Explicit statement that a group of interest was not blinded→*Definitely Not* for that group
3. Explicit statement "investigators were blinded" →*Probably Yes* for health care providers and for data collectors
4. Explicit description of the trial as "Open label" or "unblinded" → *Definitely Not* for remaining groups
5. No explicit statement about blinding status of data analysts → *Probably Not* for data analysts
6. No explicit statement about blinding status of either patients, health care providers, data collectors, or outcome adjudicators, and:
   - Placebo controlled drug trial → *Probably Yes* for those groups
   - Active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched → *Probably Yes* for those groups
   - Active control drug trial (A vs. B) but no mention of "double dummy" or that medications were identical or matched → *Probably Not* for those groups
   - Non drug trial→ *Probably Not* for those groups
7. *None of the above applies, and trial described as:*

- *"single blinded" → use best judgment to assign Probably Yes to 1 group and Probably Not to remaining groups*
- *"double blinded" or "triple blinded" → Probably Yes for patients, health care providers, data collectors, and outcome adjudicators and Probably Not for data analysts*

8. Make sure "blinding applies to the outcome of interest (i.e., outcome chosen as the primary outcome): e.g., in a trial assessing relapse rates and disability progression: blinding of radiologists assessing MRIs applies to the outcome adjudication of the 2nd but not 1st outcome.
9. If the primary outcome is a self reported outcome, and if the patients are definitely not blinded but "physicians making an assessment" are → *Definitely Not* for data collectors (Q 18)
10. If one component of the outcome adjudication process is not blinded → *Definitely Not* for outcome adjudication (Q19): e.g., when a component of the outcome is patient reported and patient is not blinded

Q19 Stopping early for benefit

- Stopping early refers to stopping recruitment before target sample size is reached and/or stopping follow-up before planned follow-up duration is completed
- Explicit statement that trial was stopped early for benefit → *Yes*
- Otherwise → *No*

Q20 Note whether the authors used an intention-to-treat (ITT) analysis

Q21 Note the type of oral pharmacotherapy or interferon beta-1a

Q22 Note the comparators.

Q23 Indicate the dosing frequency, add any writing that you feel is necessary to capture the dosing regimen in the study

Q24 Indicate the duration of treatment, add any writing that you feel is necessary to capture the dosing duration

Q25 Write the dose of all treatment arms in the space provided. Remember to include units!

Q26 Identify the route of administration. If there is more than one route, identify which medication type belongs to which route.

Q27 Indicate the duration of follow-up, after treatment randomization.

Q28 Note the number of individuals approached to take part in the study who chose not to participate.

Q29-39 These questions are specific to **individual** arms of the trial, which are to written in the appropriate box. For question #29 make sure to circle either mean or median when recording patient age data.

** If a study reports the total number of participants initially randomized, but then reports the number/arm that went through the study, it is impossible to know how many were originally randomized per arm. In this case, assume that originally randomized participants were equally split between groups.

Q40 Note how loss to follow-up was managed in the analysis – or if it was not.
Q41 Provide the number of clinical assessments and their specific time points.
Q42 Check the clinical assessments that apply. Multiple Sclerosis Functional Composite (MSFC), which comprises the average of the scores on the timed 25-foot walk, the 9-hole peg tesst and the paced auditory serial-addition test with a 3-second interstimulus interval, with each converted to a z score (higher scores represent improvement)
Q43 This question only applies to cross-over trials, and asks for the duration of the wash-out period (the time between crossing over from treatments). If the study is not a cross-over trial, chose the "not applicable" option.

Q44 Note if the study authors declared industry funding or a potential conflict of interest for the trial. Government funding or other non-industry sources of financial support are not considered by this question.

Q45 Identify the outcome(s) reported in the trial

Outcome tables:

Each endpoint/outcome requires it's own table, and there may be a need to print out additional tables depending on how many outcomes are evaluated. Please indicate which arm the outcome table is intended for. If more measurement times are documented than are included in the table, please go on to the following table to complete the abstraction for that outcome/arm.

For RATIO'S reported for dichotomous data, please always ensure that the CONTROL intervention is the DENOMINATOR.