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Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis (Review)

Gonzalez-Lorenzo M, Ridley B, Minozzi S, Del Giovane C, Peryer G, Piggott T, Foschi M, Filippini G, Tramacere I, Baldin E, Nonino F

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[Intervention Review]

Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis

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ABSTRACT

Background

Different therapeutic strategies are available for the treatment of people with relapsing-remitting multiple sclerosis (RRMS), including immunomodulators, immunosuppressants and biological agents. Although each one of these therapies reduces relapse frequency and slows disability accumulation compared to no treatment, their relative benefit remains unclear.

This is an update of a Cochrane review published in 2015.

Objectives

To compare the efficacy and safety, through network meta-analysis, of interferon beta-1b, interferon beta-1a, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine, immunoglobulins, cladribine, cyclophosphamide, diroximel fumarate, fludarabine, interferon beta 1-a and beta 1-b, leflunomide, methotrexate, minocycline, mycophenolate mofetil, ofatumumab, ozanimod, ponesimod, rituximab, siponimod and steroids for the treatment of people with RRMS.

Search methods

CENTRAL, MEDLINE, Embase, and two trials registers were searched on 21 September 2021 together with reference checking, citation searching and contact with study authors to identify additional studies. A top-up search was conducted on 8 August 2022.

Selection criteria

Randomised controlled trials (RCTs) that studied one or more of the available immunomodulators and immunosuppressants as monotherapy in comparison to placebo or to another active agent, in adults with RRMS.

Data collection and analysis

Two authors independently selected studies and extracted data. We considered both direct and indirect evidence and performed data synthesis by pairwise and network meta-analysis. Certainty of the evidence was assessed by the GRADE approach.

Main results

We included 50 studies involving 36,541 participants (68.6% female and 31.4% male). Median treatment duration was 24 months, and 25 (50%) studies were placebo-controlled.

Considering the risk of bias, the most frequent concern was related to the role of the sponsor in the authorship of the study report or in data management and analysis, for which we judged 68% of the studies were at high risk of other bias. The other frequent concerns were performance bias (34% judged as having high risk) and attrition bias (32% judged as having high risk).

Placebo was used as the common comparator for network analysis.

Relapses over 12 months: data were provided in 18 studies (9310 participants). Natalizumab results in a large reduction of people with relapses at 12 months (RR 0.52, 95% CI 0.43 to 0.63; high-certainty evidence). Fingolimod (RR 0.48, 95% CI 0.39 to 0.57; moderate-certainty evidence), daclizumab (RR 0.55, 95% CI 0.42 to 0.73; moderate-certainty evidence), and immunoglobulins (RR 0.60, 95% CI 0.47 to 0.79; moderate-certainty evidence) probably result in a large reduction of people with relapses at 12 months.

Relapses over 24 months: data were reported in 28 studies (19,869 participants). Cladribine (RR 0.53, 95% CI 0.44 to 0.64; high-certainty evidence), alemtuzumab (RR 0.57, 95% CI 0.47 to 0.68; high-certainty evidence) and natalizumab (RR 0.56, 95% CI 0.48 to 0.65; high-certainty evidence) result in a large decrease of people with relapses at 24 months. Fingolimod (RR 0.54, 95% CI 0.48 to 0.60; moderate-certainty evidence), dimethyl fumarate (RR 0.62, 95% CI 0.55 to 0.70; moderate-certainty evidence), and ponesimod (RR 0.58, 95% CI 0.48 to 0.70; moderate-certainty evidence) probably result in a large decrease of people with relapses at 24 months. Glatiramer acetate (RR 0.84, 95%, CI 0.76 to 0.93; moderate-certainty evidence) and interferon beta-1a (Avonex, Rebif) (RR 0.84, 95% CI 0.78 to 0.91; moderate-certainty evidence) probably moderately decrease people with relapses at 24 months.

Relapses over 36 months findings were available from five studies (3087 participants). None of the treatments assessed showed moderate- or high-certainty evidence compared to placebo.

Disability worsening over 24 months was assessed in 31 studies (24,303 participants). Natalizumab probably results in a large reduction of disability worsening (RR 0.59, 95% CI 0.46 to 0.75; moderate-certainty evidence) at 24 months.

Disability worsening over 36 months was assessed in three studies (2684 participants) but none of the studies used placebo as the comparator.

Treatment discontinuation due to adverse events data were available from 43 studies (35,410 participants). Alemtuzumab probably results in a slight reduction of treatment discontinuation due to adverse events (OR 0.39, 95% CI 0.19 to 0.79; moderate-certainty evidence). Daclizumab (OR 2.55, 95% CI 1.40 to 4.63; moderate-certainty evidence), fingolimod (OR 1.84, 95% CI 1.31 to 2.57; moderate-certainty evidence), teriflunomide (OR 1.82, 95% CI 1.19 to 2.79; moderate-certainty evidence), interferon beta-1a (OR 1.48, 95% CI 0.99 to 2.20; moderate-certainty evidence), laquinimod (OR 1.49, 95 % CI 1.00 to 2.15; moderate-certainty evidence), natalizumab (OR 1.57, 95% CI 0.81 to 3.05), and glatiramer acetate (OR 1.48, 95% CI 1.01 to 2.14; moderate-certainty evidence) probably result in a slight increase in the number of people who discontinue treatment due to adverse events.

Serious adverse events (SAEs) were reported in 35 studies (33,998 participants). There was probably a trivial reduction in SAEs amongst people with RRMS treated with interferon beta-1b as compared to placebo (OR 0.92, 95% CI 0.55 to 1.54; moderate-certainty evidence).

Authors' conclusions

We are highly confident that, compared to placebo, two-year treatment with natalizumab, cladribine, or alemtuzumab decreases relapses more than with other DMTs. We are moderately confident that a two-year treatment with natalizumab may slow disability progression. Compared to those on placebo, people with RRMS treated with most of the assessed DMTs showed a higher frequency of treatment discontinuation due to AEs: we are moderately confident that this could happen with fingolimod, teriflunomide, interferon beta-1a, laquinimod, natalizumab and daclizumab, while our certainty with other DMTs is lower. We are also moderately certain that treatment with alemtuzumab is associated with fewer discontinuations due to adverse events than placebo, and moderately certain that interferon beta-1b probably results in a slight reduction in people who experience serious adverse events, but our certainty with regard to other DMTs is lower.

Insufficient evidence is available to evaluate the efficacy and safety of DMTs in a longer term than two years, and this is a relevant issue for a chronic condition like MS that develops over decades. More than half of the included studies were sponsored by pharmaceutical companies and this may have influenced their results. Further studies should focus on direct comparison between active agents, with follow-up of at least three years, and assess other patient-relevant outcomes, such as quality of life and cognitive status, with particular focus on the impact of sex/gender on treatment effects.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of drugs acting on the immune system to treat relapsing-remitting multiple sclerosis ?

Key messages

- After two years of treatment, natalizumab, cladribine and alemtuzumab work best in reducing the frequency of relapses in relapsing-remitting multiple sclerosis. Natalizumab is likely to be also effective in slowing the progression of disability after two years of treatment.

- Longer studies are needed to assess the benefits and harms of drugs acting on the immune system for relapsing-remitting multiple sclerosis.

- Future research on these types of drugs should compare them against each other and focus on effects that are important to people with multiple sclerosis, such as their quality of life and their ability to think, learn, remember, use judgement, and make decisions.

What is multiple sclerosis?

Multiple sclerosis is an uncommon condition affecting relevant functions of the body, caused by an inflammation of the brain and of the spinal cord with damage that in time impairs some important activities of daily living, such as walking and taking care of yourself. People with multiple sclerosis experience symptoms such as weakness, tiredness, painful cramps in their muscles, and reduction of sensitivity in parts of their body. Over the years, such symptoms may worsen and lead to the need for a wheelchair. The most common form of multiple sclerosis is called "relapsing-remitting" as symptoms come and go over the years. The appearance of symptoms is called "relapse". In time, relapses become more and more frequent, with more troublesome symptoms and with shorter periods of well-being in between. Although uncommon, multiple sclerosis is a particularly burdensome condition in that it typically affects young people, mainly women, in the most active stage of their life, between the age of 20 and 40 years.

How is multiple sclerosis treated?

Although currently there is no treatment that can cure multiple sclerosis, it is treated with drugs called "disease-modifying", in that they are aimed at reducing the frequency of relapses and at slowing the progression of disability. Many such drugs are available to reduce inflammation in the brain or spinal cord.

What did we want to find out?

We wanted to find out which "disease-modifying" drugs work best to make people with multiple sclerosis feel better and, at the same time, are well tolerated and have the fewest unwanted effects. In particular, we wanted to find out if any drug is better than the others in reducing the frequency of relapses and the worsening of disability, and if any drug is better tolerated than the others or causes fewer unwanted events.

What did we do?

We searched thoroughly for studies comparing any "disease-modifying" drug with another drug or with no treatment in adults (≥ 18 years old) with relapsing-remitting multiple sclerosis.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and number of participants involved and precision of the results.

What did we find ?

We found 50 studies with 36,541 people with multiple sclerosis (68.6% female and 31.4% male) treated with a "disease-modifying" drug for at least one year. The biggest study included 2,244 people; the smallest included 19 people. The studies were conducted all over the world, mostly in the USA and Europe. Most studies lasted 12 or 24 months; only eight studies lasted more than 24 months. Most studies were performed by pharmaceutical companies in order to obtain authorisation from regulatory authorities for marketing the studied drug. Twenty-five studies compared a "disease-modifying" drug with no treatment; the other studies compared two different types of "disease-modifying" drugs. We are highly confident that natalizumab, cladribine and alemtuzumab are more effective than most drugs in reducing the frequency of relapses after two years of treatment. We are moderately confident that natalizumab is also likely to be effective in slowing the worsening of disability after two years of treatment. We are moderately confident that people taking fingolimod, teriflunomide, glatiramer acetate, interferon beta-1a, laquinimod, natalizumab and daclizumab are more likely to discontinue the drug because of unwanted effects.

What are the limitations of the evidence?

Our confidence in the desirable and undesirable effects of "disease-modifying" drugs is limited, mainly because the evidence is based on few cases of relapses and worsening of disability, and because we were concerned that the interests of pharmaceutical companies may have influenced the reporting of the study results.

How up-to-date is this evidence?

The evidence is up-to-date until August 8, 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Relapses at 12 months

Population: Patients with RRMS

Interventions: Azathioprine, daclizumab, fingolimod, glatiramer acetate, Immunoglobulins, interferon beta 1a -1b, interferon beta-1b (Betaferon), interferon beta-1a (Avonex, Rebif), pegylated interferon beta-1a, mitoxantrone, natalizumab, teriflunomide

Comparator (reference): Placebo

Outcome: Relapses at 12 months

Setting(s): Outpatient

Intervention (no. of studies/participants)	Relative effect** (95% CrI)	Anticipated absolute effect***(95% CrI)			Certainty of the evidence (GRADE)
		With placebo	*With intervention*	Difference	
Azathioprine (Direct evidence; 1 RCT; 59 participants)	**RR 0.91** (0.58 to 1.43)	**412 per 1000**	**375 per 1000**	**37 fewer per 1000** (from 173 fewer to 177 more)	⊕◯◯◯ Very low due to imprecision[1]
Daclizumab (Direct evidence; 1 RCT; 621 participants)	**RR 0.55** (0.42 to 0.73)	**412 per 1000**	**227 per 1000**	**185 fewer per 1000** (from 239 fewer to 111 fewer)	⊕⊕⊕◯ Moderate due to imprecision[2]
Fingolimod No direct evidence	**RR 0.48** (0.39 to 0.57)	**412 per 1000**	**198 per 1000**	**214 fewer per 1000** (from 251 fewer to 177 fewer)	⊕⊕⊕◯ Moderate due to risk of bias[3]
Glatiramer acetate (Direct evidence; 2 RCTs; 1454 participants)	**RR 0.64** (0.55 to 0.75)	**412 per 1000**	**264 per 1000**	**148 fewer per 1000** (from 185 fewer to 103 fewer)	⊕⊕◯◯ Low due to imprecision and risk of bias[4]
Immunoglobulins	**RR 0.60** (0.47 to 0.79)	**412 per 1000**	**247 per 1000**	**165 fewer per 1000** (from 218 fewer to 87 fewer)	⊕⊕⊕◯ Moderate

(Direct evidence; 2 RCTs; 91 participants)					due to imprecision[2]
Interferon beta 1a-1b No direct evidence	**RR 1.42** (0.78 to 2.60)	**412 per 1000**	**585 per 1000**	**173 more per 1000** (from 91 fewer to 659 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[5]
Interferon beta-1b (Betaferon) No direct evidence	**RR 0.82** (0.50 to 1.33)	**412 per 1000**	**338 per 1000**	**74 fewer per 1000** (from 206 fewer to 136 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[6]
Interferon beta-1a (Avonex, Rebif) (Direct evidence; 1 RCT; 560 participants)	**RR 0.76** (0.68 to 0.85)	**412 per 1000**	**313 per 1000**	**99 fewer per 1000** (from 132 fewer to 62 fewer)	⊕⊕◯◯ Low due to imprecision[7]
Pegylated interferon beta-1a (Direct evidence; 1 RCT; 1512 participants)	**RR 0.68** (0.56 to 0.82)	**412 per 1000**	**280 per 1000**	**132 fewer per 1000** (from 181 fewer to 74 fewer)	⊕⊕◯◯ Low due to imprecision and risk of bias[8]
Mitoxantrone (Direct evidence; 1 RCT; 51 participants)	**RR 0.40** (0.21 to 0.74)	**412 per 1000**	**165 per 1000**	**247 fewer per 1000** (from 326 fewer to 107 fewer)	⊕⊕◯◯ Low due to imprecision and risk of bias[8]
Natalizumab (Direct evidence; 1 RCT; 942 participants)	**RR 0.52** (0.43 to 0.63)	**412 per 1000**	**214 per 1000**	**198 fewer per 1000** (from 235 fewer to 152 fewer)	⊕⊕⊕⊕ High[9]
Teriflunomide (Direct evidence; 1 RCT; 1169 participants)	**RR 0.66** (0.55 to 0.78)	**412 per 1000**	**272 per 1000**	**140 fewer per 1000** (from 185 fewer to 91 fewer)	⊕⊕◯◯ Low

					due to imprecision and risk of bias[8]
Placebo	Reference Comparator	Not estimable	Not estimable	Not estimable	Reference Comparator

NMA-SoF table definitions

** Network Meta-analysis estimates are reported as risk ratios. CI: confidence interval.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1 Absolute observed point estimate falls in the small positive effect, 95% CI range from large positive effect to large negative effect: downgraded three levels.

2 Absolute observed point estimate falls in the large positive effect, 95% CI range from large positive effect to moderate positive effect: downgraded one level.

3 Downgraded one level for risk of bias. Absolute observed point estimate falls in the large positive effect, 95% CIs contained within positive effect.

4 Absolute observed point estimate falls in the large positive effect, 95% CI range from large positive effect to moderate positive effect: downgraded one level. Further downgraded one level for risk of bias

5 Absolute observed point estimate falls in the large negative effect, 95% CI range from moderate positive effect to large negative effect: downgraded three levels. Further downgraded one level for risk of bias

6 Absolute observed point estimate falls in the moderate positive effect, 95% CI range from large positive effect to large negative effect: downgraded three levels. Further downgraded one level for risk of bias

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8 Absolute observed point estimate falls in the large positive effect, 95% CI range from large positive effect to moderate positive effect: downgraded one level. Further downgraded one level for risk of bias

9 Absolute observed point estimate falls in the large positive effect, 95% CIs contained within positive effect.

Summary of findings 2. Relapses at 24 months

Population: Patients with RRMS

Interventions: alemtuzumab, azathriopine, cladribine, dimethylfumarate, fingolimod, glatiramer acetate, immunoglobulins, interferon beta 1a-1b, interferon beta-1b (Betaferon), interferon beta-1a (Avonex, Rebif, laquinimod, mitoxantrone, natalizumab, ponesimod, teriflunomide

Comparator (reference): Placebo

Outcome: Relapses at 24 months

Setting(s): Outpatient

Intervention (no. of studies/participants)	Relative effect**	Anticipated absolute effect***(95% CrI)	Certainty of the evidence (GRADE)

	(95% CrI)	*With placebo*	*With* intervention	Difference	
Alemtuzumab No direct evidence	**RR 0.57** (0.47 to 0.68)	**510 per 1000**	**291 per 1000**	**219 fewer per 1000** (from 270 fewer to 163 fewer)	⊕⊕⊕⊕ High[1]
Azathioprine (Direct evidence; 1 RCT; 59 participants)	**RR 0.77** (0.51 to 1.18)	**510 per 1000**	**392 per 1000**	**117 fewer per 1000** (from 250 fewer to 92 more)	⊕◯◯◯ Very low due to imprecision[2]
Cladribine (Direct evidence; 1 RCT; 1326 participants)	**RR 0.53** (0.44 to 0.64)	**510 per 1000**	**270 per 1000**	**240 fewer per 1000** (from 285 fewer to 183 fewer)	⊕⊕⊕⊕ High[1]
Dimethylfumarate (Direct evidence; 2 RCTs; 2307 participants)	**RR 0.62** (0.55 to 0.70)	**510 per 1000**	**316 per 1000**	**194 fewer per 1000** (from 229 fewer to 153 fewer)	⊕⊕⊕◯ Moderate due to risk of bias[3]
Fingolimod (Direct evidence; 2 RCTs; 2355 participants)	**RR 0.54** (0.48 to 0.60)	**510 per 1000**	**275 per 1000**	**234 fewer per 1000** (from 265 fewer to 204 fewer)	⊕⊕⊕◯ Moderate due to risk of bias[3]
Glatiramer acetate (Direct evidence; 3 RCsT; 1014 participants)	**RR 0.84** (0.76 to 0.93)	**510 per 1000**	**428 per 1000**	**82 fewer per 1000** (from 122 fewer to 36 fewer)	⊕⊕⊕◯ Moderate due to imprecision[4]
Immunoglobulins (Direct evidence; 2 RCTs; 192 participants)	**RR 0.73** (0.59 to 0.90)	**510 per 1000**	**372 per 1000**	**138 fewer per 1000** (from 209 fewer to 51 fewer)	⊕⊕◯◯ Low due to imprecision[5]
Interferon beta 1a-1b No direct evidence	**RR 1.21** (0.66 to 2.19)	**510 per 1000**	**617 per 1000**	**107 more per 1000** (from 173 fewer to 607 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[6]

Interferon beta-1b (Betaferon) (Direct evidence; 1 RCT; 372 participants)	**RR 0.85** (0.76 to 0.94)	**510 per 1000**	**433 per 1000**	**76 fewer per 1000** (from 122 fewer to 31 fewer)	⊕⊕◯◯ Low due to imprecision[7]
Interferon beta-1a (Avonex, Rebif) (Direct evidence; 3 RCTs; 1629 participants)	**RR 0.84** (0.78 to 0.91)	**510 per 1000**	**428 per 1000**	**82 fewer per 1000** (from 112 fewer to 46 fewer)	⊕⊕⊕◯ Moderate due to imprecision[8]
Laquinimod (Direct evidence; 3 RCTs; 3457 participants)	**RR 0.83** (0.76 to 0.91)	**510 per 1000**	**423 per 1000**	**87 fewer per 1000** (from 122 fewer to 46 fewer)	⊕⊕◯◯ Low due to imprecision and risk of bias[9]
Mitoxantrone (Direct evidence; 1 RCT; 51 participants)	**RR 0.47** (0.27 to 0.80)	**510 per 1000**	**240 per 1000**	**270 fewer per 1000** (from 372 fewer to 102 fewer)	⊕⊕◯◯ Low due to imprecision and risk of bias[10]
Natalizumab (Direct evidence; 1 RCT; 942 participants)	**RR 0.56** (0.48 to 0.65)	**510 per 1000**	**285 per 1000**	**224 fewer per 1000** (from 265 fewer to 178 fewer)	⊕⊕⊕⊕ High[1]
Ponesimod No direct evidence	**RR 0.58** (0.48 to 0.70)	**510 per 1000**	**296 per 1000**	**214 fewer per 1000** (from 265 fewer to 153 fewer)	⊕⊕⊕◯ Moderate due to risk of bias[3]
Teriflunomide (Direct evidence; 1 RCT; 1088 participants)	**RR 0.82** (0.71 to 0.94)	**510 per 1000**	**418 per 1000**	**92 fewer per 1000** (from 148 fewer to 31 fewer)	⊕◯◯◯ Very low due to imprecision and risk of bias[11]
Placebo	Reference Comparator	Not estimable	Not estimable	Not estimable	Reference Comparator

NMA-SoF table definitions

** Network Meta-analysis estimates are reported as risk ratios. CI: confidence interval.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanatory Footnotes

1 Absolute observed point estimate falls in the large positive effect, 95% CIs contained within positive effect.

2 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from large positive effect to moderate negative effect: downgraded three levels

3 Downgraded one level for risk of bias. Absolute observed point estimate falls in the large positive effect, 95% CIs contained within positive effect.

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6 Absolute observed point estimate falls in the moderate negative effect, 95% CIs range from large positive effect to large negative effect: downgraded three levels. Further downgraded one level for risk of bias

7 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from moderate positive effect to trivial positive effect: downgraded two levels

8 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from moderate positive effect to small positive effect: downgraded one level

9 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from moderate positive effect to small positive effect: downgraded one level. Further downgraded one level for risk of bias

10 Absolute observed point estimate falls in the large positive effect, 95% CIs range from large positive effect to moderate positive effect: downgraded one level. Further downgraded one level for risk of bias

11 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from large positive effect to trivial positive effect: downgraded three levels. Further downgraded one level for risk of bias

Summary of findings 3. Relapses at 36 months

Patients: Patients with RRMS

Interventions: interferon beta-1b (Betaferon)

Comparator (reference): Placebo

Outcome: Relapses at 36 months

Setting(s): Outpatient

Intervention (no. of studies/participants)	Relative effect** (95% CrI)	Anticipated absolute effect***(95% CrI)			Certainty of the evidence (GRADE)
		With placebo	*With intervention*	Difference	
Interferon beta-1b (Betaferon)	**RR 0.86** (0.67 to 1.11)	**862 per 1000**	**741 per 1000**	**121 fewer per 1000** (from 284 fewer to 95 more)	⊕◯◯◯ Very low

(Direct evidence; 2 RCTs; 403 participants)					due to imprecision[1]
Placebo	Reference Comparator	Not estimable	Not estimable	Not estimable	Reference Comparator

NMA-SoF table definitions
** Network Meta-analysis estimates are reported as risk ratios. CI: confidence interval.
*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.
GRADE Working Group grades of evidence (or certainty in the evidence)
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanatory Footnotes
1 Absolute observed point estimate falls in the moderate positive effect, 95% CI ranges from large positive effect to moderate negative effect: downgraded three levels

Summary of findings 4. Disability at 24 months

Population: Patients with RRMS

Interventions: Alemtuzumab, azathioprine, cladribine, dimethylfumarate, fingolimod, glatiramer acetate, immunoglobulins, interferon beta 1a-1b, interferon beta-1b (Betaferon), interferon beta-1a (Avonex, Rebif), laquinimod, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, teriflunomide

Comparator (reference): Placebo

Outcome: Disability at 24 months

Setting(s): Outpatient

Intervention (no. of studies and participants)	**Relative effect** (95% CI)**	**Anticipated absolute effect***(95% CI)**			**Certainty of the evidence (GRADE)**
		With placebo	***With intervention***	**Difference**	
Alemtuzumab No direct evidence	**RR 0.67** (0.46 to 0.99)	**188 per 1000**	**126 per 1000**	**62 fewer per 1000** (from 101 fewer to 2 fewer)	⊕⊕◯◯ Low due to imprecision[1]
Azathioprine	**RR 0.60** (0.22 to 1.63)	**188 per 1000**	**113 per 1000**	**75 fewer per 1000** (from 146 fewer to 118 more)	⊕◯◯◯ Very low

(Direct evidence; 1 RCT; 59 participants)					due to imprecision[2]
Cladribine (Direct evidence; 1 RCT; 1326 participants)	**RR 0.72** (0.56 to 0.91)	**188 per 1000**	**135 per 1000**	**53 fewer per 1000** (from 83 fewer to 17 fewer)	⊕⊕◯◯ Low due to imprecision[3]
Dimethylfumarate (Direct evidence; 2 RCTs; 2307 participants)	**RR 0.65** (0.55 to 0.77)	**188 per 1000**	**122 per 1000**	**66 fewer per 1000** (from 84 fewer to 43 fewer)	⊕⊕◯◯ Low due to imprecision and risk of bias[4]
Fingolimod (Direct evidence; 2 RCTs; 2355 participants)	**RR 0.68** (0.56 to 0.83)	**188 per 1000**	**128 per 1000**	**60 fewer per 1000** (from 83 fewer to 32 fewer)	⊕⊕◯◯ Low due to imprecision and risk of bias[5]
Glatiramer acetate (Direct evidence; 3 RCTs; 1014 participants)	**RR 0.74** (0.61 to 0.89)	**188 per 1000**	**139 per 1000**	**49 fewer per 1000** (from 73 fewer to 21 fewer)	⊕◯◯◯ Very low due to imprecision and risk of bias[6]
Immunoglobulins (Direct evidence; 2 RCTs; 190 participants)	**RR 0.75** (0.41 to 1.37)	**188 per 1000**	**141 per 1000**	**47 fewer per 1000** (from 111 fewer to 69 more)	⊕◯◯◯ Very low due to imprecision[7]
Interferon beta 1a-1b No direct evidence	**RR 3.19** (0.31 to 33.21)	**188 per 1000**	**599 per 1000**	**411 more per 1000** (from 130 fewer to 1000 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[8]
Interferon beta-1b (Betaferon) (Direct evidence; 1 RCT; 372 participants)	**RR 0.77** (0.62 to 0.94)	**188 per 1000**	**145 per 1000**	**43 fewer per 1000** (from 71 fewer to 11 fewer)	⊕⊕◯◯ Low due to imprecision[9]

Interferon beta-1a (Avonex, Rebif) (Direct evidence; 2 RCTs; 1069 participants)	**RR 0.92** (0.73 to 1.16)	**188 per 1000**	**173 per 1000**	**15 fewer per 1000** (from 51 fewer to 30 more)	⊕⊕◯◯ Low due to imprecision[10]
Laquinimod (Direct evidence; 3 RCTs; 3451 participants)	**RR 0.78** (0.63 to 0.96)	**188 per 1000**	**146 per 1000**	**41 fewer per 1000** (from 69 fewer to 8 fewer)	⊕◯◯◯ Very low due to imprecision and risk of bias[11]
Mitoxantrone (Direct evidence; 1 RCT; 51 participants)	**RR 0.20** (0.05 to 0.83)	**188 per 1000**	**38 per 1000**	**150 fewer per 1000** (from 178 fewer to 32 fewer)	⊕◯◯◯ Very low due to imprecision and risk of bias[12]
Natalizumab (Direct evidence; 1 RCT; 942 participants)	**RR 0.59** (0.46 to 0.75)	**188 per 1000**	**111 per 1000**	**77 fewer per 1000** (from 101 fewer to 47 fewer)	⊕⊕⊕◯ Moderate due to imprecision[13]
Ocrelizumab No direct evidence	**RR 0.61** (0.41 to 0.90)	**188 per 1000**	**115 per 1000**	**73 fewer per 1000** (from 111 fewer to 19 fewer)	⊕◯◯◯ Very low due to imprecision and risk of bias[14]
Ofatumumab No direct evidence	**RR 0.54** (0.38 to 0.77)	**188 per 1000**	**101 per 1000**	**86 fewer per 1000** (from 116 fewer to 43 fewer)	⊕◯◯◯ Very low due to imprecision and risk of bias[15]
Ozanimod No direct evidence	**RR 1.19** (0.74 to 1.91)	**188 per 1000**	**223 per 1000**	**6 more per 1000** (from 49 fewer to 171 more)	⊕◯◯◯ Very low due to imprecision[16]
Ponesimod	**RR 0.63** (0.41 to 0.96)	**188 per 1000**	**118 per 1000**	**69 fewer per 1000** (from 111 fewer to 8 fewer)	⊕◯◯◯

No direct evidence					Very low due to imprecision and risk of bias[17]
Teriflunomide (Direct evidence; 1 RCT; 1088 participants)	**RR 0.76** (0.61 to 0.95)	**188 per 1000**	**143 per 1000**	**45 fewer per 1000** (from 73 fewer to 9 fewer)	⊕◯◯◯ Very low due to imprecision and risk of bias[18]
Placebo	Reference Comparator	Not estimable	Not estimable	Not estimable	Reference Comparator

NMA-SoF table definitions

** Network Meta-analysis estimates are reported as risk ratios. CI: confidence interval.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanatory footnotes

1 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from moderate positive effect to trivial positive: downgraded three levels

2 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from large positive effect to large negative effect: downgraded two levels

3 Absolute observed point estimate falls in the small positive effect, 95% CIs range from moderate positive effect to trivial positive effect: downgraded two levels

4 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from moderate positive effect to small positive effect: downgraded one level. Further downgraded one level for risk of bias

5 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from moderate positive effect to small positive effect: downgraded one level. Further downgraded one level for risk of bias

6 Absolute observed point estimate falls in the small positive effect, 95% CIs range from moderate positive effect to trivial positive effect: downgraded two levels. Further downgraded one level for risk of bias

7 Absolute observed point estimate falls in the small positive effect, 95% CIs range from moderate positive effect to moderate negative effect: downgraded three levels

8 Absolute observed point estimate falls in the large negative effect, 95% CIs range from large positive effect to large negative effect: downgraded three levels. Further downgraded one level for risk of bias

9 Absolute observed point estimate falls in the small positive effect, 95% CIs range from moderate positive effect to trivial positive effect: downgraded two levels

10 Absolute observed point estimate falls in the trivial positive effect, 95% CIs range from small positive effect to trivial negative effect: downgraded two levels

11 Absolute observed point estimate falls in the small positive effect, 95% CIs range from moderate positive effect to trivial positive effect: downgraded two levels. Further downgraded one level for risk of bias

12 Absolute observed point estimate falls in the large positive effect, 95% CIs range from large positive effect to small positive effect: downgraded two levels. Further downgraded one level for risk of bias

13 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from moderate positive effect to small positive effect: downgraded one level

14 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from moderate positive effect to trivial positive effect: downgraded two levels. Further downgraded one level for risk of bias
15 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from large positive effect to small positive effect: downgraded two levels. Further downgraded one level for risk of bias
16 Absolute observed point estimate falls in the trivial negative effect, 95% CIs range from small positive effect to large negative effect: downgraded three levels
17 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from moderate positive effect to trivial positive effect: downgraded two levels. Further downgraded one level for risk of bias
18 Absolute observed point estimate falls in the moderate positive effect, 95% CIs range from moderate positive effect to trivial positive effect: downgraded two levels. Further downgraded one level for risk of bias

Summary of findings 5. Discontinuation due to adverse effects

Population: Patients with RRMS

Interventions: Alemtuzumab, azathioprine, cladribine, daclizumab, dimethylfumarate, fingolimod, glatiramer acetate, immunoglobulins, interferon beta 1a-1b, interferon beta-1b (Betaferon), interferon beta-1a (Avonex, Rebif), laquinimod, pegylated interferon beta1a, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, teriflunomide

Comparator (reference): Placebo

Outcome: Treatment discontinuation due to adverse events

Setting(s): Outpatient

Intervention (no. of studies/participants)	Relative effect** (95% CrI)	Anticipated absolute effect***(95% CrI)			Certainty of the evidence (GRADE)
		With placebo	*With intervention*	Difference	
Alemtuzumab No direct evidence	**OR 0.39** (0.19 to 0.79)	**50 per 1000**	**20 per 1000**	**30 fewer per 1000** (from 40 fewer to 10 fewer)	⊕⊕⊕◯ Moderate due to risk of bias[1]
Azathioprine (Direct evidence; 1 RCT; 54 participants)	**OR 6.26** (0.67 to 58.05)	**50 per 1000**	**246 per 1000**	**196 more per 1000** (from 16 fewer to 702 more)	⊕◯◯◯ Very low due to imprecision[2]
Cladribine (Direct evidence; 1 RCT; 1326 participants)	**OR 1.38** (0.46 to 4.15)	**50 per 1000**	**67 per 1000**	**18 more per 1000** (from 26 fewer to 128 more)	⊕⊕◯◯ Low due to imprecision[3]
Daclizumab	**OR 2.55**	**50 per 1000**	**117 per 1000**	**68 more per 1000**	⊕⊕⊕◯

(Direct evidence; 1 RCT; 600 participants)	(1.40 to 4.63)			(from 18 more to 145 more)	Moderate due to imprecision[4]
Dimethylfumarate (Direct evidence; 2 RCTs; 2300 participants)	**OR 1.35** (0.94 to 1.95)	**50 per 1000**	**66 per 1000**	**16 more per 1000** (from 3 fewer to 43 more)	⊕⊕◯◯ Low due to imprecision and risk of bias[5]
Fingolimod (Direct evidence; 2 RCTs; 2355 participants)	**OR 1.84** (1.31 to 2.57)	**50 per 1000**	**87 per 1000**	**38 more per 1000** (from 14 more to 69 more)	⊕⊕⊕◯ Moderate due to risk of bias[6]
Glatiramer acetate (Direct evidence; 4 RCTs; 2419 participants)	**OR 1.48** (1.02 to 2.14)	**50 per 1000**	**72 per 1000**	**22 more per 1000** (from 1 more to 51 more)	⊕⊕⊕◯ Moderate due to risk of bias[6]
Immunoglobulins (Direct evidence; 3 RCTs; 243 participants)	**OR 2.49** (0.37 to 16.50)	**50 per 1000**	**115 per 1000**	**65 more per 1000** (from 31 fewer to 413 more)	⊕◯◯◯ Very low due to imprecision[7]
Interferon beta 1a-1b No direct evidence	**OR 3.02** (0.27 to 33.65)	**50 per 1000**	**136 per 1000**	**86 more per 1000** (from 36 fewer to 587 more)	⊕◯◯◯ Very low due to imprecision[7]
Interferon beta-1b (Direct evidence; 1 RCT; 372 participants)	**OR 2.27** (1.05 to 4.91)	**50 per 1000**	**106 per 1000**	**56 more per 1000** (from 2 more to 154 more)	⊕⊕◯◯ Low due to imprecision and risk of bias[8]
Interferon beta-1a (Direct evidence; 2 RCTs; 1457 participants)	**OR 1.48** (0.99 to 2.20)	**50 per 1000**	**72 per 1000**	**22 more per 1000** (from 0 fewer to 53 more)	⊕⊕⊕◯ Moderate due to risk of bias[6]

Laquinimod (Direct evidence; 3 RCTs; 3457 participants)	**OR 1.46** (1.00 to 2.15)	**50 per 1000**	**71 per 1000**	**21 more per 1000** (from 0 fewer to 51 more)	⊕⊕⊕◯ Moderate due to risk of bias[6]
Pegylated interferon beta-1a (Direct evidence; 1 RCT; 1512 participants)	**OR 3.58** (1.47 to 8.73)	**50 per 1000**	**157 per 1000**	**108 more per 1000** (from 22 more to 263 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[9]
Natalizumab (Direct evidence; 1 RCT; 939 participants)	**OR 1.57** (0.81 to 3.05)	**50 per 1000**	**76 per 1000**	**26 more per 1000** (from 9 fewer to 88 more)	⊕⊕⊕◯ Moderate due to imprecision[10]
Ocrelizumab No direct evidence	**OR 0.82** (0.42 to 1.60)	**50 per 1000**	**41 per 1000**	**9 fewer per 1000** (from 28 fewer to 27 more)	⊕⊕◯◯ Low due to imprecision and risk of bias[11]
Ofatumumab No direct evidence	**OR 2.00** (1.05 to 3.81)	**50 per 1000**	**94 per 1000**	**45 more per 1000** (from 2 more to 116 more)	⊕⊕◯◯ Low due to imprecision and risk of bias[12]
Ozanimod No direct evidence	**OR 1.01** (0.52 to 1.95)	**50 per 1000**	**50 per 1000**	**0 fewer per 1000** (from 23 fewer to 43 more)	⊕⊕◯◯ Low due to imprecision and risk of bias[13]
Ponesimod No direct evidence	**OR 5.04** **(2.15 to 11.82)**	**50 per 1000**	**208 per 1000**	**158 more per 1000** (from 51 more to 332 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[14]
Teriflunomide	**OR 1.82**	**50 per 1000**	**87 per 1000**	**37 more per 1000**	⊕⊕⊕◯

(Direct evidence; 2 RCTs; 2253 participants)	(1.19 to 2.79)			(from 9 more to 77 more)	Moderate due to risk of bias[6]
Placebo	Reference Comparator	Not estimable	Not estimable	Not estimable	Reference Comparator

NMA-SoF table definitions

** Network Metanalysis estimates are reported as risk ratios. CI: confidence interval.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanatory Footnotes

1 Downgraded one level for risk of bias. Absolute observed point estimate falls in the trivial positive effect; 95% CIs contained within positive effect.

2 Absolute observed point estimate falls in the small negative effect, 95% CIs range from trivial positive effect to large negative effect: downgraded three levels

3 Absolute observed point estimate falls in the trivial negative effect, 95% CIs range from trivial positive effect to small negative effect: downgraded two levels

4 Absolute observed point estimate falls in the trivial negative effect, 95% CIs range from trivial negative effect to small negative effect: downgraded one level

5 Absolute observed point estimate falls in the trivial negative effect, 95% CIs range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias

6 Downgraded one level for risk of bias. Absolute observed point estimate falls in the trivial negative effect; 95% CIs contained within negative effect.

7 Absolute observed point estimate falls in the trivial negative effect, 95% CIs range from trivial positive effect to large negative effect: downgraded three levels

8 Absolute observed point estimate falls in the trivial negative effect, 95% CIs range from trivial negative effect to small negative effect: downgraded one level. Further downgraded one level for risk of bias

9 Absolute observed point estimate falls in the small negative effect, 95% CIs range from trivial negative effect to large negative effect: downgraded two levels. Further downgraded one level for risk of bias

10 Absolute observed point estimate falls in the trivial negative effect, 95% CIs range from trivial positive effect to trivial negative effect: downgraded one level

11 Absolute observed point estimate falls in the trivial positive effect, 95% CIs range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias

12 Absolute observed point estimate falls in the trivial negative effect, 95% CIs range from trivial negative effect to small negative effect: downgraded one level. Further downgraded one level for risk of bias

13 Absolute observed point estimate falls in the null effect, 95% CIs range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias

14 Absolute observed point estimate falls in the small negative effect, 95% CIs range from trivial negative effect to moderate negative effect: downgraded two levels. Further downgraded one level for risk of bias

Summary of findings 6. Serious adverse events

Population: Patients with RRMS

Interventions: Alemtuzumab, cladribine, daclizumab, dimethylfumarate, fingolimod, glatiramer acetate, interferon beta-1b (Betaferon), interferon beta-1a (Avonex, Rebif), laquinimod, pegylated interferon beta-1a, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, teriflunomide

Comparator (reference): Placebo

Outcome: Serious adverse events

Setting(s): Outpatient

Intervention (no. of studies/participants)	Relative effect** (95% CrI)	Anticipated absolute effect***(95% CrI)			Certainty of the evidence (GRADE)
		With placebo	*With intervention*	Difference	
Alemtuzumab No direct evidence	**OR 1.52** (0.94 to 2.48)	**79 per 1000**	**120 per 1000**	**36 more per 1000** (from 4 fewer to 96 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[1]
Cladribine (Direct evidence; 1 RCT; 1326 participants)	**OR 1.39** (0.80 to 2.40)	**79 per 1000**	**106 per 1000**	**27 more per 1000** (from 15 fewer to 92 more)	⊕◯◯◯ Very low due to imprecision[2]
Daclizumab (Direct evidence; 1 RCT; 600 participants)	**OR 1.90** (1.21 to 2.99)	**79 per 1000**	**140 per 1000**	**61 more per 1000** (from 15 more to 125 more)	⊕⊕◯◯ Low due to imprecision[3]
Dimethylfumarate (Direct evidence; 2 RCTs; 2300 participants)	**OR 1.04** (0.71 to 1.52)	**79 per 1000**	**82 per 1000**	**3 more per 1000** (from 22 fewer to 36 more)	⊕⊕◯◯ Low due to imprecision and risk of bias[4]
Fingolimod (Direct evidence; 2 RCTs; 2355 participants)	**OR 0.86** (0.64 to 1.13)	**79 per 1000**	**69 per 1000**	**10 fewer per 1000** (from 27 fewer to 9 more)	⊕⊕◯◯ Low due to imprecision and risk of bias[5]
Glatiramer acetate	**OR 0.94** (0.68 to 1.28)	**79 per 1000**	**75 per 1000**	**4 fewer per 1000** (from 24 fewer to 20 more)	⊕⊕◯◯

(Direct evidence; 3 RCTs; 2371 participants)					Low due to imprecision and risk of bias[5]
Interferon beta-1b (Betaferon) No direct evidence	**OR 0.92** (0.55 to 1.54)	**79 per 1000**	**73 per 1000**	**6 fewer per 1000** (from 34 fewer to 38 more)	⊕⊕⊕◯ Moderate due to imprecision[6]
Interferon beta-1a (Rebif, Avonex) (Direct evidence; 1 RCT; 897 participants)	**OR 1.21** (0.88 to 1.67)	**79 per 1000**	**94 per 1000**	**15 more per 1000** (from 9 fewer to 46 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[7]
Laquinimod (Direct evidence; 3 RCTs; 3457 participants)	**OR 1.25** (0.92 to 1.70)	**79 per 1000**	**97 per 1000**	**18 more per 1000** (from 6 fewer to 48 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[8]
Pegylated interferon beta-1a (Direct evidence; 1 RCT; 1512 participants)	**OR 1.08** (0.59 to 1.96)	**79 per 1000**	**85 per 1000**	**6 more per 1000** (from 31 fewer to 65 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[9]
Mitoxantrone (Direct evidence; 1 RCT; 53 participants)	**OR 0.89** (0.02 to 47.22)	**79 per 1000**	**71 per 1000**	**8 fewer per 1000** (from 77 fewer to 723 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[10]
Natalizumab (Direct evidence; 1 RCT; 939 participants)	**OR 1.24** (0.73 to 2.09)	**79 per 1000**	**96 per 1000**	**17 more per 1000** (from 20 fewer to 73 more)	⊕⊕◯◯ Low due to imprecision[11]
Ocrelizumab No direct evidence	**OR 1.00** (0.58 to 1.72)	**79 per 1000**	**79 per 1000**	**0 fewer per 1000** (from 32 fewer to 50 more)	⊕◯◯◯ Very low

					due to imprecision and risk of bias[12]
Ofatumumab No direct evidence	**OR 1.52** (0.89 to 2.57)	**79 per 1000**	**115 per 1000**	**36 more per 1000** (from 8 fewer to 102 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[13]
Ozanimod No direct evidence	**OR 1.50** (0.85 to 2.64)	**79 per 1000**	**114 per 1000**	**35 more per 1000** (from 11 fewer to 106 more)	⊕◯◯◯ Very low due to imprecision[14]
Ponesimod No direct evidence	**OR 1.24** (0.66 to 2.35)	**79 per 1000**	**96 per 1000**	**17 more per 1000** (from 25 fewer to 89 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[15]
Teriflunomide (Direct evidence; 2 RCTs; 2253 participants)	**OR 1.16** (0.81 to 1.64)	**79 per 1000**	**90 per 1000**	**11 more per 1000** (from 14 fewer to 44 more)	⊕◯◯◯ Very low due to imprecision and risk of bias[16]
Placebo	Reference Comparator	Not estimable	Not estimable	Not estimable	Reference Comparator

NMA-SoF table definitions

** Network Metanalysis estimates are reported as risk ratio. CI: confidence interval.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

1 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels. Further downgraded one level for risk of bias.

2 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels.
3 Absolute observed point estimate falls in the small negative effect, 95% CI range from trivial negative effect to moderate negative effect: downgraded two levels.
4 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias.
5 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from trivial positive effect to trivial negative effect: downgraded one level. Further downgraded one level for risk of bias.
6 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from trivial positive effect to trivial negative effect: downgraded one level.
7 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.
8 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.
9 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.
10 Absolute observed point estimate falls in the trivial positive effect: (below small effect threshold), 95% CI range from moderate positive effect to large negative effect: downgraded three levels. Further downgraded one level for risk of bias.
11 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels.
12 Absolute observed point estimate falls in the null effect, 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.
13 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels. Further downgraded one level for risk of bias.
14 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels.
15 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to moderate negative effect: downgraded three levels. Further downgraded one level for risk of bias.
16 Absolute observed point estimate falls in the trivial negative effect: (below small effect threshold), 95% CI range from trivial positive effect to small negative effect: downgraded two levels. Further downgraded one level for risk of bias.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the brain and spinal cord resulting from a complex interaction between genetic background and environmental factors. Its pathophysiology encompasses several pathological processes, including immune system dysregulation, demyelination, remyelination, microglial activation, and chronic neuroaxonal loss (Filippi 2018). In most patients, the clinical course is initially characterised by attacks of neurological dysfunction, with or without residual deficits. MS has been traditionally viewed as a two-stage disease with early inflammation responsible for the initial relapsing-remitting (RR) course and delayed neurodegeneration causing secondary disability progression. However, more recent evidence has pointed out a pathological continuum between the relapsing and progressive phases, with active ongoing inflammation and demyelination which can also be seen in end-stage MS (Lucchetti 2018). On the other hand, neurodegeneration and neuronal loss leading to brain atrophy have also been observed in the earlier stages of the disease, at least in some cases, as demonstrated by the high prevalence of a certain degree of cognitive impairment even at disease onset (Haider 2021).

MS is amongst the most common causes of neurological disability in young people and currently affects about 2.8 million people worldwide (Atlas of MS [https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms, last accessed on 01/13/23]). Since the 1950s, MS incidence has gradually increased and currently ranges from 2 to 10 per 100,000 persons per year with a latitudinal gradient and a lower incidence closer to the equator (Koch-Henriksen 2021). Similarly, the female to male ratio has enlarged over time, settling at over 3:1 during the 2000s (Alonso 2008).

RRMS has a typical onset between 20 and 40 years of age, with a heterogeneous clinical presentation depending on the involvement of various regions of the central nervous system (CNS) (e.g. optic nerve, brainstem-cerebellum, cerebral hemispheres, and spinal cord). The chronic course of MS typically evolves over 30 to 40 years, involving distinct clinical phenotypes. RRMS accounts for ~85% of patients and ~2–3% of patients per year will develop secondary progressive (SP) MS which is characterised by increasing and irreversible disability that occurs independently of the presence of relapses (Lublin 1996). Male sex, older age at onset and high early relapse frequency predict higher risk of unremitting disability worsening (Scalfari 2014). A minority of patients (~10-15%) have a progressive disease course from onset, which is referred to as primary progressive MS (PPMS). These phenotypes have been subsequently revised based on the presence of inflammatory activity related to the disease which could be potentially targeted by disease-modifying treatments (DMTs) (Lublin 2014). Such classification includes the "clinically isolated syndrome" (CIS), when the first clinical attack does not completely fulfil MS diagnostic criteria. Furthermore, within each subtype, MS can be classified as active or not active, depending on the occurrence of relapses and/or new, enlarging or contrast-enhancing, lesions detected with magnetic resonance imaging (MRI).

The diagnosis of MS relies on the demonstration of two subsequent clinical attacks (dissemination in time - DIT) with the involvement of at least two different CNS areas (dissemination in space - DIS) (Korteweg 2006). Although MS diagnosis remains primarily based on clinical criteria, the 2001 McDonald criteria and their 2005 and 2010 revisions have incorporated criteria for DIT and DIS, thus allowing diagnosis at the time of its first symptoms (McDonald 2001; Polman 2005; Polman 2011). Specifically, DIS can be demonstrated by greater than or equal to one MRI lesion in at least two CNS regions including: periventricular, juxtacortical, infratentorial and spinal cord. DIT is demonstrated by: (i) simultaneous asymptomatic contrast-enhancing and non-enhancing MRI lesions at any time; or (ii) a new lesion and/or contrast-enhancing lesion(s) on follow-up MRI, irrespective of its timing. Additionally, a more recent revision of the McDonald criteria (Thompson 2018) allows diagnosing MS when DIS criteria are fulfilled and cerebrospinal fluid-specific oligoclonal bands are detected, without detection in the serum. Other possible diagnoses must be excluded before confirming MS, as "no better explanation" should be demonstrated according to diagnostic criteria.

Pharmacological therapies for MS include MS-specific DMTs and symptomatic treatments, the latter aimed at relieving symptoms resulting from neurological impairment. As the number of effective DMTs has constantly increased during the last decades, interest in early MS treatment has grown in order to prevent long-term disability. Additionally, growing evidence suggests that early intervention with high-efficacy DMTs is associated with a significantly greater reduction of either inflammatory activity and long-term disease progression compared to escalating from lower efficacy drugs (Daruwalla 2023; He 2020). Whilst historically DMTs have been mostly immunosuppressant or immunomodulatory, requiring ongoing administration to keep disease activity suppressed, immune reconstitution therapies that can be given as short courses have recently emerged. This enlarged treatment scenario raises the question whether a DMT should be initiated early, or even in pre-symptomatic MS (e.g. when only MRI lesions are accidentally detected, in absence of clinical manifestations, a condition described as "radiologically isolated syndrome") and there are demands for an updated network meta-analysis of randomised clinical trials (RCTs) assessing the efficacy and safety profile of the available DMTs.

Description of the intervention

Several DMTs are available for people with RRMS. Given the broad range of DMTs currently available, many factors related to context and to patients' preferences, expectations and values are usually taken into account when clinicians and patients make shared treatment decisions. For this review update, we considered all immunomodulators and immunosuppressants that, up to September 2021, have been studied in people with RRMS in randomised clinical trials (RCTs) with at least 12 months' follow-up.

Interferon beta-1b (EMEA 2002; FDA 1993), interferon beta-1a (Rebif) (EMEA 1998; FDA 2002), interferon beta-1a (Avonex) (EMEA 1997; FDA 2003), and glatiramer acetate (FDA 1996) were the first agents approved by national regulatory agencies. Interferon beta-1b, interferon beta-1a (Rebif), and glatiramer acetate are administered by subcutaneous injection; interferon beta-1a (Avonex) by intramuscular injection. The main adverse effects of interferon beta are local injection site reactions and flu-like symptoms with hyperthermia.

Natalizumab was initially approved by the US Food and Drug Administration (FDA) in November 2004 (FDA 2004), but was withdrawn by the manufacturer in February 2005, after three participants in the drug's clinical trials developed progressive multifocal leukoencephalopathy (PML), a rare and serious viral infection of the brain. Two of the participants died. Following a re-examination of the participants in the previous clinical trials, the FDA allowed a clinical trial of natalizumab to proceed in February 2006. No additional cases of PML were reported and marketing of the drug for severe RRMS resumed (EMA 2006; FDA 2006; Yousry 2006). Natalizumab is administered by intravenous infusion, as a dose of 300 mg every four weeks.

Mitoxantrone was approved in 2000 under the indication "for reducing neurological disability and/or the frequency of clinical relapses in people with worsening RRMS, SPMS or PRMS" (FDA 2000). Safety issues of concern for people treated with mitoxantrone are cardiotoxicity and acute leukaemia.

Fingolimod was the first oral treatment approved for people with RRMS to reduce the frequency of relapses and delay the accumulation of physical disability (EMA 2011; FDA 2010). Even at the recommended low dose of 0.5 mg once daily, the FDA and European Medicines Agency (EMA) warned about decrease in heart rate following initiation of fingolimod treatment, recommending that all patients be monitored for at least six hours for signs and symptoms of bradycardia, considering that, in some patients, the nadir of heart rate can be observed up to 24 hours after the first dose.

Teriflunomide was the second oral agent approved for people with RRMS (EMA 2013a; FDA 2012). It is taken orally as a 7 mg or 14 mg tablet once daily. Warnings issued about this drug were hepatotoxicity and risk of teratogenicity.

Two other oral drugs, both with a mainly immunomodulatory mode of action, are available for the treatment of RRMS: teriflunomide is the active metabolite of leflunomide (Oh 2013), inhibiting pyrimidine de novo synthesis, and dimethyl fumarate (Linker 2011), the methyl ester of fumaric acid, is converted after administration into the active metabolite monomethyl fumarate. They were both approved for RRMS in the US in 2012 and in 2013, respectively.

Dimethyl fumarate has been approved as a first-line oral treatment for people with RRMS (EMA 2014a; FDA 2013). The recommended dose is 240 mg twice a day. The most commonly reported adverse events leading to discontinuation in clinical trials were flushing and gastrointestinal events.

Alemtuzumab has been approved for treatment of people with RRMS who have had an inadequate response to two or more drugs indicated for the treatment of MS (EMA 2013b; FDA 2014a). The drug is administered by intravenous infusion, as a dose of 12 mg/day for five consecutive days (60 mg total dose) followed by 12 mg/day for three consecutive days (36 mg total dose) administered 12 months after the initial treatment course. Particular warnings and precautions have to be taken into account for the treatment with alemtuzumab, since serious and sometimes fatal autoimmune conditions, life-threatening infusion reactions, and increased risk of malignancies were observed in people treated with alemtuzumab.

Peg-interferon beta-1a, which has been designed to maintain the effects of interferon beta in the body for a longer period of time, was approved by the FDA and EMA for people with RRMS (EMA 2014b; FDA 2014b). It is administered by subcutaneous injection at a dose of 125 µg every 14 days. The most common adverse reactions are injection site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia.

Daclizumab is a monoclonal antibody licenced in 2016 for the treatment of RRMS but, due to safety concerns, it was withdrawn worldwide from the market by its manufacturer in 2018 (EMA 2018a;EMA 2018; FDA 2018)

Ocrelizumab was approved as a treatment for relapsing MS and PPMS (EMA 2018b; FDA 2017). It is administered by intravenous injection.

Laquinimod is an oral immunomodulator investigated in two phase 3 trials for the treatment of people with RRMS. It is taken orally as a 0.6 mg tablet once daily. Its use in treating people with RRMS was approved in Russia but not in the EU, since in 2014 EMA refused authorisation. The EMA recommended refusal of the marketing authorisation for laquinimod as a treatment for RRMS due to concerns about potentially increased risks of cancer and teratogenicity in humans, especially given that the drug's mechanism of action is unclear (EMA 2014c).

Azathioprine is a purine analogue exerting its immunosuppressive action by affecting DNA replication through inhibition of the synthesis of nucleic acids. It has been used for the treatment of people with MS in many countries on the basis of favourable results reported by placebo-controlled RCTs (Laurson-Doube 2021). It is taken orally as a 2 mg/kg or 3 mg/kg tablet daily. It was reported that chronic immunosuppression with azathioprine increases the risk of malignancy in humans (FDA 2014c).

Intravenous immunoglobulins may have a role for people with severe and frequent relapses for whom other treatments are contraindicated (Association of British Neurologists 2005). Severe adverse events, including thrombosis of the jugular vein and allergic reaction leading to treatment discontinuation, were noted in 4% of 84 treatment courses with a total of 341 infusions under routine clinical conditions (Elovaara 2008).

The current update includes the following additional interventions compared to the previous version of the review. Compounds with similar mechanism of action to fingolimod have been developed, in order to increase efficacy and improve safety, such as siponimod (EMA 2020; FDA 2019b), as well as ozanimod and ponesimod, licenced in 2020 and 2021, respectively (EMA 2021a; EMA 2021b; FDA 2020; FDA 2021). Cladribine is a synthetic chlorinated deoxyadenosine analog approved for the treatment of RRMS in Russia and Australia in 2010, while in the EU and the US it was licenced in 2017 and 2019, respectively, for highly active RRMS and active SPMS (EMA 2017; FDA 2019a; Leist 2011). Recently, diroximel fumarate, a compound similar to dimethyl fumarate, was approved in 2019 in the US and EU for the treatment of RRMS (EMA 2021c). The anti-CD20 monoclonal antibody ofatumumab was approved as a treatment for relapsing MS (EMA 2021d).

Given the limited efficacy of currently available DMTs in delaying the progression of RRMS, many clinicians commonly prescribe immunosuppressant drugs with registered indications for conditions other than MS (mainly in rheumatological or

autoimmune diseases, or in people undergoing transplant). As such, in addition to those included previously (azathioprine, intravenous immunoglobulins), we decided to include in our review the following interventions used in MS as off-label treatments: rituximab, methotrexate, cyclophosphamide and long-term corticosteroids. Rituximab is an anti-CD20 monoclonal antibody similar to ocrelizumab and ofatumumab, commonly used to treat malignant blood cell neoplasms and several autoimmune diseases, such as rheumatoid arthritis, idiopathic thrombocytopenic purpura, and pemphigus vulgaris. Its efficacy and safety have also been studied in MS and in several countries, since rituximab is frequently prescribed off-label (Berntsson 2018; Brancati 2021; Laurson-Doube 2021). Methotrexate, cyclophosphamide, and long-term corticosteroids are systemic immunosuppressors. Methotrexate is a common treatment for autoimmune diseases. Cyclophosphamide, a DNA-alkylating agent used for the treatment of people with autoimmune disorders, has also been administered to people with MS (Awad 2009). Long-term corticosteroids, given their anti-inflammatory properties, have been proposed for the treatment of patients with MS since 1961 with mixed results. They have been administered by different schedules as pulsed periodic high-dose methylprednisolone or oral continuous low-dose prednisolone (Ciccone 2008). Fludarabine is a cytotoxic agent effectively used as a treatment for patients with lymphoproliferative disorders and haematologic malignancies. It has also been used as an add-on treatment in patients with MS experiencing breakthrough disease with an increase in the frequency of relapses and active MRI disease during treatment with other DMTs (Greenberg 2016). The antibiotic minocycline has been studied as a potential treatment for MS due to its anti-inflammatory properties (Love 2002; Metz 2017). Mycophenolate mofetil is an immunosuppressor mainly used as an anti-rejection therapy in organ transplant recipients, that has also been considered as a potential treatment for MS (Frohman 2004).

How the intervention might work

Immunosuppressive or immunomodulatory effects are common to all treatments included in the review. Although they all target the immune system, their effects vary as follows:

1. Immunomodulation (IFNβ-1b, IFNβ-1a, glatiramer acetate, pegylated IFNβ-1a, immunoglobulins, dimethyl fumarate and diroximel fumarate, laquinimod)

The mechanism of action of interferons beta in MS is incompletely understood. Interferons beta are naturally occurring cytokines possessing antiviral activity and a wide range of anti-inflammatory properties. Recombinant forms of interferons beta are believed to directly increase expression and concentration of anti-inflammatory agents, while down-regulating the expression of pro-inflammatory cytokines (Kieseier 2011). Glatiramer acetate has an immunomodulatory action by inducing tolerance or anergy of myelin-reactive lymphocytes (Schmied 2003). It is furthermore believed to promote neuroprotective repair processes (Aharoni 2014). Pegylated interferon beta-1a has a polyethylene glycol group attached to the α-amino group of the N terminus of interferon beta-1a (Avonex). Pegylation of interferon beta-1a may improve its pharmacokinetic and pharmacodynamic properties, allowing for reduced dosing frequency, while maintaining the clinical effectiveness and safety of intramuscular interferon beta-1a (Hu 2012). The mechanism of action of intravenous immunoglobulins in MS remains unclear, although remyelination of demyelinated axons may occur through the mediation of the effects of cytokines (Stangel 1999). Dimethyl fumarate is a derivative of fumaric acid. It acts primarily by triggering the activation of a nuclear factor (Nrf2) transcriptional pathway, the primary cellular defence against the cytotoxic effects of oxidative stress. It promotes anti-inflammatory activity and can inhibit expression of pro-inflammatory cytokines and adhesion molecules (Wilms 2010). Exactly how laquinimod works is unknown, but it is believed to have an immunomodulatory effect on the peripheral and central nervous systems. Data from animal studies indicate that laquinimod has a primary effect on innate immunity. The drug modulates the function of various myeloid antigen-presenting cell populations, which then down regulate pro-inflammatory T-cell responses. Furthermore, data indicate that laquinimod acts directly on resident cells within the central nervous system to reduce demyelination and axonal damage (Varrin-Doyer 2014). Minocycline is a tetracycline antibiotic agent with immune-modulating properties.

2. Systemic immunosuppression, inducing a reduction in the activation or efficacy of the immune system through cytostatic or cytotoxic effects (mitoxantrone, methotrexate, cyclophosphamide, long-term corticosteroids, cladribine, azathioprine, teriflunomide, and leflunomide)

Mitoxantrone is a cytotoxic drug that intercalates with DNA and inhibits both DNA and RNA synthesis, thus reducing the number of lymphocytes (Fox 2004). Methotrexate is commonly used in autoimmune diseases and, since 1996, has been used in the treatment of MS. By acting as an antagonist to folic acid, it interferes with DNA synthesis, repair, and cellular replication, limiting cellular reproduction. Cyclophosphamide, a DNA-alkylating agent used for the treatment of people with autoimmune disorders, has also been administered to people with MS (Awad 2009). Long-term corticosteroids have been proposed (such as pulsed periodic high-dose methylprednisolone or oral continuous low-dose prednisolone) for the treatment of patients with MS with mixed results (Ciccone 2008). Cladribine is a purine antimetabolite, generally recommended for patients who are unresponsive or intolerant to an alternate drug indicated for the treatment of MS and administered orally divided into two treatment courses separated by one year. It provides a reduction of circulating T (CD4+ and CD8+) and B lymphocytes with relative sparing of other immune cells (Beutler 1992). Azathioprine is a classical cytotoxic immunosuppressive drug that acts as a prodrug for mercaptopurine, inhibiting an enzyme that is required for DNA synthesis. Thus, it most strongly affects proliferating cells, such as the T-cells and B-cells of the immune system (Tiede 2003). Fludarabine is a purine nucleoside analog prodrug determining systemic immunosuppression through a cytotoxic action by interfering with DNA synthesis of dividing lymphocytes and monocytes (Zinzani 1994). Mycophenolate mofetil is an inhibitor of purine synthesis with anti-inflammatory properties exerted on T and B lymphocytes and macrophages (Barten 2002).

Teriflunomide, the active metabolite of leflunomide, is an inhibitor of new pyrimidine synthesis for DNA replication. Consequently, the drug reduces T- and B-lymphocyte activation, proliferation, and function in response to autoantigens. The exact mechanism of action in MS is not fully understood. The drug is thought to reduce the number of activated lymphocytes, which would cause inflammation and damage myelin in the central nervous system (Claussen 2012).

3. Selective immunosuppression, as with monoclonal antibodies or biological agents directed towards specific antigenic targets (natalizumab, fingolimod, siponimod, ozanimod, ponesimod, alemtuzumab, ofatumumab, daclizumab, rituximab and ocrelizumab)

Natalizumab is a monoclonal antibody against the alfa4 integrin on the surface of lymphocytes. This integrin is essential in the process by which lymphocytes gain access to the brain by allowing the cells to penetrate the blood brain barrier. Natalizumab blocks the action of the alfa4 integrin so that lymphocytes are unable to enter the brain and attack myelin protein (Yednock 1992). Fingolimod acts as a functional antagonist of sphingosine-1-phosphate (S1P) receptor on lymphocytes, resulting in a reduced egress of lymphocytes from the lymph nodes. In particular, auto-aggressive T-cells are prevented from recirculating to the central nervous system (Mandala 2002). Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator acting as a functional antagonist on S1P1 receptors on lymphocytes. By preventing egress of T cells from lymph nodes, it reduces their recirculation into the central nervous system, limiting inflammation (Behrangi 2019). The mechanisms of action of ozanimod and ponesimod is similar to that of siponimod, with higher receptor selectivity for the latter and short half life, facilitating faster reversibility of its effects on the immune system after discontinuation (Scott 2016; Ruggieri 2022). Alemtuzumab is a monoclonal antibody against the CD52 antigen expressed on lymphocytes and monocytes. Its effects in MS are thought to be mediated by an extended lymphocyte depletion and change in the composition of lymphocytes that accompanies lymphocyte reconstitution (Hill-Cawthorne 2012). Ofatumumab is a CD20+ B-cell-targeting recombinant human monoclonal antibody. It was initially approved for the treatment of chronic lymphocytic leukaemia and is now approved in several countries as a subcutaneous injection for the treatment of RRMS (Kang 2021). Daclizumab is a monoclonal antibody against the CD25 antigen (interleukin 2 receptor) expressed on immune cells. The mechanisms by which the drug exerts effects in MS are not clear. Daclizumab leads to expansion of regulatory CD56 natural killer T lymphocytes, which may be an important mechanism of action in MS. Furthermore, daclizumab modulates the function of dendritic cells, resulting in decreased T-cell activation (Wuest 2011). Rituximab is a chimeric monoclonal B-cell-depleting anti-CD20 antibody similar to ocrelizumab and ofatumumab, administered intravenously, commonly used in the treatment of malignant blood cell neoplasms and several autoimmune diseases, such as rheumatoid arthritis, idiopathic thrombocytopenic purpura, and pemphigus vulgaris. It has been used off-label in the treatment of MS for more than two decades (Salzer 2016; Laurson-Doube 2021).

Ocrelizumab is a monoclonal antibody against the CD20 antigen expressed on B-lymphocytes. The antibody depletes circulating B-lymphocytes predominately through antibody-mediated cytotoxicity (Oh 2013).

Mechanisms of action must be considered while assessing the risk of adverse events associated with the use of a drug, since safety is usually a consequence of the drug's main pharmacological effect (Compston 2008; Hauser 2020; Massacesi 2002; Meinl 2008).

Why it is important to do this review

Although there is consensus that immunotherapies reduce the frequency of relapses in MS, their relative benefit in delaying new relapses or disability worsening remains unclear. This uncertainty is due to the limited number of direct comparison trials, which provide the most rigorous and valid research evidence on the relative efficacy and safety of different, competing treatments. Since the previous version of the review (Tramacere 2015), new DMTs have been approved by regulatory agencies, offering a broader spectrum of treatment options for people with MS. Evidence of efficacy in chronic autoimmune conditions, relatively good tolerability and reasonable cost has prompted the off-label use of several immunosuppressants and immunomodulators for the treatment of MS in many countries, particularly in settings with budget constraints (Zeineddine 2020). A summary of the results, including both direct and indirect comparisons, may help to clarify the stated uncertainty (Caldwell 2005; Glenny 2005).

The data underlying the present review and NMA served as the evidence base for the development of a separate clinical practice guideline on the treatment of RRMS and PMS by an international, highly representative multi-stakeholder panel (Multiple Sclerosis Essential Medicines Panel, MEMP) appointed by the Multiple Sclerosis International Federation (MSIF). The panel included people with MS and advocacy group representatives, clinicians from different speciality areas involved in the management of MS, pharmaco-epidemiologists and health economists. The guidelines were developed with methodological guidance by the Department of Health Research Methods, Evidence and Impact (HEI), McMaster University, Hamilton, Ontario, Canada, according to the GRADE Working Group method for guideline development (Alonso-Coello 2016; Alonso-Coello 2016b). The MEMP recommendations were used as the evidence base for an application for the inclusion of disease-modifying treatments in the 23rd WHO Model List of Essential Medicines. The nine critical outcomes identified by MEMP were differentiated into primary and secondary outcomes in this review (see Methods).

This is an update of a Cochrane review published in 2015 (Tramacere 2015).

OBJECTIVES

To compare, through network meta-analysis, the efficacy and safety of interferon beta-1b, interferon beta-1a (Avonex, Rebif), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine, immunoglobulins, cladribine, cyclophosphamide, diroximel fumarate, fludarabine, interferon beta 1-a and beta 1-b, leflunomide, methotrexate, minocycline, mycophenolate mofetil, ofatumumab, ozanimod, ponesimod, rituximab, siponimod and steroids for the treatment of people with RRMS.

METHODS

Criteria for considering studies for this review

Types of studies

We included individually randomised parallel controlled clinical trials (RCTs). We considered studies published in abstracts whenever sufficient information was available on study design, characteristics of participants, interventions, and outcomes. Only studies with a follow-up of 12 months or longer were included.

Types of participants

We included adult participants aged 18 years or older with a diagnosis of RRMS according to Poser (Poser 1983) or McDonald (McDonald 2001; Polman 2005; Polman 2011) diagnostic criteria. We included all participants regardless of sex, degree of disability, and disease duration.

We included studies primarily focused on RRMS but also including a subgroup of people with PMS only if the proportion of people with RRMS was ≥ 80%. Evidence from studies including 80% to 99% of people with RRMS were considered for downgrading because of indirectness while assessing the certainty of the evidence, according to GRADE methodology (Guyatt 2011).

Types of interventions

We included all immunomodulators or immunosuppressants (even if they were not licenced in any country). We excluded: (i) combination treatments; (ii) trials in which a drug regimen was compared with a different regimen of the same drug without another active agent or placebo as a control arm; (iii) all non-pharmacological treatments; and (iv) interventions with over-the-counter drugs.

We included RCTs that evaluated one or more of the following pharmacological interventions as monotherapy, compared to placebo or to another active agent:

- interferon beta-1b
- interferon beta-1a (Avonex, Rebif)
- glatiramer acetate
- natalizumab
- mitoxantrone
- fingolimod
- teriflunomide
- dimethyl fumarate
- alemtuzumab
- pegylated interferon beta-1a
- daclizumab
- ocrelizumab
- laquinimod
- azathioprine
- immunoglobulins

In this update, we also considered the following additional interventions for inclusion:

- cladribine
- cyclophosphamide
- diroximel fumarate
- fludarabine
- interferon beta 1-a and beta 1-b (when both are used in the same experimental arm as 'interferon beta products').
- leflunomide
- methotrexate
- minocycline
- mycophenolate mofetil
- ofatumumab
- ozanimod
- ponesimod
- rituximab
- siponimod
- steroids

We included regimens as defined in primary studies, irrespective of their dose.

Types of outcome measures

Primary outcomes

We estimated the relative effects of the competing interventions according to the following primary outcomes:

Efficacy

- Relapses: proportion of participants who experienced new relapses over 12, 24, or 36 months after randomisation or at the end of the study. A relapse is defined as newly developed or recently worsened symptoms of neurologic dysfunction that last for at least 24 hours, occurring in the absence of fever or other acute diseases and separated in time from any previous episode by more than 30 days (McDonald 2001; Polman 2005). A more stringent 48-hour criterion has been used in some RCTs. A relapse can resolve either partially or completely.
- Disability worsening: proportion of participants who experienced disability worsening over 24 or 36 months after randomisation or at the end of the study. Worsening is defined as at least a 1-point Expanded Disability Status Scale (EDSS) increase or a 0.5-point increase if the baseline EDSS was greater than or equal to 5.5, confirmed during two subsequent neurological examinations separated by at least a six-month interval free of attacks (Kurtzke 1983). Disability worsening confirmed after only three months of follow-up is considered a surrogate marker for unremitting disability. EDSS is a common measure of MS disability (where 0 is normal, 3 mild disability, 6 care requirement, 7 wheelchair use, and 10 is death from MS) and is used to measure disability worsening in clinical trials for MS.

Safety

- Discontinuation due to adverse events: measured by the number of participants who withdrew due to any adverse event at the end of the study
- Serious adverse events (SAEs): number of participants with any (one or more) SAEs, defined according to the authors of the study

Secondary outcomes

- Cognitive decline: assessed as a continuous outcome considering the variation in the score of the Symbol Digit Modalities Test (SDMT) (Benedict 2017) when available or, alternatively, the Paced Auditory Serial Addition Test (PASAT) (Gronwall 1977);
- Quality-of-life impairment: assessed as a continuous outcome considering the variation in the score of scales reporting quality-of-life impairment. Any available scale was considered;
- New or enlarging T2-weighted magnetic resonance imaging (MRI) lesions: measured by the number of participants with new

or enlarging T2-weighted MRI lesions at 12, 24, and 36 months after randomisation;
- New gadolinium-enhancing positive T1-weighted MRI lesions: measured by the number of participants with new gadolinium-enhancing T1-weighted MRI lesions at 12, 24, and 36 months after randomisation;
- Mortality: overall number of MS-related deaths.

Search methods for identification of studies

Electronic searches

The previous version of this review searched the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group Trials Register (on 30 September 2014). As this was not possible for this version of the review, a bespoke search was created by the Information Specialist of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group. Searches were run in September 2021, then topped up on 8 August 2022:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 8 2022)(Appendix 1);
- MEDLINE (PubMed) (January 2012 to 8 August 2022) (Appendix 2);
- Embase (Embase.com) (January 2012 to 2022 week 32) (Appendix 3).

We did not apply any search limitation with respect to study outcomes, methods of analysis, or language.

Searching other resources

In addition to considering all studies from Tramacere 2015, to identify eligible studies prior to 2012, we consulted the identified studies in Filippini 2013, a prior Cochrane NMA review concerning immunomodulators and immunosuppressants for multiple sclerosis, where the search was performed until February 2012.

We searched for ongoing studies on the following databases (see Appendix 4 for search strings):
• World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch). Search terms: relapsing multiple sclerosis, filtered for "Phase 2" "Phase 3" trials;
• US National Institutes of Health clinical trial register (www.clinicaltrials.gov). Search term: "relapsing multiple sclerosis".

We checked reference lists of all included studies and any relevant systematic reviews identified for additional references to studies. We examined any relevant retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

For this version of the review, study selection was conducted with the Rayyan platform (https://rayyan.ai/) in accordance with the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Six review authors in pairs (BR, EB, FN, GP, IT, MF) independently screened the titles and abstracts. Potentially relevant articles were acquired in full text and assessed for eligibility by the same six authors in pairs.

Data extraction and management

Two review authors (SM, MGL) independently extracted data from the studies using a predefined data extraction form in an Excel spreadsheet and piloting the data extraction form on at least five studies in the review. We resolved disagreements by discussion with a third author (FN). Whenever data were available from both peer-reviewed journals as full publications as well as from trials registries (such as ClinicalTrials.gov or WHO ICTRP), we extracted them from the former. We extracted results from trials registers when these were the only available data.

We extracted from each included study data the following information:

- Study: first author or acronym, number of centres, year of publication, years that the study was conducted (recruitment and follow-up), publication (full-text publication, abstract publication, unpublished data);
- Study design: inclusion criteria, number of randomised participants, duration of follow-up (12, 24, or 36 months);
- Population: baseline mean age, gender, definition of relapse;
- Potential effect modifiers: diagnostic criteria (Poser or McDonald criteria), previous treatments with DMTs, by structuring four categories: “no previous treatment with DMTs”, “previous treatment with DMTs”, “uncertain information on previous treatment with DMTs” and “mixed population of patients, previously treated and previously untreated with DMTs”;
- Intervention: active agent, dose, frequency, or duration of treatment;
- Funding source.

Outcome data

For dichotomous outcomes, we extracted the number of participants experiencing the event of interest over the number of randomised participants.

For continuous outcomes relative to the outcomes 'cognitive decline' and 'quality-of-life impairment', we extracted the mean and standard deviation of the comparison groups, where possible. We extracted data at baseline and end point, as well as change scores. We used change scores in case end point scores were not reported (Da Costa 2013). We extracted data at the authors' defined timing points.

When outcomes were not reported at our predefined time points, we extracted data as close as possible to that time point. We extracted the authors' definition of relapses and disability worsening. We extracted arm-level data, when available.

We further extracted the characteristics associated with the monitoring and reporting of adverse events, considering specific factors that may have a large influence on adverse event data. We evaluated methods of monitoring and detecting adverse events in each primary study: Did the researchers actively monitor for adverse events, or did they simply provide spontaneous reporting of adverse events that arose? Did the authors define adverse events according to an accepted international classification and report the number of SAEs? We reported this information in an additional table called 'Assessment of Adverse Events Monitoring' (Table 1).

Assessment of risk of bias in included studies

We assessed the risk of bias of each included study using the Cochrane Collaboration's tool for assessing the risk of bias (Higgins 2011). These include: random sequence generation, allocation concealment, blinding of participants and providers, blinding of outcome assessor(s), incomplete outcome data, and selective outcome reporting. Other potential risks of bias included the role of the sponsor: we judged a study as being at high risk of bias if it was funded by industry, and it was stated that the funder was involved in data management, analysis and interpretation, in writing of the study report, or where it was reported that the funders approved the final version of the paper; we judged studies as being at high risk of bias also if the first or last author and authors who performed the statistical analysis were employed by industry. We explicitly judged the risk of bias of each study on each criterion and classified it as being at 'low', 'high', or 'unclear' risk of bias. We judged incomplete outcome data as at low risk of bias when numbers and causes of dropouts were balanced (i.e. absence of a significant difference) between arms and appeared to be unrelated to the studied outcomes. We assessed selective outcome reporting bias by comparing outcomes reported in the study protocol along with published outcome results. If a study protocol was not available, we assigned a judgement of unclear risk of bias.

Two authors (SM, MGL) assessed the risk of bias of each study independently and resolved any disagreement by discussion to reach consensus.

Measures of treatment effect

Relative treatment effects

For dichotomous outcomes (i.e. disability and relapses), we reported risk ratios (RRs) and 95% confidence intervals (CIs). If the number of observed events had been small (less than 5% of the sample per group), and if studies had balanced treatment groups, we reported the Peto odds ratios (ORs) with 95% CIs.
For continuous outcomes, we calculated the mean difference (MD) or standardised mean difference (SMD) if the same continuous outcome was measured with different metrics. To interpret SMD, we used the guiding principles (Guyatt 2013) of thresholds for small (SMD = ±0.2), moderate (SMD = ±0.5), and large effects (SMD = ±0.8). We presented results from network meta-analysis as summary relative effect sizes (RR, MD, or SMD) for each possible pair of treatments.

Relative treatment ranking

We estimated the ranking probabilities for all treatments at each possible rank for each intervention. We obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA was expressed as the percentage representing the relative probability of a treatment being amongst the best options without uncertainty (Salanti 2011).

Unit of analysis issues

Studies with multiple treatment groups

For pairwise meta-analysis, we considered the multi-arm studies as multiple independent two-arm studies. For network meta-analysis (NMA), we accounted for the correlation between the effect sizes from multi-arm studies (Salanti 2012). For studies with multi-arm trials involving the same agent at different doses compared to a control treatment, we converted the treatment arms into a single arm by merging the different doses, summing the number of events, and calculating the sample size.

Studies with multiple outcome scales

MS-specific scales (e.g. MSQOL-54, MSIS 29) were not combined with non-MS-specific scales (e.g. SF-36 or EQ-5D index). Where several scales were used in one RCT, we selected the scale that provided lower heterogeneity in combination (via SMD) with the others across studies.

Dealing with missing data

We used data that reflected the intention-to-treat (ITT) analysis for each included outcome. Primary analysis was performed considering the number of patients with the event in relation to the number of randomised individuals. In the case of participants with missing data, primary analysis was performed without any imputation. For adverse events, we used data from participants who received at least one dose of the study medication. Where standard deviations were missing for continuous outcomes, we calculated them according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Assessment of heterogeneity

Assessment of clinical heterogeneity within treatment comparisons

To evaluate the presence of heterogeneity deriving from different characteristics of study participants, we assessed differences in age, disease duration, and baseline EDSS scores across the trials using information reported in the table 'Characteristics of included studies'.

Assessment of transitivity across treatment comparisons

We expected that the transitivity assumption held, assuming that all pairwise comparisons did not differ with respect to the distribution of effect modifiers. We evaluated the assumption of transitivity by comparing potential effect modifiers, which are reported in the 'Data extraction and management' section, across the different pairwise comparisons.

Assessment of reporting biases

We planned to evaluate the possibility of reporting bias by means of contour-enhanced funnel plots (Peters 2008). Contour-enhanced funnel plots show areas of statistical significance, and they can help in distinguishing reporting bias from other possible reasons for asymmetry. In a network of interventions, each study estimates the relative effect of different interventions, so asymmetry in the funnel plot cannot be judged. To account for this, we used an adaptation of the funnel plot by subtracting from each study-specific effect size the mean of meta-analysis of the study-specific comparison and plotted it against the study's standard error (Chaimani 2012; Chaimani 2013). We employed the comparison-adjusted funnel plot for all placebo-controlled trials. Note that any asymmetry in the plot indicates the presence of small study effects and not necessarily reporting bias.

Data synthesis

Methods for direct treatment comparisons

We performed conventional pairwise meta-analyses for each primary outcome using a random-effects model for each treatment comparison with at least two studies (DerSimonian 1986).

Methods for indirect and mixed comparisons

We performed network meta-analysis using a random-effects model within a frequentist setting assuming equal heterogeneity across all comparisons, and we accounted for correlations induced by multi-arm studies (Miladinovic 2014; Salanti 2012). The models enabled us to estimate the probability of each intervention being at each possible rank for each outcome, given the relative effect sizes as estimated in network meta-analysis. We summarised the probabilities of a treatment being at each possible rank using SUCRAs and mean rank. We performed network meta-analysis in Stata 13 using the 'mvmeta' command and self-programmed Stata routines available at http://www.mtm.uoi.gr (Chaimani 2013; White 2011; White 2012).

Assessment of statistical heterogeneity

We statistically assessed the presence of heterogeneity for all direct pairwise comparisons using the common τ^2 and I^2 statistics. The assessment of statistical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the network meta-analysis models (Jackson 2014).

Assessment of statistical inconsistency

Consistency in a network of treatments refers to the agreement between direct and indirect estimates. Joint analysis of treatments can be misleading if the network is substantially inconsistent. Inconsistency can be present if the trials in the network have different protocols and their inclusion/exclusion criteria are not comparable or may result in an uneven distribution of the effect modifiers across groups of trials that compare different treatments. To evaluate the presence of inconsistency locally, we used both the loop-specific approach and the node splitting approach by using the software STATA (Chaimani 2013; Veroniki 2013). We used the 'design-by-treatment' model to evaluate the assumption of consistency in the entire network (Higgins 2012). This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results, as well as disagreement between direct and indirect evidence. Using this approach, we inferred the presence of inconsistencies from any source in the entire network based on a Chi^2 test. We performed the design-by-treatment model in Stata using the 'mvmeta' command.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses for efficacy outcomes at 12, 24, and 36 months' follow-up by using the following effect modifiers as possible sources of inconsistency or heterogeneity, or both:

- Diagnostic criteria (Poser or McDonald criteria);
- Previous treatment with immunomodulators or immunosuppressants (no or yes), i.e. first- or second-line treatments.

Sensitivity analysis

We planned to perform the following sensitivity analyses:

- Including only trials with low risk of selection bias and attrition bias;
- Excluding trials with a total sample size of fewer than 50 randomised participants to detect potential small study effects.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in a Summary of findings (SoF) table, according to recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022a). We assessed the certainty of the NMA estimates for the outcomes below using the GRADE approach (Brignardello-Petersen 2018):

- Proportion of people who experienced new relapses over 12, 24 and 36 months;
- Proportion of people who experienced disability worsening over 24 months;
- Proportion of people who withdrew due to any adverse event;
- Number of participants with any (one or more) SAEs.

Since the results of this review and NMA will serve as the evidence base for guidance on the use of DMTs in people with RRMS, the certainty of the evidence for this review was assessed using a fully contextualised approach. A fully contextualised approach is important in NMAs to incorporate the value of individual outcomes in the overall interpretation of the results (Schünemann 2022b). This involved predefining quantitative thresholds to determine the magnitude of each health effect (desirable or undesirable) measured by means of each outcome. The magnitudes of desirable and undesirable health effects were defined according to the GRADE wording as 'trivial', 'small', 'moderate', and 'large'.

For this NMA, we used outcomes assessed by the MSIF Essential Medicines Panel – which was convened to make recommendations on essential medicines for MS. The value of the outcomes was assessed by the guideline panel to judge both the priority of outcomes (not important/important/critical) and a health state utility value (HSUV) corresponding to the outcome in question. The panel identified nine critical outcomes. In this review, the authors further differentiated and reported those outcomes as four primary and five secondary outcomes. The HSUV was derived from a review of reviews or panel judgement if not identified from the literature. The HSUV is utilised to calculate thresholds for the magnitude of effects. The thresholds between trivial/small (T1), small/moderate (T2), and moderate/large (T3) were predefined through calculation informed by the health state utility value (HSUV) of each outcome (Appendix 5).

Thresholds were based on absolute anticipated effects of each intervention's outcome estimate using the formula: Threshold = (threshold coefficient/(1 - utility) x 1000). The threshold coefficient was derived from an interim analysis of an ongoing global survey on decision thresholds by assessing respondent judgements across varied disease category examples (Morgano 2022).

We followed GRADE guidance for assessing imprecision using a fully contextualised approach (Schünemann 2022b). We graded

the certainty of evidence for each outcome considering study limitations, indirectness, inconsistency, imprecision of effect estimates, and risk of reporting bias. According to the software GRADEpro 2008, we assigned four levels of certainty of evidence: high, moderate, low, and very low.

In order to determine the imprecision of estimates, and therefore make imprecision judgements including downgrading by 1, 2, or 3 levels for certainty, point estimates of observed effects and their 95% CIs were contextualised in relation to the predefined thresholds (Hultcrantz 2017). In accordance with the GRADE guidance on imprecision, the overall imprecision of interventions was assessed across all outcomes with guideline panel input. If most outcomes were not downgraded for imprecision, the overall certainty was not necessarily downgraded to the lowest certainty (Schünemann 2022b).

RESULTS

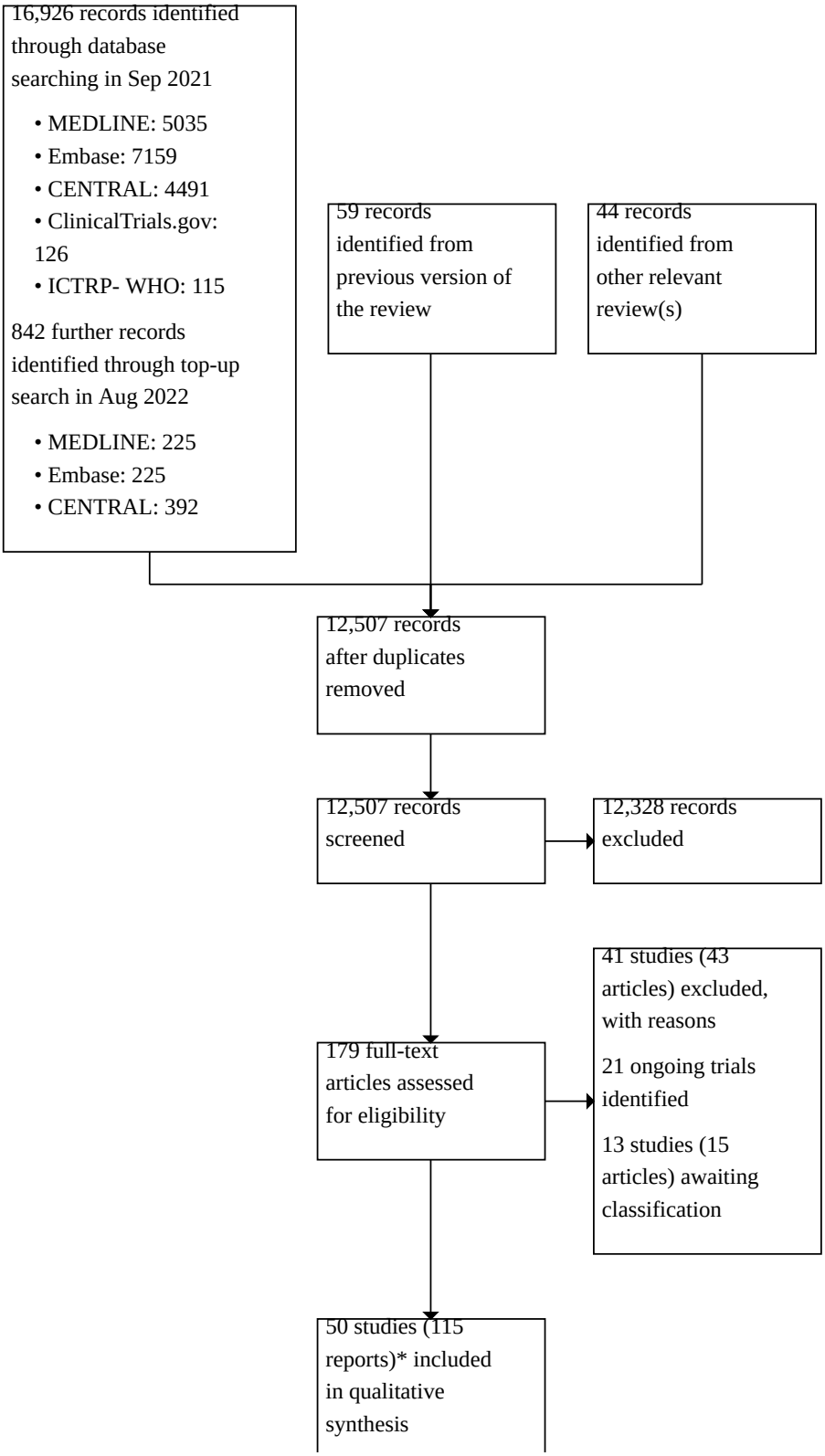
Description of studies

Results of the search

We identified 16,926 reports through an electronic database search on 21 September 2021. A top-up search conducted on 8 August 2022 identified a further 842 records (See Figure 1). A total of 59 reports were carried over from the previous version of this review (Tramacere 2015), and 44 reports from another relevant NMA review which included studies with people with both RRMS and PMS (Filippini 2013). We screened a total of 12,507 de-duplicated records, of which 12,328 were excluded based on the titles and abstracts. We evaluated 179 full texts as potentially meeting inclusion criteria. We excluded 41 studies with reasons (Characteristics of excluded studies), and identified 21 ongoing studies (Characteristics of ongoing studies). After full-text review, we included 50 studies. A total of 13 studies were identified as potentially meeting inclusion criteria. These studies are summarised in Characteristics of studies awaiting classification and will undergo full-text review in a future update of this review.

Figure 1. PRISMA flow chart * Several of the studies were reported in the same reports: ASCLEPIOS I 2020; ASCLEPIOS II 2020 (reported in Hauser 2020); CARE-MS I 2012; CARE-MS II 2012 (reported in Arroyo 2017); OPERA I 2017; OPERA II 2017 (reported in the same four reports); CONFIRM 2012; DEFINE 2012 (reported in Fernandez 2017

and Havrdova 2017); FREEDOMS 2010; FREEDOMS II 2014 (reported in Vermersch 2017); DECIDE 2015; SELECT 2013 (reported in Giovannoni 2016 and Rose 2017).



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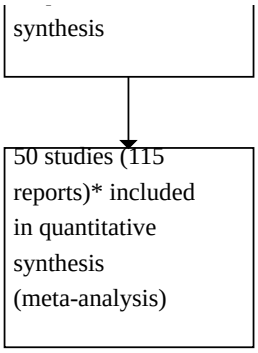


On the following DMTs, we found no studies satisfying our inclusion criteria: cyclophosphamide, diroximel fumarate, fludarabine, leflunomide, methotrexate, minocycline, mycophenolate mofetil, rituximab, siponimod, and steroids.

Included studies

We included 50 studies involving 36,541 participants (68.6% female and 31.4% male) and published between 1987 and 2021 in this review.

We included 34 studies already included in previous reviews (Achiron 1998; ADVANCE 2014; AFFIRM 2006; ALLEGRO 2012; BECOME 2009; BEYOND 2009; Bornstein 1987; BRAVO 2014; CAMMS223 2008; CARE-MS I 2012; CARE-MS II 2012; CombiRx 2013; CONFIRM 2012; DEFINE 2012; Etemadifar 2007; Fazekas 1997; FREEDOMS 2010; FREEDOMS II 2014; GALA 2013; Goodkin 1991; IFNB MS Group 1993; INCOMIN 2002; Johnson 1995; Koch-Henriksen 2006; Lewanska 2002; MAIN 2014; Millefiorini 1997; MSCRG 1996; PRISMS 1998; REGARD 2008; SELECT 2013; TEMSO 2011; TOWER 2014; TRANSFORMS 2010). Three studies that were previously identified as ongoing in Tramacere 2015 were also included: DECIDE 2015; OPERA I 2017; OPERA II 2017. We also included two studies that were previously excluded in Tramacere 2015 as we obtained further information and found that they met our pre-defined inclusion criteria (Etemadifar 2006; Knobler 1993).

The updated search identified an additional 11 new studies meeting our inclusion criteria, which were not previously included (ASCLEPIOS I 2020; ASCLEPIOS II 2020; ASSESS 2020; CLARITY 2010; CONCERTO 2021; Gobbi 2013; GOLDEN 2017; Mokhber 2014; OPTIMUM 2021; RADIANCE 2019; SUNBEAM 2019).

Of the 50 included studies, seven studies (ASCLEPIOS I 2020; ASCLEPIOS II 2020; BECOME 2009; RADIANCE 2019; SUNBEAM 2019; TEMSO 2011; TOWER 2014) included a mixed sample of participants with not only relapsing but also other forms of MS. As per the methods, only those with more than 80% of the sampled population affected by relapsing forms were included in analyses.

Median follow-up was 24 months (including 12-month follow-up (11 studies); 18 months (1); 24 months (32), 25 months (1); 30 months (2) and 36 months (4)). Twenty-five studies were placebo-controlled and 25 were head-to-head studies. Funding came from industry in 40 studies, from public sources in six cases (Bornstein 1987; CombiRx 2013; Gobbi 2013; INCOMIN 2002; Lewanska 2002; MAIN 2014) and funding sources were not reported in four cases (Etemadifar 2006; Etemadifar 2007; Millefiorini 1997; Mokhber 2014).

Of the 50 included studies, one (CARE-MS II 2012) included only people with MS previously treated with DMTs; five (BEYOND 2009; CAMMS223 2008; CARE-MS I 2012; INCOMIN 2002; Mokhber 2014) included only people with MS previously untreated with DMTs, 17 (Achiron 1998; AFFIRM 2006; BECOME 2009; Bornstein 1987; CombiRx 2013; Etemadifar 2006; Etemadifar 2007; Fazekas 1997; Goodkin 1991; IFNB MS Group 1993; Johnson 1995; Knobler 1993; Koch-Henriksen 2006; Lewanska 2002; Millefiorini 1997; MSCRG 1996; REGARD 2008) did not report data about previous treatments with DMTs, and 27 (ADVANCE 2014; ALLEGRO 2012; ASCLEPIOS I 2020; ASCLEPIOS II 2020; ASSESS 2020; BRAVO 2014; CLARITY 2010; CONCERTO 2021; CONFIRM 2012; DECIDE 2015; DEFINE 2012; FREEDOMS 2010; FREEDOMS II 2014; GALA 2013; Gobbi 2013; GOLDEN 2017; MAIN 2014; OPERA I 2017; OPERA II 2017; OPTIMUM 2021; PRISMS 1998; RADIANCE 2019; SELECT 2013; SUNBEAM 2019; TEMSO 2011; TOWER 2014; TRANSFORMS 2010) included a mixed population of patients with and without previous treatment with DMTs, but did not report separate outcome data for the two subgroups.

The table, Characteristics of included studies, provides details of the included studies. Table 1 provides the characteristics associated with the monitoring and reporting of adverse events, considering specific factors.

We identified 21 ongoing trials (EUCTR2013-003884-71-BE; EUCTR2012-003647-30-SK; EUCTR2014-001012-19-NL; EUCTR2012-000540-10-PL;EUCTR2018-000284-93-BG; EUCTR2019-001505-24-NO; EUCTR2020-002981-15-DK; EUCTR2018-005038-39-GB; IRCT20130812014333N; IRCT201404195280N; NCT04121221; NCT04056897; NCT04121403; NCT04688788; NCT04578639; WHO-ICTRP 002519; WHO-ICTRP PER-024-14). Of these, four studies have been withdrawn, and results are unlikely to be available (EUCTR2013-002082-19-SE; NCT01404117; NCT01975298; NCT01941004). The remaining 17 studies will be assessed and included, where appropriate, in a future update of this review. Please see Characteristics of ongoing studies for further details.

Excluded studies

After full-text review, we excluded 41 studies with reasons (see Characteristics of excluded studies):

Fifteen were excluded where the randomised, blinded portion of the trial was less than one year (Bar-Or 2017; Boyko 2016; Cohen 2015; Cohen 2016; Comi 2001; Fazekas 2008; IMPROVE 2010; Le Page 2015; Newsome 2015; Ochi 2018; OWIMS 1999; Saida 2017; Simaniv 2019; TENERE 2014; Ziemssen 2017); one study was non-randomised (Boiko 2018); one was a pooled post hoc analysis (Agius 2014) and five used a comparator that was not admissible under our inclusion criteria (Cascione 2018; Coyle 2017; Cree 2018; Fox 2014; Lampl 2013).

Studies excluded at full-text review included five that were previously included in Tramacere 2015 for insufficient follow-up duration (Comi 2001; Fazekas 2008; OWIMS 1999; TENERE 2014) and incorrect comparator (EVIDENCE 2007), as well as four included in Filippini 2013 for wrong intervention (SENTINEL 2006), wrong publication type (Ghezzi 1989) and mixed populations where < 80% were people with relapsing MS (British and Dutch 1988; Milanese 1993).

The previous version of this review excluded the following studies: six studies for insufficient duration (CHOICE 2010; Kappos 2006; Kappos 2008; Kappos 2011; Saida 2012; Sorensen 2014), five studies evaluating combination therapies (ACT 2009; Freedman 2012; Havrdova 2009; Khoury 2010; SENTINEL 2006), two studies evaluating treatments that are not included in this review (Ashtari 2011; ATAMS 2014), a study that was non-randomised (Calabrese 2012), and one dose-finding study without a control group (FORTE 2011). Etemadifar 2006 and Knobler 1993 were included in this version of the review, though they were excluded in the previous version.

Risk of bias in included studies

The risks of bias in the included studies for individual domains are summarised in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

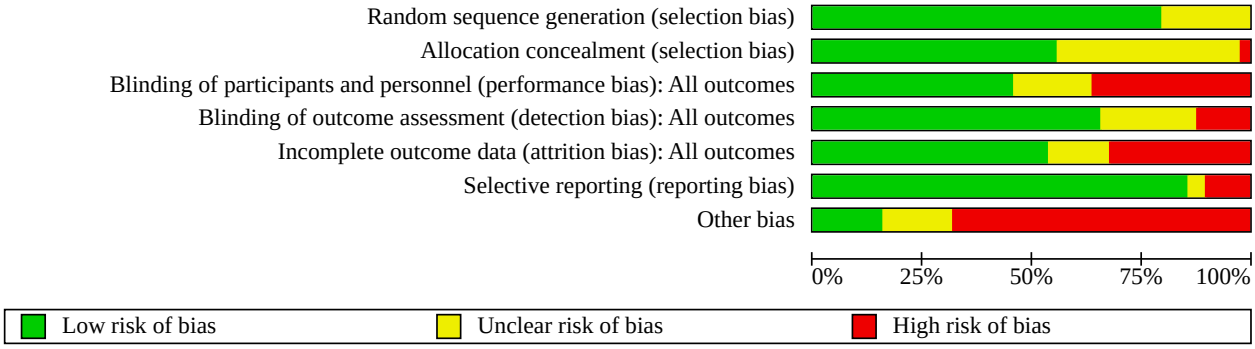
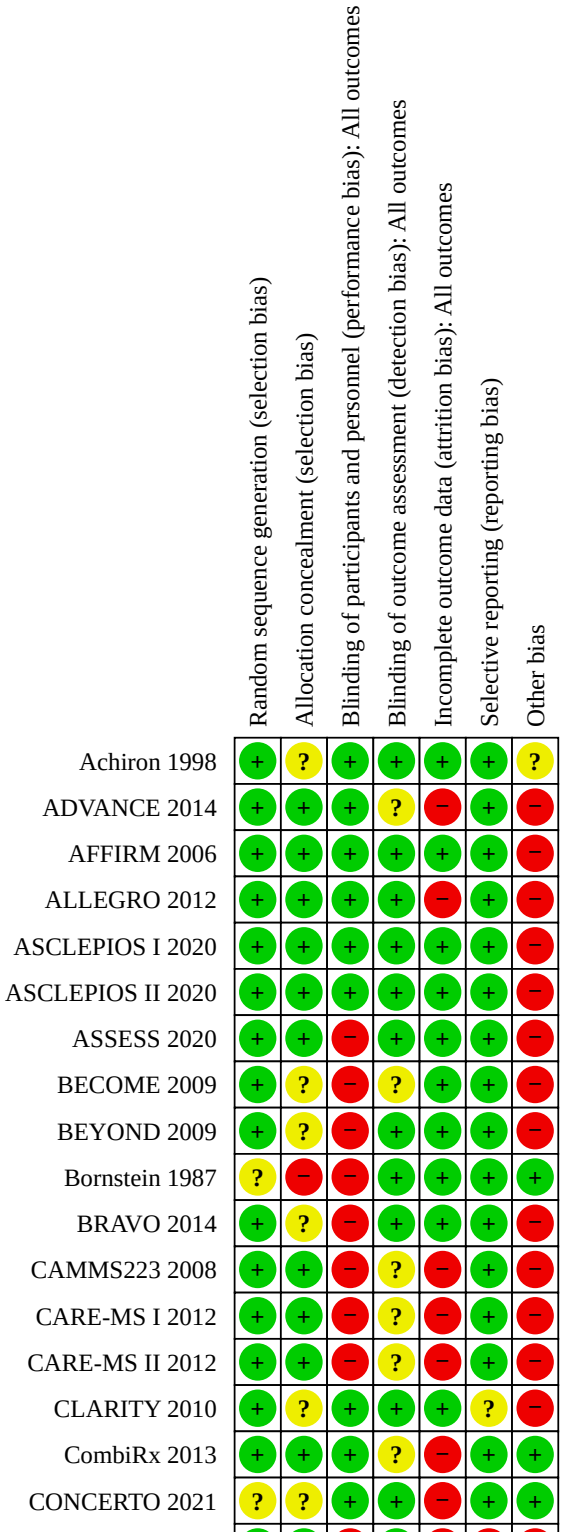


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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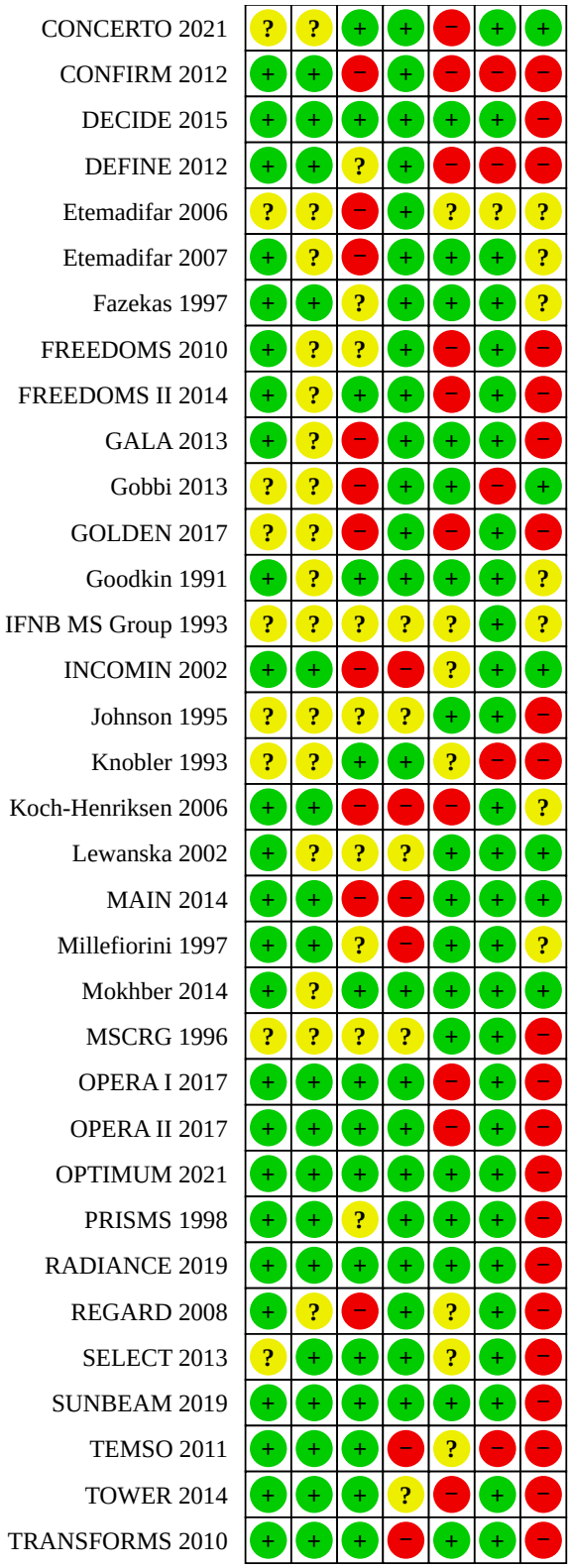


Allocation

Sequence generation

Ten studies (20%) did not provide enough information to assess sequence generation (unclear risk) (Bornstein 1987; CONCERTO 2021; Etemadifar 2006; Gobbi 2013; GOLDEN 2017; IFNB MS Group 1993; Johnson 1995; Knobler 1993; MSCRG 1996; SELECT 2013), and the remaining 40 (80%) reported adequate methods (low risk).

Allocation concealment

One trial (2%) used an unconcealed procedure (high risk) (Bornstein 1987). Twenty-one (42%) did not provide sufficient information to enable a risk of bias judgement (unclear risk) (Achiron 1998; BECOME 2009; BEYOND 2009; BRAVO 2014; CLARITY 2010; CONCERTO 2021; Etemadifar 2006; Etemadifar 2007; FREEDOMS 2010; FREEDOMS II 2014; GALA 2013; Gobbi 2013; GOLDEN 2017; Goodkin 1991; IFNB MS Group 1993; Johnson 1995; Knobler 1993; Lewanska 2002; Mokhber 2014; MSCRG 1996; REGARD 2008). The remaining 38 (76%) studies reported adequate methods of allocation concealment (low risk).

Blinding

Blinding of participants and personnel (performance bias)

Seventeen (34%) studies were not blinded (high risk)(ASSESS 2020; BECOME 2009; BEYOND 2009; Bornstein 1987; BRAVO 2014; CAMMS223 2008; CARE-MS I 2012; CARE-MS II 2012; CONFIRM 2012; Etemadifar 2006; Etemadifar 2007; Gobbi 2013; GOLDEN 2017; INCOMIN 2002; Koch-Henriksen 2006; MAIN 2014; REGARD 2008); nine (18%) studies did not provide sufficient information to enable assessment (unclear risk) (DEFINE 2012; Fazekas 1997; FREEDOMS 2010; IFNB MS Group 1993; Johnson 1995; Lewanska 2002; Millefiorini 1997; MSCRG 1996; PRISMS 1998); the remaining 24 (48%) studies reported that participants and investigators were blinded (low risk).

Blinding of outcome assessor (detection bias)

Six studies (12%) were at high risk (INCOMIN 2002; Koch-Henriksen 2006; MAIN 2014; Millefiorini 1997; TEMSO 2011; TRANSFORMS 2010), eleven studies (22%) did not provide sufficient information to enable assessment (unclear risk), and the remaining 33 studies (66%) were at low risk of detection bias (i.e. they reported that outcome assessors were blinded).

Incomplete outcome data

We judged 16 of 50 (32%) included studies as meeting the criteria for high risk of bias due to incomplete outcome data (balanced numbers across intervention groups with similar reasons for loss to follow-up) (ADVANCE 2014; ALLEGRO 2012; CAMMS223 2008; CARE-MS I 2012; CARE-MS II 2012; CombiRx 2013; CONCERTO 2021; CONFIRM 2012; DEFINE 2012; FREEDOMS 2010; FREEDOMS II 2014; GOLDEN 2017; Koch-Henriksen 2006; OPERA I 2017; OPERA II 2017; TOWER 2014) and seven (14%) (Etemadifar 2006; IFNB MS Group 1993; INCOMIN 2002; Knobler 1993; REGARD 2008; SELECT 2013; TEMSO 2011) did not provide sufficient information to assess risk of incomplete outcome data (unclear risk). The remaining 27 (54%) studies were judged to be low risk.

Selective reporting

Five studies (10%) were judged as being at high risk of bias for selective reporting because of non-reporting all prespecified primary benefit outcomes (CONFIRM 2012; DEFINE 2012; Gobbi 2013; Knobler 1993; TEMSO 2011). Two studies (4%) were judged as being at unclear risk of bias in this domain because of the lack of a protocol (Etemadifar 2006) or because primary and secondary outcomes were submitted to Clinical Trials.gov after study completion (CLARITY 2010). The remaining 43 (86%) reported all prespecified primary benefit outcomes and were judged as having low risk of bias.

Other potential sources of bias

We judged 34 studies (68%) as being at high risk of other bias; this includes the role of the sponsor in authorship of the study report or in data management or analysis (ADVANCE 2014; AFFIRM 2006; ALLEGRO 2012; ASCLEPIOS I 2020; ASCLEPIOS II 2020; ASSESS 2020; BECOME 2009; BEYOND 2009; BRAVO 2014; CAMMS223 2008; CARE-MS I 2012; CARE-MS II 2012; CLARITY 2010; CONFIRM 2012; DECIDE 2015; DEFINE 2012; FREEDOMS 2010; FREEDOMS II 2014; GALA 2013; GOLDEN 2017; Johnson 1995; Knobler 1993; MSCRG 1996; OPERA I 2017; OPERA II 2017; OPTIMUM 2021; PRISMS 1998; RADIANCE 2019; REGARD 2008; SELECT 2013; SUNBEAM 2019; TEMSO 2011; TOWER 2014; TRANSFORMS 2010); eight studies (16%) were judged as being at unclear risk of bias for this domain because the role of the study sponsor was unclear (Achiron 1998; Etemadifar 2006; Etemadifar 2007; Fazekas 1997; Goodkin 1991; IFNB MS Group 1993; Koch-Henriksen 2006; Millefiorini 1997). The remaining 8 (16%) were judged as being at low risk of bias.

Effects of interventions

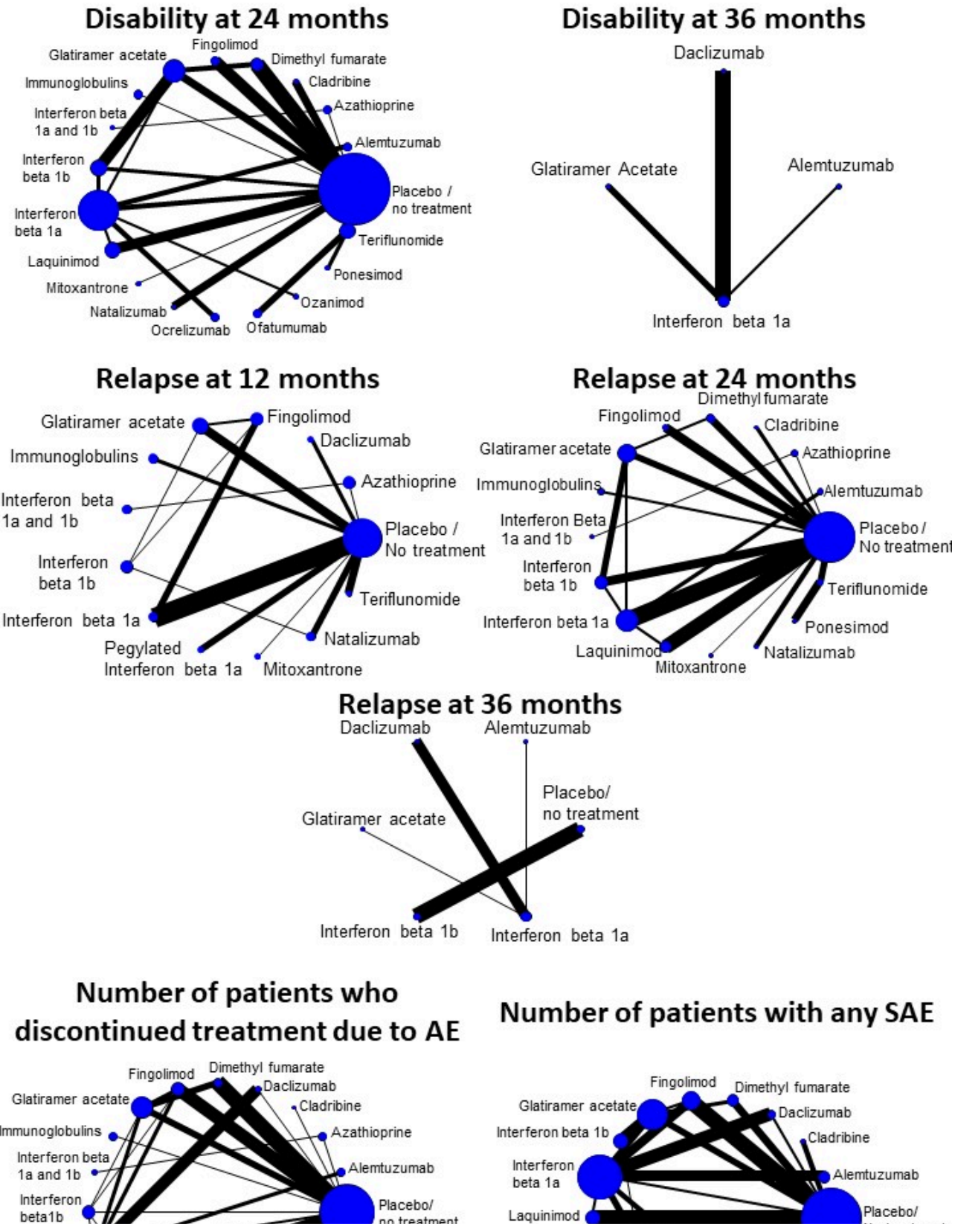
See: **Summary of findings 1** Relapses at 12 months; **Summary of findings 2** Relapses at 24 months; **Summary of findings 3** Relapses at 36 months; **Summary of findings 4** Disability at 24 months; **Summary of findings 5** Discontinuation due to adverse effects; **Summary of findings 6** Serious adverse events

Summary of findings 1, Summary of findings 2, Summary of findings 3, Summary of findings 4, Summary of findings 5, and Summary of findings 6 provide overall estimates of treatment effects compared with placebo and the certainty of the available evidence obtained through network meta-analyses for the four efficacy outcomes (chance of experiencing one or more relapses over 12 months, chance of experiencing one or more relapses over 24 months, chance of experiencing one or more relapses over 36 months, chance of disability getting worse over 24 months), and for the two safety outcomes (discontinuation due to adverse events and SAEs).

Figure 4, Figure 5, and Figure 6 show the network geometries for the efficacy and safety outcomes of immunomodulators and immunosuppressants included in the review (Primary outcomes; Secondary outcomes). Each line links the treatments that have been directly compared in studies. The thickness of the line is proportional to the number of participants included in the comparison and the width of each circle is proportional to the number of studies included in the comparison.

Figure 4. Network plots of treatment comparisons for primary efficacy and safety outcomes (Primary outcomes). The width of the lines is proportional to the precision of each pair of treatments, and the size of every circle is

proportional to the number of trials comparing every pair of treatments. AE, adverse effects; SAE, serious adverse events.



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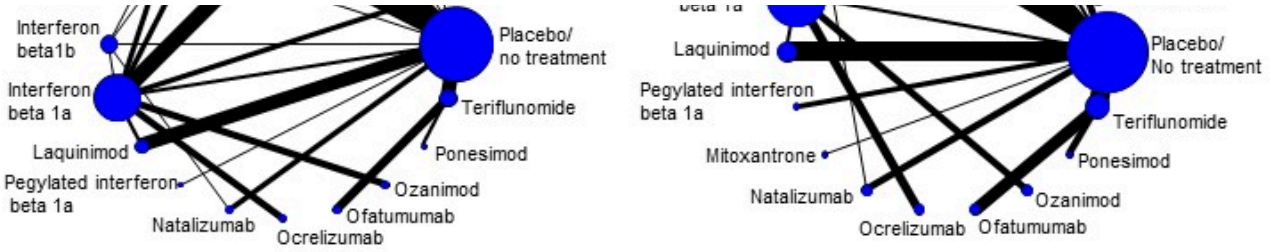
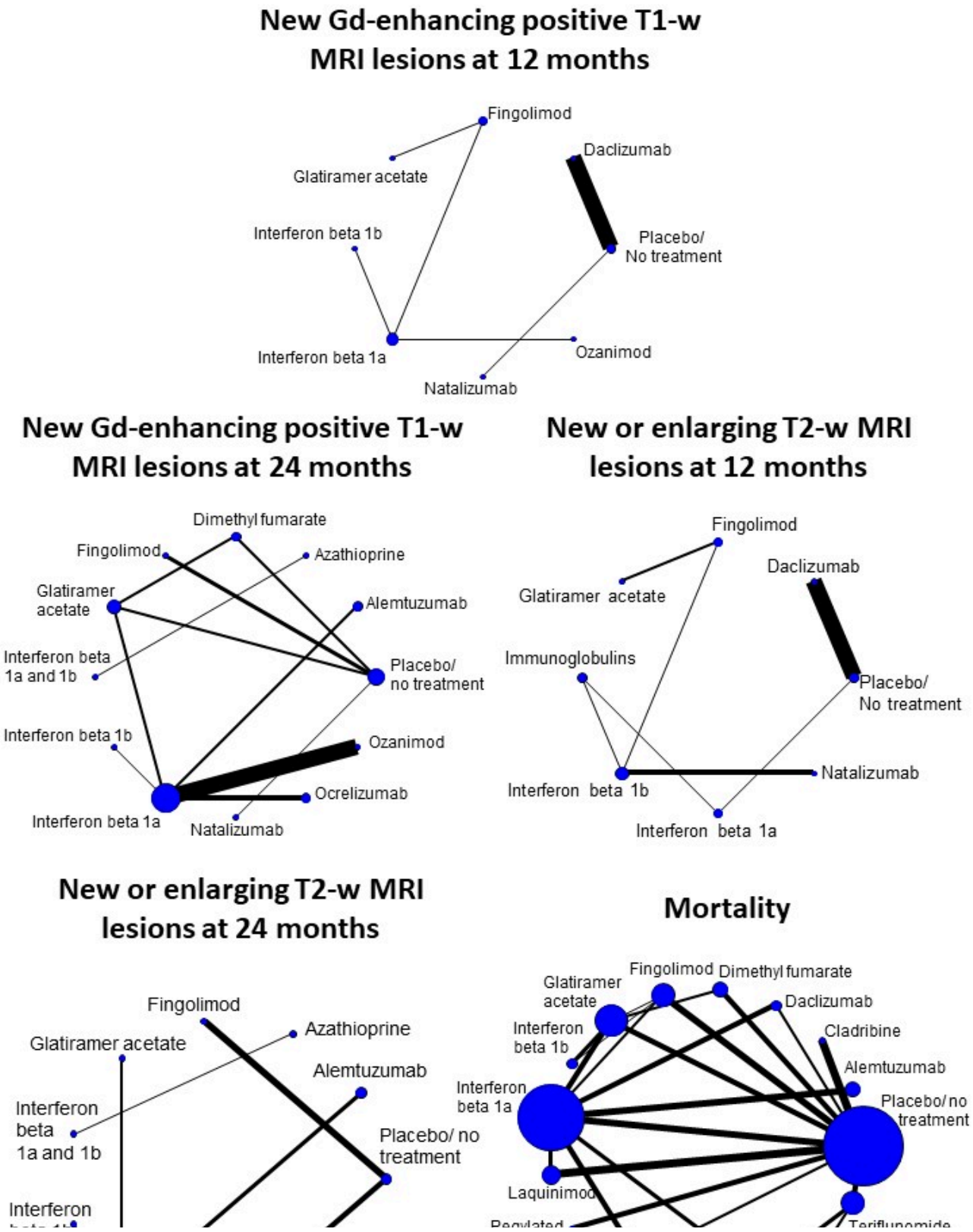


Figure 5. Network plots of treatment comparisons for secondary efficacy and safety outcomes (Secondary outcomes). The width of the lines is proportional to the precision of each pair of treatments, and the size of every

circle is proportional to the number of trials comparing every pair of treatments. Gd, gadolinium; MRI, magnetic resonance imaging; w, weighted.



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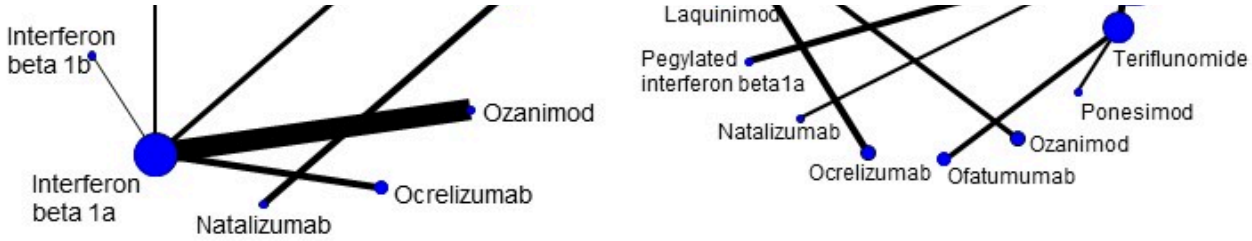
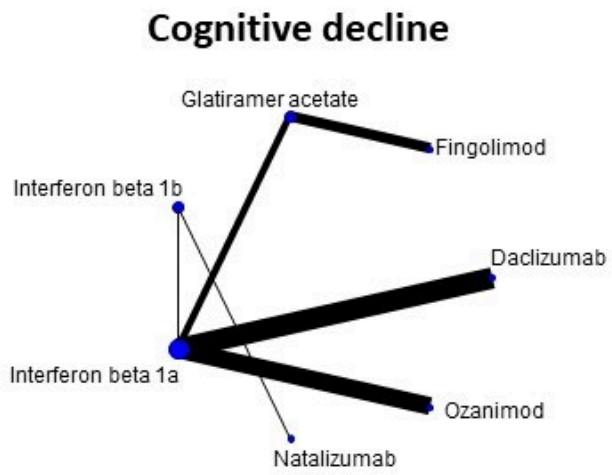
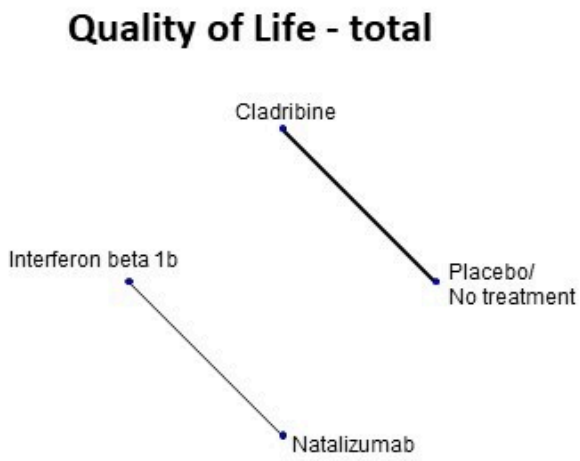
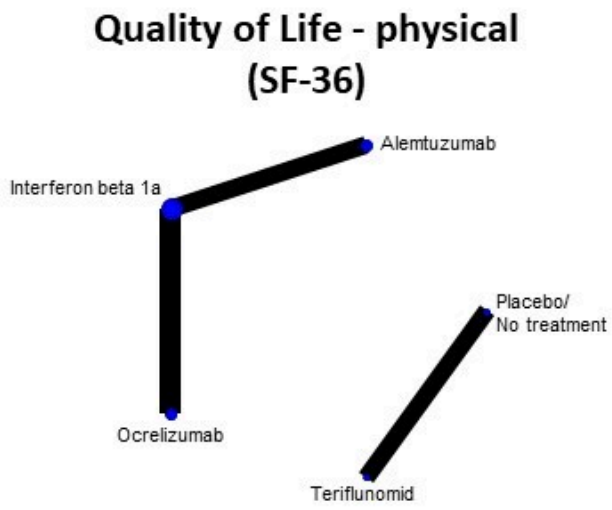


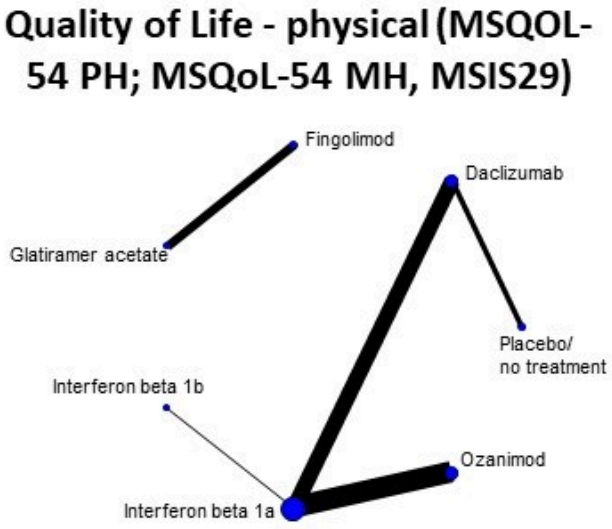
Figure 6. Network plots of treatment comparisons for cognitive decline and quality of life*. The width of the lines is proportional to the precision of each pair of treatments, and the size of every circle is proportional to the number of

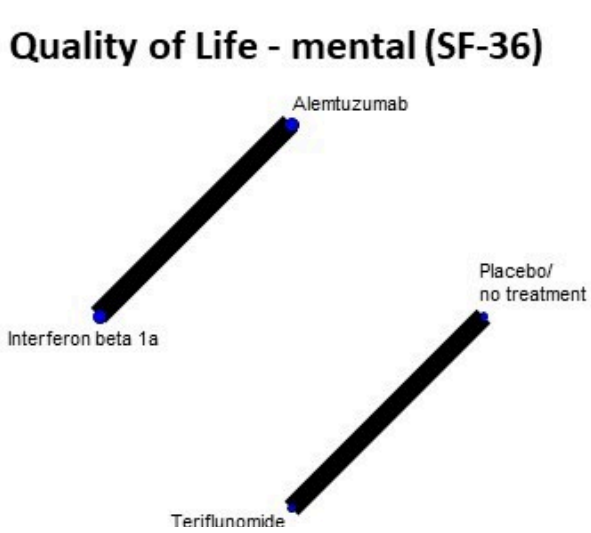
trials comparing every pair of treatments. * Please refer to Effects of interventions for further details on the quality-of-life scales used. Abbreviations: MH,; MSQOL,: PH,; SF-36,.











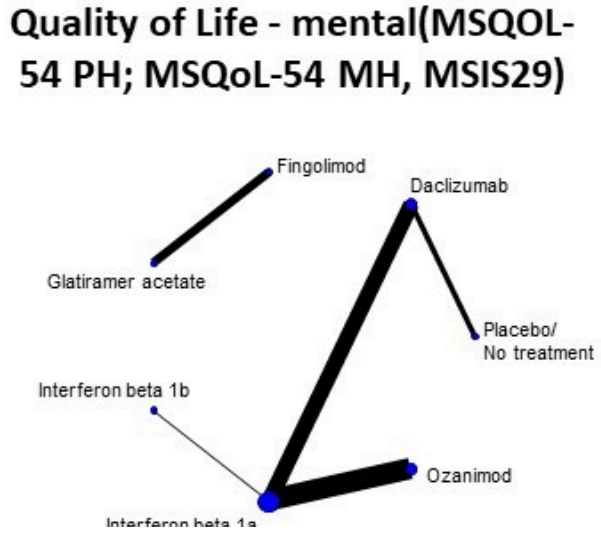


Figure 6. (Continued)

Figure 7 shows network estimates of primary efficacy and safety outcomes of each treatment against placebo within the networks.

Figure 7. Network meta-analysis (NMA) estimates of primary efficacy and safety outcomes in comparisons against placebo. AE, adverse effects; CI, confidence interval; RR, risk ratio; SAE, serious adverse events.

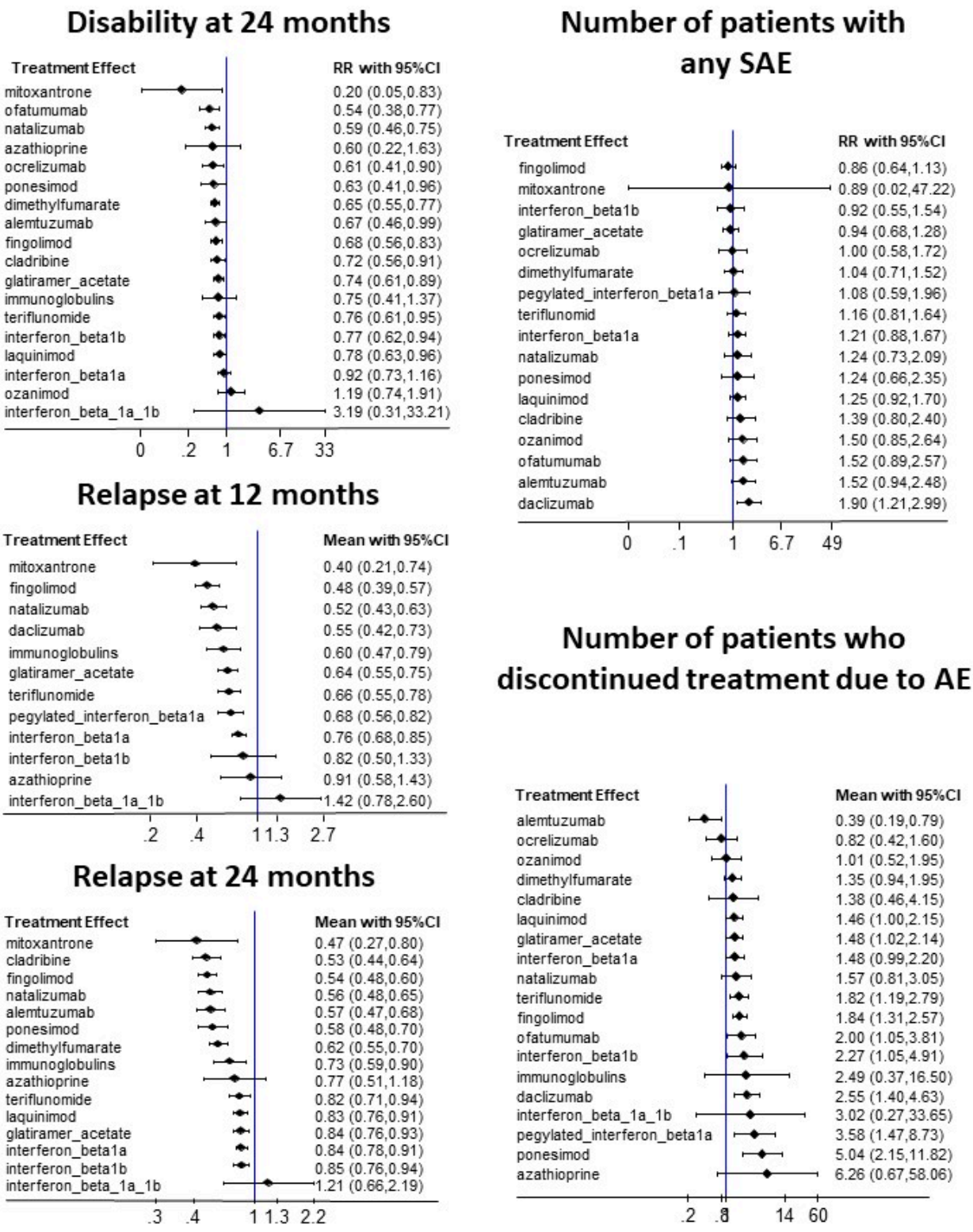


Figure 7. (Continued)

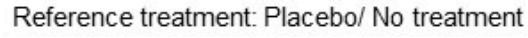


Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8 show network estimates of primary efficacy and safety outcomes of each treatment against placebo and against each other treatment included in the network.

Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10, Appendix 11, Appendix 12, and Appendix 13 show estimates of secondary efficacy and safety outcomes of each treatment against placebo and against each other treatment included in the network.

1. Primary outcomes

1.1 Efficacy

Relapses (over 12, 24 and 36 months) and disability worsening (over 24 and 36 months)

Pairwise meta-analysis (direct comparisons)

Treatment estimates from pairwise meta-analyses for each efficacy outcome are reported in Analysis 1.1, Analysis 1.2, Analysis 1.3, Analysis 1.4, and Analysis 1.5.

Network meta-analysis estimates (combination of direct and indirect comparisons) of treatment effects

See: Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4.

a) **Relapses over 12 months** were provided in 18 studies involving 9310 participants with RRMS (25.49% of the participants in this review) (Achiron 1998; ADVANCE 2014; AFFIRM 2006; ASSESS 2020; BECOME 2009; Bornstein 1987; Etemadifar 2007; GALA 2013; Gobbi 2013; GOLDEN 2017; Goodkin 1991; Lewanska 2002; MAIN 2014; Millefiorini 1997; PRISMS 1998; SELECT 2013; TOWER 2014; TRANSFORMS 2010) and assessing 13 treatments. The network geometry for relapses over 12 months is shown in Figure 4.

Nine treatments assessed in 18 studies were compared to placebo, of which seven treatments were evaluated in head-to-head comparisons in seven studies. Using placebo as a common comparator (see Figure 7), treatment with natalizumab results in a large reduction of people with relapses (RR 0.52, 95% CI 0.43 to 0.63; high-certainty evidence). Treatment with fingolimod (RR 0.48, 95% CI 0.39 to 0.57; moderate-certainty evidence), daclizumab (RR 0.55, 95% CI 0.42 to 0.73; moderate-certainty evidence) or immunoglobulins (RR 0.60, 95% CI 0.47 to 0.79; moderate-certainty evidence) probably results in a large reduction of people with relapses. Treatment with mitoxantrone (RR 0.40, 95% CI 0.21 to 0.74; low-certainty evidence), teriflunomide (RR 0.66, 95% CI 0.55 to 0.78; low-certainty evidence), pegylated interferon beta-1a (RR 0.68, 95% CI 0.56 to 0.82; low-certainty evidence) or glatiramer acetate (RR 0.64, 95% CI 0.55 to 0.75; low-certainty evidence) may result in a large reduction of people with relapses. Treatment with interferon beta-1a (Avonex, Rebif) (RR 0.76, 95% CI 0.68 to 0.85; low-certainty evidence) may moderately reduce the number of people with relapses. Treatment with interferon beta-1b (RR 0.82, 95% CI 0.50 to 1.33; very low-certainty evidence) may moderately reduce the number of people with relapses, but the evidence is very uncertain. When interferon beta 1-a and beta 1-b (RR 1.42, 95% CI 0.78 to 2.60; very low-certainty evidence) were both used in the same intervention, there may have been a large increase in the number of people with relapses, but the evidence is very uncertain. Differences across treatments were found and are shown in Table 2.

b) **Relapses over 24 months** were provided in 28 studies involving 19,869 participants with RRMS (54.37% of those included in this review) (Achiron 1998; AFFIRM 2006; ALLEGRO 2012; BECOME 2009; BEYOND 2009; Bornstein 1987; BRAVO 2014; CAMMS223 2008; CARE-MS I 2012; CARE-MS II 2012; CLARITY 2010; CONCERTO 2021; CONFIRM 2012; DEFINE 2012; Etemadifar 2006; Fazekas 1997; FREEDOMS 2010; FREEDOMS II 2014; Goodkin 1991; IFNB MS Group 1993; INCOMIN 2002; Johnson 1995; Koch-Henriksen 2006; MAIN 2014; Millefiorini 1997; MSCRG 1996; OPTIMUM 2021; PRISMS 1998; REGARD 2008; TEMSO 2011) and assessing 15 treatments. The network geometry for relapses over 24 months is shown in Figure 4.

Twelve treatments, assessed in 21 studies, were compared to placebo, ten treatments were evaluated in head-to-head comparisons in 11 studies and two studies involving 2751 participants had both placebo and active treatment arms. Using placebo as a common comparator, treatment with cladribine (RR 0.53, 95% CI 0.44 to 0.64; high-certainty evidence), alemtuzumab (RR 0.57, 95% CI 0.47 to 0.68; high-certainty evidence) and natalizumab (RR 0.56, 95% CI 0.48 to 0.65; high-certainty evidence) resulted in a large decrease in people with relapses. Treatment with fingolimod (RR 0.54, 95% CI 0.48 to 0.60; moderate-certainty evidence), dimethyl fumarate (RR 0.62, 95% CI 0.55 to 0.70; moderate-certainty evidence), and ponesimod (RR 0.58, 95% CI 0.48 to 0.70; moderate-certainty evidence) probably results in a large decrease of people with relapses. Treatment with glatiramer acetate (RR 0.84, 95%, CI 0.76 to 0.93; moderate-certainty evidence) and interferon beta-1a (Avonex, Rebif) (RR 0.84, 95% CI 0.78 to 0.91; moderate-certainty evidence) probably moderately decreases people with relapses. Treatment with mitoxantrone (RR 0.47, 95% CI 0.27 to 0.80; low-certainty evidence) may result in a large decrease in people with relapses. Treatment with immunoglobulins (RR 0.73, 95% CI 0.59 to 0.90; low-certainty evidence) may result in a large reduction of people with relapses. Treatment with interferon beta-1b (Betaferon) (RR 0.85, 95% CI 0.76 to 0.94; low-certainty evidence) and laquinimod (RR 0.83, 95% CI 0.76 to 0.91; low-certainty evidence) may moderately decrease the number of

people with relapses. Treatment with teriflunomide (RR 0.82, 95% CI 0.71 to 0.94; very low-certainty evidence) and azathioprine (RR 0.77, 95% CI 0.51 to 1.18; very low-certainty evidence) may moderately decrease people with relapses but the evidence is very uncertain. When interferon beta 1-a and beta 1-b (RR 1.21, 95% CI 0.66 to 2.19; very low-certainty evidence) were both used in the same intervention arm, there may have been a moderate increase in the number of people with relapses, but the evidence is very uncertain. Differences across treatments were found and are shown in Table 3.

c) **Relapses over 36 months** were provided in five studies involving 3087 participants with RRMS (8.44% of the participants in this review) (CAMMS223 2008; CombiRx 2013; DECIDE 2015; IFNB MS Group 1993; Knobler 1993) and assessing five treatments. The network geometry for relapses over 36 months is shown in Figure 4.

Only one treatment, assessed in two studies, was compared to placebo. Three treatments were evaluated in head-to-head comparisons in three studies. Treatment with interferon beta-1b (Betaferon) (RR 0.86, 95% CI 0.67 to 1.11; very low-certainty evidence) may moderately decrease people with relapses, but the evidence is very uncertain. Differences across treatments were found and are shown in Table 4.

d) **Disability worsening over 24 months** was available from 31 studies and 24,303 participants with RRMS (66.51% of those included in this review) (Achiron 1998; AFFIRM 2006; ALLEGRO 2012; ASCLEPIOS I 2020; ASCLEPIOS II 2020; BECOME 2009; BEYOND 2009; Bornstein 1987; BRAVO 2014; CARE-MS I 2012; CARE-MS II 2012; CLARITY 2010; CONCERTO 2021; CONFIRM 2012; DEFINE 2012; Fazekas 1997; FREEDOMS 2010; FREEDOMS II 2014; Goodkin 1991; IFNB MS Group 1993; INCOMIN 2002; Johnson 1995; Koch-Henriksen 2006; MAIN 2014; Millefiorini 1997; MSCRG 1996; OPERA I 2017; OPERA II 2017; OPTIMUM 2021; RADIANCE 2019; REGARD 2008; TEMSO 2011) and assessing 18 treatments. The network geometry for disability worsening over 24 months is shown in Figure 4.

Eleven treatments, assessed in 20 studies, were compared to placebo (see Figure 7), thirteen treatments were evaluated in head-to-head comparisons in 15 studies and two studies involving 2751 participants had both placebo and active treatment arms. Using placebo as a common comparator, treatment with natalizumab (RR 0.59, 95% CI 0.46 to 0.75; moderate-certainty evidence) probably results in a moderate reduction of people with disability worsening. Treatment with dimethylfumarate (RR 0.65, 95% CI 0.55 to 0.77; low-certainty evidence), alemtuzumab (RR 0.67, 95% CI 0.46 to 0.99; low-certainty evidence), and fingolimod (RR 0.68, 95% CI 0.56 to 0.83; low-certainty evidence) may moderately reduce people with disability worsening. Treatment with cladribine (RR 0.72, 95% CI 0.56 to 0.91; low-certainty evidence) and interferon beta-1b (Betaferon) (RR 0.77 95% CI 0.62 to 0.94; low-certainty evidence) may result in a small reduction of people with disability worsening. Treatment with mitoxantrone (RR 0.20, 95% CI 0.05 to 0.83; very low-certainty evidence) may result in a large reduction of people who experience disability worsening, but the evidence is very uncertain. The evidence is very uncertain about the following effects on numbers of people experiencing disability worsening: moderate reductions with ofatumumab (RR 0.54, 95% CI 0.38 to 0.77; very low-certainty evidence), ocrelizumab (RR 0.61, 95% CI 0.41 to 0.90; very low-certainty evidence), azathioprine (RR 0.60, 95% CI 0.22 to 1.63; very low-certainty evidence) and ponesimod (RR 0.63, 95% CI 0.41 to 0.96; very low-certainty evidence). The evidence is very uncertain about the following effects on numbers of people experiencing disability worsening: small reductions with glatiramer acetate (RR 0.74, 95% CI 0.61 to 0.89; very low-certainty evidence), teriflunomide (RR 0.76, 95% CI 0.61 to 0.95; very low-certainty evidence) and laquinimod (RR 0.78, 95% CI 0.63 to 0.96; very low-certainty evidence). Treatment with interferon beta-1a (RR 0.92, 95% CI 0.73 to 1.16; low-certainty evidence) may result in a trivial reduction in the number people who experience disability worsening. Treatment with immunoglobulins (RR 0.75, 95% CI 0.41 to 1.37; very low-certainty evidence) may result in a small reduction in the number of people with disability worsening, but the evidence is very uncertain. When interferon beta 1-a and beta 1-b (RR 3.19, 95% CI 0.31 to 33.21; very low-certainty evidence) were both used in the same intervention arm, there may have been a large increase in the number of people with disability progression, but the evidence is very uncertain. Treatment with ozanimod (RR 1.19, 95% CI 0.74 to 1.91; very low-certainty evidence) may result in a trivial increase in the number of people with disability progression, but the evidence is very uncertain. Differences across treatments were found and are shown in Table 5.

e) **Disability worsening over 36 months** was available from three studies and 2684 participants with RRMS (7.35% of those included in this review)(CAMMS223 2008; CombiRx 2013; DECIDE 2015) and assessing four treatments. No studies were compared to placebo. Differences across treatments were found and are shown in Table 6. The network geometry for disability worsening over 36 months is shown in Figure 4.

1.2 Safety

Treatment discontinuation due to adverse events and serious adverse events (SAEs)

Pairwise meta-analysis (direct comparisons)

Treatment estimates for pairwise meta-analyses are reported in Analysis 2.1; Analysis 2.2.

Network meta-analysis estimates (combination of direct and indirect comparisons) of treatment effects

See: Summary of findings 5; Summary of findings 6.

a) **Treatment discontinuation due to adverse events** was available from 43 studies and 35,410 participants with RRMS (96.9% of those included in this review) (Achiron 1998; ADVANCE 2014; AFFIRM 2006; ALLEGRO 2012;ASCLEPIOS I 2020; ASCLEPIOS II 2020; ASSESS 2020; BEYOND 2009; Bornstein 1987; BRAVO 2014; CAMMS223 2008; CARE-MS I 2012; CARE-MS II 2012; CLARITY 2010; CombiRx 2013; CONCERTO 2021; CONFIRM 2012; DEFINE 2012; DECIDE 2015; Etemadifar 2007; Fazekas 1997; FREEDOMS 2010; FREEDOMS II 2014; GALA 2013; Gobbi 2013; GOLDEN 2017; Goodkin 1991; IFNB MS Group 1993; INCOMIN 2002; Johnson 1995; Lewanska 2002; MAIN 2014; OPERA II 2017; OPERA II 2017; OPTIMUM 2021; PRISMS 1998; RADIANCE 2019; REGARD 2008; SELECT 2013; SUNBEAM 2019; TEMSO 2011; TOWER 2014; TRANSFORMS 2010) and assessing 19 treatments. The network geometry for treatment discontinuation due to adverse events is shown in Figure 4.

Thirteen treatments, assessed in 24 studies, were compared to placebo, 16 treatments were evaluated in head-to-head comparisons in 21 studies and two studies involving 2751 participants had both placebo and active treatment arms. Using

placebo as a common comparator, treatment with alemtuzumab probably results in a trivial reduction of people who discontinued due to adverse events (OR 0.39, 95% CI 0.19 to 0.79; moderate-certainty evidence). Treatment with ocrelizumab may result in a trivial reduction in people who discontinue due to adverse events (OR 0.82, 95% CI 0.42 to 1.60; low-certainty evidence). Treatment with daclizumab (OR 2.55, 95% CI 1.40 to 4.63; moderate-certainty evidence), fingolimod (OR 1.84, 95% CI 1.31 to 2.57; moderate-certainty evidence), teriflunomide (OR 1.82, 95% CI 1.19 to 2.79; moderate-certainty evidence), interferon beta-1a (OR 1.48, 95% CI 0.99 to 2.20; moderate-certainty evidence), laquinimod (OR 1.49, 95 % CI 1.00 to 2.15; moderate-certainty evidence), natalizumab (OR 1.57, 95% CI 0.81 to 3.05), and glatiramer acetate (OR 1.48, 95% CI 1.02 to 2.14; moderate-certainty evidence) probably result in a trivial increase in people who discontinued due to adverse events. Treatment with interferon beta-1b (Betaferon) (OR 2.27, 95% CI 1.05 to 4.91; low-certainty evidence), ofatumumab (OR 2.00, 95% CI 1.05 to 23.81; low-certainty evidence), cladribine (OR 1.38, 95% CI 0.46 to 4.15; low-certainty evidence) and dimethyl fumerate (OR 1.35, 95% CI 0.94 to 1.95; low-certainty evidence) may result in a trivial increase in people who discontinued due to adverse events. Treatment with ozanimod (OR 1.01, 95% CI 0.52 to 1.95; low-certainty evidence) may have little to no effect on people who discontinued due to adverse effects. Treatment with pegylated interferon beta-1a (OR 3.58, 95% CI 1.47 to 8.73; very low-certainty evidence), azathioprine (OR 6.26, 95% CI 0.67 to 58.05) and ponesimod (OR 5.04, 95% CI 2.15 to 11.82; very low-certainty evidence) may result in a small increase in people who discontinued due to adverse events, but the evidence is very uncertain (see Figure 7). Treatment with immunoglobulins (OR 2.49, 95% CI 0.37 to 16.50; very low-certainty evidence) and interferon beta 1a-1b (OR 3.02, 95% Ci 0.27 to 33.65; very low-certainty evidence) may result in a trivial increase in people who discontinued due to adverse effects, but the evidence is very uncertain. Differences across treatments were found and are shown in Table 7.

b) **SAEs** were available from 35 studies and 33,998 participants with RRMS (93% of those included in this review) (ADVANCE 2014; AFFIRM 2006; ALLEGRO 2012; ASCLEPIOS I 2020; ASCLEPIOS II 2020; ASSESS 2020; BEYOND 2009; BECOME 2009; BRAVO 2014; CAMMS223 2008; CARE-MS I 2012 ; CARE-MS II 2012; CLARITY 2010; CombiRx 2013; CONCERTO 2021; CONFIRM 2012; DEFINE 2012; DECIDE 2015; FREEDOMS 2010; FREEDOMS II 2014; GALA 2013; Gobbi 2013;GOLDEN 2017; Johnson 1995; Millefiorini 1997; OPERA I 2017; OPERA II 2017; OPTIMUM 2021; RADIANCE 2019; REGARD 2008; SELECT 2013; SUNBEAM 2019; TEMSO 2011; TOWER 2014; TRANSFORMS 2010) and assessing 17 treatments. The network geometry for SAEs is shown in Figure 4.

Eleven treatments, assessed in 18 studies, were compared to placebo, 14 treatments were evaluated in head-to-head comparisons in 21 studies, and two studies involving 2751 participants had both placebo and active treatment arms. Compared to placebo (see Figure 7), treatment with interferon beta-1b (OR 0.92, 95% CI 0.55 to 1.54; moderate-certainty evidence) probably results in a trivial reduction in people who experience SAEs. Treatment with fingolimod (OR 0.86, 95% CI 0.64 to 1.13; low-certainty evidence) and glatiramer acetate (OR 0.94, 95% CI 0.68 to 1.28; low-certainty evidence) may result in a trivial reduction in people who experience SAEs. Treatment with mitoxantrone (OR 0.89, 95% CI 0.02 to 47.22; very low-certainty evidence) may result in a trivial reduction in people who experience SAEs, but the evidence is very uncertain. Treatment with daclizumab may result in a small increase in people with SAEs (OR 1.90, 95% CI 1.21 to 2.99; low-certainty evidence). Treatment with dimethyl fumerate (OR 1.04, 95% CI 0.71 to 1.52; low-certainty evidence) and natalizumab (OR 1.24, 95% CI 0.73 to 2.09; low-certainty evidence) may result in a trivial increase in people who experience SAEs. Treatment with ocrelizumab (OR 1.00, 95% CIs 0.58 to 1.72; very low-certainty evidence) may result in little or no effect on people who experince SAEs, but the evidence is very uncertain. Treatment with the remaining DMTS may result in a trivial increase in the people experiencing SAEs, but the evidence is very uncertain: alemtuzumab (OR 1.52, 95% CI 0.94 to 2.48; very low-certainty evidence), cladribine (OR 1.39, 95% CI 0.80 to 2.40; very low-certainty evidence), interferon beta-1a (OR 1.21, 95% CI 0.88 to 1.67; very low-certainty evidence), laquinimod (OR 1.25, 95% CI 0.92 to 1.70; very low-certainty evidence), pegylated beta-1a (OR 1.08, 95% CI 0.59 to 1.96; very low-certainty evidence), ofatumumab (OR 1.52, 95% CI 0.89 to 2.57; very low-certainty evidence), ozanimod (OR 1.50, 95% CI 0.85 to 2.64; very low-certainty evidence), ponesimod (OR 1.24, 95% CI 0.66 to 2.35; very low-certainty evidence) and teriflunomide (OR 1.16, 95% CI 0.81 to 1.64); very low-certainty evidence). Differences across treatments were found and are shown in Table 8.

2. Secondary outcomes

2.1 Efficacy

Cognitive decline, quality-of-life impairment, new or enlarging T2-weighted MRI lesions, new gadolinium-enhancing positive T1-weighted MRI lesions (at 12, 24, and 36 months)

Pairwise meta-analysis (direct comparisons)

Treatment estimates for pairwise meta-analyses for each outcome are reported in Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.6; Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 3.10.

Network meta-analysis estimates (combination of direct and indirect comparisons) of treatment effects

The network geometry for each outcome is presented in Figure 5 and Figure 6, and Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; and Appendix 12 show the network estimates for each treatment against placebo or against another treatment within the network of each outcome.

a) **New gadolinium-enhancing positive T1-weighted MRI lesions at 12 months** were reported in six studies involving 5212 participants with RRMS (14.3% of those included in this review) (AFFIRM 2006; ASSESS 2020; INCOMIN 2002; SELECT 2013; SUNBEAM 2019; TRANSFORMS 2010) and assessing seven treatments. Two treatments assessed in two studies were compared to placebo. Using placebo as a common comparator, treatment with natalizumab results in a large reduction of new gadolinium-enhancing positive T1-weighted MRI lesions (RR 0.11, 95% CI 0.07 to 0.17). A trivial increase in new gadolinium-enhancing positive T1-weighted MRI lesions probably resulted in people treated with daclizumab (RR 1.00, 95% CI 0.97 to 1.04). Differences across treatments were found and are shown in Appendix 6.

b) Data on **new gadolinium-enhancing positive T1-weighted MRI lesions at 24 months** was available from 11 studies involving 7935 participants with RRMS (21% of those included in this

review) (AFFIRM 2006; CARE-MS I 2012; CARE-MS II 2012; CONFIRM 2012; FREEDOMS 2010; INCOMIN 2002; MAIN 2014; OPERA I 2017; OPERA II 2017; RADIANCE 2019; REGARD 2008) and assessing eleven treatments. Four treatments assessed in three studies were compared to placebo, seven treatments were evaluated in head-to-head comparisons in nine studies and one study involving 1417 participants had both placebo and active treatment arms.

Using placebo as a common comparator, natalizumab (RR 0.11, 95% CI 0.07 to 0.17) resulted in a large reduction in new gadolinium-enhancing positive T1-weighted MRI lesions. Treatment with ocrelizumab (RR 0.09, 95% CI 0.05 to 0.16) and alemtuzumab (RR 0.13, 95% CI 0.08 to 0.23) probably resulted in a large reduction in new gadolinium-enhancing positive T1-weighted MRI lesions. Treatment with interferon beta-1b (Betaferon) (RR 0.16, 95% CI 0.08 to 0.31) may have resulted in a large reduction in new gadolinium-enhancing positive T1-weighted MRI lesions. Treatment with interferon beta-1a (Avonex, Rebif) (RR 0.34, 95% CI 0.21 to 0.55), fingolimod (RR 0.29, 95% CI 0.23 to 0.38), dimethyl fumarate (RR 0.50, 95% CI 0.37 to 0.69), ozanimod (RR 0.30, 95% CI 0.18 to 0.49), and glatiramer acetate (RR 0.59, 95% CI 0.42 to 0.84) may have resulted in a moderate reduction in new gadolinium-enhancing positive T1-weighted MRI lesions. Differences across treatments were found and are shown in Appendix 7.

c) No studies assessed new gadolinium-enhancing positive T1-weighted MRI lesions at 36 months.

d) **New or enlarging T2-weighted MRI lesions at 12 months** was reported in seven studies involving 5234 participants with RRMS (14.32% of those included in this review) (AFFIRM 2006; ASSESS 2020; Gobbi 2013; INCOMIN 2002; SELECT 2013; SUNBEAM 2019; TRANSFORMS 2010) and assessing seven treatments. Two treatments, assessed in two studies, were compared to placebo, and six treatments were evaluated in head-to-head comparisons in five studies. Using placebo as a common comparator, treatment with interferon beta-1a (Avonex, Rebif) resulted in a large reduction of new or enlarging T2-weighted MRI lesions (RR 0.51, 95% CI 0.45 to 0.57). Treatment with immunoglobulins may have resulted in a trivial reduction in new or enlarging T2-weighted MRI lesions (RR 0.98, 95% CI 0.30 to 3.28). There was probably little or no effect on new or enlarging T2-weighted MRI lesions with daclizumab (RR 1.00, 95% CI 0.97 to 1.04). A large increase in new or enlarging T2-weighted MRI lesions may have resulted in people treated with glatiramer acetate (RR 2.37, 95% CI 0.50 to 11.30), interferon beta-1b (RR 2.12, 95% CI 0.45 to 9.97), natalizumab (RR 2.01, 95% CI 0.43 to 9.51) and fingolimod (RR 1.89, 95% CI 0.40 to 8.99). Differences across treatments were found and are shown in Appendix 8.

e) **New or enlarging T2-weighted MRI lesions at 24 months** were reported in ten studies involving 6893 participants with RRMS (19% of those included in this review) (AFFIRM 2006; CARE-MS I 2012; CARE-MS II 2012; FREEDOMS 2010; INCOMIN 2002; MAIN 2014; OPERA I 2017; OPERA II 2017; RADIANCE 2019; REGARD 2008) and assessing ten treatments. Two treatments, assessed in two studies, were compared to placebo. Using placebo as a common comparator, treatment with natalizumab (RR 0.50, 95% CI 0.45 to 0.55) resulted in a large reduction of new or enlarging T2-weighted MRI lesions. Treatment with fingolimod (RR 0.62, 95% CI 0.56 to 0.68) may have resulted in a large reduction of new or enlarging T2-weighted MRI lesions. Differences across treatments were found and are shown in Appendix 9.

f) No studies assessed new or enlarging T2-weighted MRI at 36 months.

g) **Cognitive decline** was available from six studies involving 4243 participants with RRMS (11.6% of those included in this review) (ASSESS 2020; CombiRx 2013; DECIDE 2015; Gobbi 2013; Mokhber 2014; SUNBEAM 2019) and assessing seven treatments. No studies were compared to placebo, and six treatments were evaluated in head-to-head comparisons in seven studies. Differences across treatments were found and are shown in Appendix 10.

h) Data on**quality-of-life impairment** were reported in studies with different scales (non-MS related quality of health questionnaires and MS related questionnaires) and subscales (physical and mental).

Quality-of-life impairment (non-MS related; total) was available from two studies involving 1061 participants with RRMS (3% of those included in this review) and assessing three treatments (CLARITY 2010; Gobbi 2013). One study was compared to placebo. Compared to placebo, cladribine (SMD 0.19 SD, 95% CI 0.06 to 0.32) probably resulted in a trivial improvement in quality of life.

Quality of life impairment (non-MS related; index) was available from one study involving 1042 participants with RRMS (3% of those included in this review) and assessing one treatment (CLARITY 2010). Compared to placebo, cladribine probably resulted in a trivial improvement in quality of life (SMD 0.24 SD, 95% CI 0.11 to 0.37).

Quality-of-life impairment (non-MS related; physical subscale) was available from five studies involving 4073 participants with RRMS (11% of those included in this review) and assessing four treatments (CARE-MS I 2012; CARE-MS II 2012; OPERA I 2017; OPERA II 2017; TOWER 2014). Compared to placebo, teriflunomide may have resulted in a trivial improvement in quality of life (non-MS related; physical subscale) (SMD 0.1 SD, 95% CI -0.02 to 0.22).

Quality of life impairment (MS related; physical) was available from six studies involving 6261 participants with RRMS (17% of those included in this review) (ASSESS 2020; DECIDE 2015; Mokhber 2014; RADIANCE 2019; SELECT 2013; SUNBEAM 2019) and assessing six treatments. One treatment, assessed in one study, was compared to placebo, and six treatments were evaluated in head-to-head comparisons in five studies. Using placebo as a common comparator, treatment with daclizumab (SMD 0.22 SD, 95% CI 0.05 to 0.38) probably resulted in a trivial improvement in quality of life on this scale. Ozanimod (SMD 0.5 SD, 95% CI 0.29 to 0.71), interferon beta-1a (Avonex, Rebif) (SMD 0.36 SD, 95% CI 0.16 to 0.55) and interferon beta-1b (SMD 0.41 SD, 95% CI -0.13 to 0.95) may have resulted in a trivial improvement in quality of life on this scale. Differences across treatments were found and are shown in Appendix 11.

Quality of life impairment (non-MS related; mental subscale) was available from three studies involving 2417 participants with RRMS (6.61% of those included in this review) (CARE-MS I 2012; CARE-MS II 2012; TOWER 2014) and assessing three treatments. One treatment, assessed in one study, was compared to placebo, and two treatments were evaluated in head-to-head comparisons in two studies. Compared to placebo, teriflunomide may have resulted in a trivial improvement in quality of life (non-MS related; mental subscale) (SMD 0.1 SD, 95% CI -0.02 to 0.22).

Quality-of-life impairment (MS related; mental) was available from six studies involving 6261 participants with RRMS (17% of those included in this review) (ASSESS 2020; DECIDE 2015; Mokhber 2014; RADIANCE 2019; SELECT 2013; SUNBEAM 2019) and assessing six treatments. One treatment, assessed in one study, was compared to placebo, and six treatments were evaluated in head-to-head comparisons in five studies. Using placebo as a common comparator, interferon beta-1b (SMD 0.30 SD, 95% CI -0.24 to 0.84) may have resulted in a small improvement in quality of life (MS related; mental subscale). Treatment with daclizumab (SMD 0.12 SD, 95% CI -0.05 to 0.28), iozanimod (SMD 0.05 SD, 95% CI -0.15 to 0.26) and interferon beta-1a(SMD 0.03 SD, 95% CI -0.17 to 0.22) may have resulted in a trivial improvement in quality of life (MS related; mental subscale). Differences across treatments were found and are shown in Appendix 12.

2.2 Safety

MS-related mortality

Pairwise meta-analysis (direct comparisons)

Treatment estimates for pairwise meta-analyses are reported in Analysis 3.11.

Network meta-analysis estimates (combination of direct and indirect comparisons) of treatment effects

The network geometry is presented in Figure 5, and Appendix 13 shows the network estimates of each treatment against placebo or against another treatment within the network.

Data on mortality were available from 33 studies involving 34,500 participants with RRMS (94% of those included in this review) (ADVANCE 2014; AFFIRM 2006; ALLEGRO 2012; ASCLEPIOS I 2020; ASCLEPIOS II 2020; ASSESS 2020; BEYOND 2009; BRAVO 2014; CAMMS223 2008; CARE-MS I 2012; CARE-MS II 2012; CLARITY 2010; CombiRx 2013; CONCERTO 2021; CONFIRM 2012; DEFINE 2012; DECIDE 2015; FREEDOMS 2010; FREEDOMS II 2014; GALA 2013; GOLDEN 2017; MSCRG 1996; PRISMS 1998; OPERA I 2017; OPERA II 2017; OPTIMUM 2021; RADIANCE 2019; REGARD 2008; SELECT 2013; SUNBEAM 2019; TOWER 2014; TEMSO 2011; TRANSFORMS 2010) and assessing 16 treatments.

Ten treatments assessed in 15 studies were compared to placebo, thirteen treatments were evaluated in head-to-head comparisons in 15 studies and two studies involving 2751 participants had both a placebo and active treatment arms. Using placebo as a common comparator, a trivial reduction in the number of deaths probably occurred in people treated with daclizumab (OR 0.32, 95% CI 0.04 to 2.37) and laquinimod (OR 0.51, 95% CI 0.12 to 2.18). A trivial reduction in the number of deaths may have occurred in people treated with ponesimod (OR 0.30, 95% CI 0.01 to 13.20), interferon beta-1b (OR 0.37, 95% CI 0.02 to 5.81), fingolimod (OR 0.38, 95% CI 0.07 to 1.98), ocrelizumab (OR 0.39, 95% CI 0.03 to 4.50), ofatumumab (OR 0.49, 95% CI 0.01 to 24.84), glatiramer acetate (OR 0.49, 95% CI 0.10 to 2.38), pegylated interferon (OR 0.49, 95% CI 0.07 to 3.51), interferon beta-1a (OR 0.63, 95% CI 0.18 to 2.17), and dimethyl fumerate (OR 0.75, 95% CI 0.11 to 5.24). A trivial increase in the number of deaths probably occurred in the people treated with cladribine (OR 0.98, 95% CI 0.18 to 5.39). A trivial increase in the number of deaths may have occurred in the people treated with ozanimod (OR 0.96, 95% CI 0.03 to 29.63), alemtuzumab (OR 1.38, 95% CI 0.16 to 12.14), teriflunomide (OR 1.50, 95% CI 0.16 to 14.45) and natalizumab (OR 2.52, 95% CI 0.12 to 52.69). Differences across treatments were found and are shown in Appendix 13.

Relative treatment rankings (SUCRA and mean rank) for each primary and secondary outcome are presented in Appendix 14. Due to the small number of studies for comparisons and large number of treatments, interpretation of these results should be considered with caution.

3. Assessment of heterogeneity and incoherence within the network analyses

We performed an assessment of heterogeneity and incoherence within the network analyses for all analyses whenever possible. The values for common heterogeneity ($\tau 2$) for the network for each outcome seem to show no evidence of heterogeneity (Appendix 15). Assessment of incoherence was possible for disability worsening over 24 months, relapses over 12 and 24 months, number of patients with any serious adverse events, number of patients who discontinued due to adverse events, and mortality (Appendix 16). We observed evidence of local statistical incoherence, estimated as a difference between direct and indirect treatment estimates in networks, for one loop for relapses over 24 months, for the number of patients with any serious adverse events, and for treatment discontinuation due to adverse events.

4. Subgroup and sensitivity analyses

Subgroup analysis

In the subgroup analysis by diagnostic criteria, for the efficacy outcomes, we didn't find any relevant difference in the dimension or direction of the effect for those drugs that were represented in both subgroups. For safety outcomes, we found that, in the studies using Poser criteria, the incidence of SAEs was higher for some drugs compared to studies using Mc Donald criteria; however, the estimates were highly imprecise (Appendix 17).

We could not perform a subanalysis based on previous treatment with immunomodulators or immunosuppressants because the vast majority of the included studies did not report data about previous treatments with DMTs or included a mixed population of patients with and without previous treatment with DMTs, but did not report separate outcome data for the two subgroups. Moreover, amongst the studies including people with MS previously treated with DMTs, we found notable heterogeneity in the definition of “previous treatment”, with different washout criteria adopted for different DMTs.

Sensitivity analysis

In the analysis including only studies at low risk of selection bias (allocation concealment), we did not find any important difference in the direction or dimension of the effect estimate for all outcomes except "discontinuation due to adverse events". For this outcome, the direction of the effect remained the same and the dimension increased for some drugs while decreased for others. The direction of the effect changed only for pegylated interferon beta-1a.

In the analysis, including only studies at low risk of attrition bias, the estimates of the effect of the interventions changed in the dimension of the effect, increasing for some drugs and decreasing for others, but not in the direction for all the outcomes for several drugs. For disability at 24 months, the estimate of effect of fingolimod changed direction (Appendix 18).

We did not perform sensitivity analyses excluding studies with a sample size smaller than 50 randomised participants because only two studies satisfied this criterion.

5. Reporting bias

We did not produce a contour-enhanced funnel plot for each pairwise comparison due to the low number of studies. We employed a comparison-adjusted funnel plot for all placebo-controlled trials for relapses over 12 and 24 months and disability worsening over 24 months. Small study effects (not necessarily due to reporting bias) appeared to be present for relapses over 12 and 24 months, but not for disability worsening over 24 months (data not shown).

DISCUSSION

Summary of main results

This updated review of the effects of treatments for RRMS included 50 studies involving 36,541 randomised adult participants. Twenty-five (50%) studies were placebo-controlled and 25 (50%) were head-to-head comparisons. The majority of studies were short-term trials, with the median treatment duration being 24 months. Four studies reported a 36-month follow-up; therefore, the effects of these treatments beyond two years remain uncertain.

1. Recurrence of relapses

Considering placebo as a common comparator, 12-month follow-up treatment with natalizumab resulted in a large reduction of people with relapses. Treatment with fingolimod, daclizumab, and immunoglobulins probably resulted in a large reduction of people with relapses. Treatment with mitoxantrone, teriflunomide, glatiramer acetate and pegylated interferon beta-1a may result in a large reduction of people with relapses. Treatment with interferon beta-1a (Avonex, Rebif) may moderately reduce people with relapses. Treatment with interferon beta-1b may moderately reduce the number of people with relapses, but the evidence is very uncertain. When interferon beta 1-a and beta 1-b were both used in the same intervention, there may have been a large increase in the number of people with relapses, but the evidence is very uncertain.

At 24 months follow-up, treatment with cladribine, alemtuzumab, and natalizumab resulted in a large decrease in people with relapses. Treatment with fingolimod, dimethyl fumarate and ponesimod probably resulted in a large decrease in people with relapses. Treatment with glatiramer acetate and interferon beta-1a (Avonex, Rebif), probably moderately decreases people with relapses. Treatment with mitoxantrone and immunoglobulins may result in a large decrease in people with relapses. Treatment with interferon beta-1b (Betaferon) and laquinimod may moderately decrease people with relapses. Treatment with teriflunomide and azathioprine may moderately decrease people with relapses, but the evidence is very uncertain. When interferon beta 1-a and beta 1-b were both used in the same intervention arm, there may have been a moderate increase in the number of people with relapses, but the evidence is very uncertain.

At 36 months follow-up, we found that interferon beta-1b (Betaferon) may moderately decrease the number of people with relapses, but the evidence is very uncertain.

2. Disability worsening

At 24 months follow-up, treatment with natalizumab probably results in a moderate reduction of people with disability worsening. Treatment with dimethyl fumarate, alemtuzumab, and fingolimod may moderately reduce people with disability worsening. Treatment with cladribine and interferon beta-1b (Betaferon) may result in a small reduction of people with disability worsening. Treatment with mitoxantrone may result in a large reduction of people who experience disability worsening, but the evidence is very uncertain. Treatment with interferon beta-1a may result in a trivial reduction in the number of people who experience disability worsening. Treatment with mitoxantrone may result in a large reduction of people who experience disability worsening, but the evidence is very uncertain. Treatment with ofatumumab, ocrelizumab, azathioprine and ponesimod may moderately reduce the number of people who experience disability worsening, but the evidence is very uncertain. Treatment with glatiramer acetate, teriflunomide, immunoglobulins and laquinimod may result in a small reduction of people who experience disability worsening, but the evidence is very uncertain. When interferon beta 1-a and beta 1-b were both used in the same intervention arm, there may have been a large increase in the number of people with disability progression, but the evidence is very uncertain. When treated with ozanimod, there may have been a trivial increase in the number of people with disability progression, but the evidence is very uncertain.

At 36 months follow-up, we did not find any study that compared our drugs of interest with placebo.

3. Safety

Using placebo as the common comparator, treatment with alemtuzumab probably results in a trivial reduction of people who discontinued treatment due to adverse events. Treatment with ocrelizumab may result in a trivial reduction in people who discontinue treatment due to adverse events. Treatment with daclizumab, fingolimod, teriflunomide, interferon beta-1a, laquinimod, natalizumab, and glatiramer acetate probably result in a trivial increase in people who discontinued due to adverse events. Treatment with interferon beta-1b, ofatumumab, cladribine, and dimethyl fumarate may result in a trivial increase in people who discontinued due to adverse events. Treatment with ozanimod may have little to no effect on people who discontinued due to adverse effects. Treatment with pegylated interferon beta-1a, azathioprine, and ponesimod may result in a small increase in people who discontinued due to adverse events, but the evidence is very uncertain. Treatment with immunoglobulins and interferon beta 1a-1b may result in a trivial increase in people who discontinued due to adverse effects, but the evidence is very uncertain.

Compared to placebo, treatment with interferon beta-1b probably results in a trivial reduction in people who experience serious adverse effects. Treatment with fingolimod and glatiramer acetate may result in a trivial reduction in people who experience SAEs. Treatment with mitoxantrone may result in a trivial reduction in people who experience SAEs, but the evidence is very uncertain. Treatment with daclizumab may result in a small increase in people with SAEs. Treatment with dimethyl fumarate and natalizumab may result in a trivial increase in people who experience SAEs. Treatment with ocrelizumab may result in little or no effect on people who experience SAEs, but the evidence is

very uncertain. Treatment with the remaining DMTS may result in a trivial increase in the people experiencing SAEs, but the evidence is very uncertain: alemtuzumab, cladribine, interferon beta-1a, laquinimod, pegylated beta-1a; ofatumumab, ozanimod, ponesimod and teriflunomide (very low-certainty evidence).

Overall completeness and applicability of evidence

Nine critical outcomes were identified by the Multiple Sclerosis Essential Medicines Panel appointed by the Multiple Sclerosis International Federation. These informed the current review, but the outcomes were further differentiated into primary and secondary outcomes and assessed solely for certainty and efficacy/harm, in line with standard Cochrane methodology. The data underlying the review, from all nine outcomes, served as the evidence base for the MEMP guideline panel, where it was contextualised with the perspective of low-resource settings by considering further evidence related to other domains, in line with GRADE Evidence to Decision Framework methodology (Alonso-Coello 2016; Alonso-Coello 2016b). The MEMP recommendations were used as the basis of an application for the inclusion of disease-modifying treatments in the 23rd WHO Model List of Essential Medicines.

Many of the trials included in this review provided evidence on the proportion of participants who experienced new relapses, disability worsening, and adverse events over 12 or 24 months' follow-up, but only five studies reported data on these outcomes over 36 months. Considering that MS is a chronic disease of 30 to 40 years' duration, such findings limit the applicability of the available evidence for both efficacy and safety, particularly for long-term and uncommon adverse events.

Evidence relevant to 29 treatments considered in this review was derived from 50 studies involving 36,541 adult participants, half of which (25/50 studies; 17,294 participants, 50% of those included in this review) compared the intervention with placebo and not with another DMT. There is, therefore, uncertainty whether the results of the review fit into the context of current practice since about 50% of people with MS are treated with at least one DMT (Carroll 2014).

The reasons why the 50 available randomised studies for RRMS are mostly placebo-controlled and outcome data are reported mainly over 24 months, are probably due to the following reasons: i) comparison with placebo in one double-blind, superiority RCT is sufficient for approval of DMTs for RRMS by many national regulatory agencies ; ii) the lack of interest by pharmaceutical companies in conducting longer and more expensive studies, given that it is only recently that some regulatory agencies have recommended a duration of three years for confirmatory trials (*EMA - Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis, 2015 https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-multiple-sclerosis-revision-2_en.pdf)*; iii) the unlikely advantage of pharmaceutical companies in conducting head-to-head trials directly comparing active treatments.

In order to increase the comprehensiveness of this review, in addition to outcomes present in the previous version of the review, this update also included new/enlarging T1- and T2-weighted MRI lesions, cognitive and quality of life as secondary outcomes, which are considered relevant by people with MS (Secondary outcomes).

Quality of the evidence

Considering the risk of bias, the most frequent concern was related to the role of the sponsor in the authorship of the study report or in data management and analysis, for which we judged that 68% of the studies were at high risk of bias. The other most frequent concerns were performance bias with 34% of the studies at high risk of bias and attrition bias with 32% of studies at high risk of bias.

The most frequent reasons for downgrading the certainty of evidence were study limitations and imprecision, across all the outcomes and comparisons.

For relapses at 12 and 24 months, we judged several treatments as having high (natalizumab, alemtuzumab, cladribine) and moderate (daclizumab, fingolimod, immunoglobulins, dimethylfumarate, glatiramer acetate, interferon beta-1a, ponesimod) certainty of evidence. On the other hand, for the outcome disability at 24 months, we found moderate certainty of evidence only for natalizumab, while the certainty of evidence for all the other treatments was low or very low.

For treatment discontinuation due to adverse events, we judged several treatments as having moderate certainty of evidence (natalizumab, alemtuzumab, daclizumab, fingolimod, glatiramer acetate, interferon beta-1a, laquinimod, and teriflunomide). For the outcome SAEs, only interferon beta-1b provided a moderate certainty of evidence.

Considering all the outcomes, natalizumab was the drug for which we found the highest certainty of evidence.

Potential biases in the review process

1. Transitivity assumption

We assumed that any patient who met the inclusion criteria was, in principle, equally likely to have been randomised to any of the eligible interventions. However, as we discussed in the Background section, several participant characteristics have changed in newer trials, and thus a transitivity hypothesis may not have been a reasonable assumption to make, due to differences in patient or trial characteristics. Thus, we evaluated the assumption of transitivity by assessing differences in patient characteristics such as age, disease duration, and baseline Expanded Disability Status Scale (EDSS) scores across the trials and by comparing the predefined potential effect modifiers across the different comparisons in the networks. We did not find any evidence that important variables varied across comparisons or altered the effectiveness of the treatments; although some confounders may be hidden and unmeasured, it might be reasonable to analyse the network as a whole. Thus, we assumed that the transitivity held and a network meta-analytical approach was reasonable. However, few studies per comparison were available and limitations in study reporting cannot exclude the possibility of intransitivity.

2. Heterogeneity and inconsistency

We did not find any strong evidence of the presence of heterogeneity either in direct pairwise comparisons or in the entire networks. Similarly, the loop-specific approach and the 'design-by-treatment' model did not provide any clear indication of the presence of inconsistency either locally or in the entire networks. Thus, we believe that the consistency assumption is reasonable for this type of data. However, the power of these tests and approaches

to detect inconsistency is low, particularly for networks with few included studies per comparison.

3. Subgroup and sensitivity analyses

In the subgroup analysis by diagnostic criteria, for the efficacy outcomes, we didn't find any relevant difference in the dimension or direction of the effect for those drugs that were represented in both subgroups. For safety outcomes, we found that, in the studies using Poser criteria, the incidence of SAEs was higher for some drugs compared to studies using Mc Donald criteria; however, the estimates were highly imprecise.

In sensitivity analysis including only studies at low risk of selection bias, we found that the outcome "discontinuation due to adverse effects" changed in the dimension of the effect, increasing for some treatments and decreasing for others. When we included only studies at low risk of attrition bias, this phenomenon happened also for other outcomes, though differences were not substantial. These findings indicate that attrition bias could have an impact on the dimension of the estimates, though it is not possible to identify a consistent direction across the interventions.

4. Reporting bias

The possible presence of reporting bias, partially supported by the comparison-adjusted funnel plot for comparisons versus placebo for relapses over 12 and 24 months, could not be totally excluded.

5. Certainty of the evidence

As reported in the Data collection and analysis (Summary of findings and assessment of the certainty of the evidence) section, the certainty of the evidence for this review was assessed using a fully contextualised approach, involving the definition of quantitative thresholds to determine the magnitude ('trivial', 'small', 'moderate', and 'large') of each health effect measured by each outcome. Quantitative thresholds between magnitudes of health effects were considered when assessing imprecision, one of the domains contributing to the certainty of the evidence. Thresholds were calculated from outcome-specific numerical health state utility values (HSUVs). Whenever HSUVs were not obtainable from published evidence, they were set through panel judgement, therefore reflecting the panel members' potentially biased views and expectations.

Agreements and disagreements with other studies or reviews

In this review, which included 50 RCTs on 29 pharmacological treatments for patients with RRMS, we found with high certainty that, compared to placebo, people with RRMS receiving natalizumab, cladribine or alemtuzumab for 24 months had a lower risk of experiencing new relapses at both 12 and 24 months compared to people receiving other DMTs. Moreover, people receiving natalizumab may also have a lower risk of disability progression at 24 months. Results from our previous review (Tramacere 2015) on disability worsening at 24 months were confirmed and extended in this current review update.

In terms of safety, compared to those receiving placebo, we are moderately confident that a higher proportion of people treated with daclizumab, fingolimod, teriflunomide, interferon beta-1a, laquinimod, natalizumab, and glatiramer or glatiramer acetate are at a higher risk of withdrawing due to AEs. Our certainty that the same conclusion could be drawn for the other DMTs except alemtuzumab (all with higher risk than placebo) was low or very low. Indirect comparisons show that alemtuzumab was the only DMT with a lower number of patients discontinuing for AEs than placebo (moderate certainty).

Daclizumab, dimethyl fumerate and natalizumab are associated with a higher proportion of severe adverse events than other DMTs, when taking placebo as the common comparator, although the certainty of such evidence is low. There is low-certainty evidence that people treated with interferon beta-1b, fingolimod and glatiramer acetate may experince a slightly lower number of SAEs. For the remaining DMTs, we found only very low-certainty evidence.

According to an NMA (Li 2020) including 23 RCTs on DMTs for RRMS with methodology similar to that of our review, in that the authors adopted the GRADE methodology to assess certainty in the evidence, alemtuzumab, natalizumab, ocrelizumab and fingolimod were the regimens associated with both the lowest risks of relapse rate and of treatment discontinuation due to AEs. However, in interpreting such similarities and differences in the results compared to those of our review, it has to be noted that this NMA considered only studies with a minimum follow-up of 24 months assessing the 12 DMTs approved by the FDA, and did not include cladribine and daclizumab.

A recent NMA (Liu 2021), including 21 studies involving 23 DMTs, showed that all of them, except interferon beta-1b, were more effective than placebo in reducing the annualised relapse rate (ARR) over 24 months while, in a multi-comparison analysis, ofatumumab ranked as the most effective, and alemtuzumab, dimethyl fumarate and ocrelizumab were ranked in second place. Considering the effectiveness in reducing relapse frequency and tolerability in terms of discontinuation rate due to AEs, alemtuzumab showed the best combination and, according to the authors, could be considered the optimal treatment, together with ofatumumab and natalizumab. In terms of undesirable effects, drug discontinuation due to AEs was more frequent with most DMTs compared to placebo, but such difference was not statistically significant, except for dimethyl fumarate. Although conclusions on alemtuzumab and natalizumab may be considered as in agreement with our review, and safety relative to discontinuation due to AEs is in disagreement, it should be noted that, in contrast to our review, in the review by Liu and colleagues, the risk of bias of the included studies was assessed by means of the Cochrane Risk of Bias 2 (RoB2) but outcome-specific certainty of the reported estimates according to the GRADE methodology was not assessed.

Similar to our conclusions, in respect to placebo, a NMA on the safety of immunotherapies for MS (Tramacere 2023) found an increased proportion of people discontinuing treatment for teriflunomide, interferon beta-1a, interferon beta-1b, glatiramer acetate, fingolimod, immunoglobulins, and daclizumab.

Favourable results relative to alemtuzumab and natalizumab in terms of efficacy were also reported by a NMA (Lucchetta 2018), including most of the available licensed DMTs for RRMS, and azathioprine and rituximab as off-label treatments. In contrast to our review, ocelizumab also, together with alemtuzumab and natalizumab, were reported as the most effective DMTs in reducing ARR and disability accumulation. This NMA, though, included

studies with a minimum follow-up of 12 weeks and used interferon beta-1a as a common comparator in the NMA.

A NMA of RCTs on DMTs for RRMS (Fogarty 2016), considering ARR and disability progression as primary efficacy outcomes, found that natalizumab and alemtuzumab ranked higher than other DMTs across outcomes. This review, however, did not include amongst the considered interventions most of the recent selective immunosuppressors (i.e. ponesimod, siponimod, ozanimod, ofatumumab, daclizumab), cladribine and off-label treatments.

AUTHORS' CONCLUSIONS

Implications for practice

Conservative interpretation of these results is warranted, since most of the included treatments have been evaluated in few trials. Nevertheless, we used a comprehensive, transparent, and pragmatic approach for rating the certainty of the evidence (i.e. the GRADE approach), so the results of this review may provide guidance to clinicians and patients. According to the GRADE approach, implications for practice should be based on moderate to high certainty of evidence, since any estimate of effect based on low to very low certainty of evidence is very uncertain and further research is likely to change the estimate. The results of this updated review show that, for preventing clinical relapses in the short term (24 months), natalizumab, alemtuzumab, and cladribine may be preferable to several other treatments, based on high certainty of evidence. For preventing disability from worsening in the short term (24 months), natalizumab is superior to several other treatments based on moderate certainty of evidence. Moreover, alemtuzumab may also have a better treatment durability, being associated with less discontinuation due to AEs. The number of SAEs seems, from the available evidence, to be only slightly affected by treatment with DMTs amongst people with RRMS.

In addition to the available evidence for benefit provided above, there are two major concerns that have to be considered. First, the efficacy of all of these treatments beyond two years is uncertain and this is a relevant issue for a disease with a duration of 30 to 40 years. Second, short-term trials provide limited safety data and do not provide useful evidence to obtain a reliable risk profile of treatments. In order to provide information on the long-term safety of the treatments included in this review, non-randomised studies should be considered.

Finally, more than 68% of the studies included in this review were sponsored by pharmaceutical companies and this may have influenced their results.

Implications for research

The research agenda on DMTs for MS should address the following needs: first, randomised trials of direct comparisons between active agents would be useful, avoiding further placebo-controlled studies that in the current context do not comply with the principle of clinical equipoise for RRMS, given the broad availability of therapeutic alternatives. Second, follow-up of at least 36 months should be mandatory for confirmatory RCTs on DMTs for MS. Third, more studies are needed to evaluate the medium and long-term benefit and safety of immunotherapies and the comparative safety of the different agents. As the number of drugs, including biological agents, that are available for the treatment of RRMS increases, more options will become available to participants and clinicians. In the absence of comparative trials, national and international registries and other types of large non-randomised studies might be relevant sources for providing complementary data regarding the long-term benefit and safety of immunotherapies for RRMS. Fourth, future clinical research on MS may benefit from long-term data on outcomes deemed as relevant by people with MS, such as cognitive status and quality of life, as well as definition and validation of health state utility values. Finally, methods of outcome assessment should be more consistent across studies. Although relapses and disability progression are commonly used in MS research as efficacy outcomes, comparison of the relative effectiveness and safety across DMTs is challenging due to the heterogeneity in the way such outcomes are measured (e.g. annualised relapse rate rather than number of people with relapse; mean EDSS scores rather than number of people with MS presenting disability progression). Therefore, consistency in the choice of recommended efficacy and safety outcome measures is highly desirable, particularly in industry-initiated trials, in which the findings may inform regulatory approval of novel DMTs.

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Editorial and peer-review contributions

Cochrane Multiple Sclerosis and Rare Diseases of the CNS supported the authors in the development of this review update. Ben Ridley, Graziella Filippini, Elisa Baldin, and Francesco Nonino are members of Cochrane Multiple Sclerosis and Rare Diseases of the CNS but were not involved in the editorial process or decision-making for this update. The following people conducted the editorial process for this update:

- Sign-off Editor (final editorial decision)*: Toby Lasserson, Cochrane Evidence Production & Methods Directorate
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial comments/guidance to authors, edited the article): Joey Kwong, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service
- Copy Editor (copy-editing and production): Anne Lethaby, c/o Cochrane Central Production Service

- Peer-reviewers (provided comments and recommended an editorial decision): Iván Pérez-Neri, National Institute of Neurology and Neurosurgery, Manuel Velasco Suárez (consumer review), Jennifer Hilgart, Cochrane Evidence Production & Methods Directorate (methods review), Jo Platt, Cochrane GNOC *(*closed in March 2023)* (search review). Two additional peer reviewers provided clinical/content peer review but chose not to be publicly acknowledged.

**Robert Boyle, Imperial College London, acted as Sign-off Editor in May 2023 and submitted the first editorial decision post-peer review.*

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Achiron 1998

Study characteristics	
Methods	RCT
Participants	Age: 19 to 60 years; definite RRMS; mean disease duration 4 years; mean EDSS 3.0; prior use of DMT not reported
Interventions	Loading dose of immunoglobulins 0.4 g/kg body weight intravenously daily for 5 consecutive days followed by additional booster doses of immunoglobulins 0.4 g/kg body weight intravenously daily every 2 months for 24 months (n = 20) Placebo consisting of 0.9% saline administered with the same schedule as the active treatment (n = 20)
Outcomes	Relapse at 12 and 24 months. Disability worsening at 24 months
Notes	Funding: Miles Inc. Cutter Biological, Bayer and Promedico

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Patients were assigned to receive immunoglobulin or placebo by a block-stratified randomisation procedure, designed to ensure groups balanced for YER, age, and disease duration*" (page 399).
Allocation concealment (selection bias)	Unclear risk	"*Randomization was performed at the pharmacy, and the bottles of immunoglobulin or placebo were wrapped in sealed opaque bags and brought to the patients' rooms. The entire IV set was covered by an opaque plastic bag to ensure that any possible fluid turbidity or frothing would not be evident to the investigators or patients*" (page 399).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*All patients and evaluators were blinded to treatment*" (page 399).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*A relapse was confirmed only when the patient's symptoms were accompanied by objective changes on neurologic examination by the treating neurologist who was blind to the patient's treatment*", and "*Upon entry, and monthly thereafter,*

Achiron 1998 *(Continued)*

		every patient underwent a neurologic examination by two examining neurologists, and an independent EDSS score was recorded by each" (page 399).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 5.0% were lost to follow-up (5.0% in immunoglobulins and 5.0% in placebo), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Unclear risk	The study was sponsored by Triton Biosciences and the role of the study sponsor was unclear.

ADVANCE 2014

Study characteristics		
Methods	RCT	
Participants	Age: 18 to 65 years; definite RRMS; mean disease duration 7 years; mean EDSS 2.5; prior use of any MS medication at any time prior to the start of study: 17%	
Interventions	Peg-interferon beta-1a 125 µg subcutaneously once every 2 weeks for 12 months (n = 512) Peg-interferon beta-1a 125 µg subcutaneously once every 4 weeks for 12 months (n = 500) Placebo subcutaneously once every 2 weeks for 12 months (n = 500)	
Outcomes	Relapse at 12 months	
Notes	Funding: Biogen Idec	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Patients were randomly assigned (1:1:1) to receive subcutaneous injections with pre-filled syringes of placebo, peginterferon beta-1a at a dose of 125 µg once every 2 weeks, or peginterferon beta-1a 125 µg once every 4 weeks, stratified by site*" (page 658).
Allocation concealment (selection bias)	Low risk	"*Randomisation was done by a centralised interactive voice response and web system. Placebo was a matched diluent, given with a matched pre-filled syringe. Patients received either study drug or placebo every 2 weeks to maintain masking; those assigned to receive study drug every 4 weeks received alternate injections of placebo and peginterferon beta-1a every 2 weeks*" (page 658).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*All study management and site personnel, investigators, and patients were masked to treatment assignment*" (page 658).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Each site had separate examining and treating neurologists, thereby maintaining rater masking for all treatment groups*" and "*relapse was confirmed by the independent neurological evaluation committee*" (page 658).

ADVANCE 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 11.9% were lost-to follow-up (14.5% in peg-interferon beta-1a 125 µg every 2 weeks, 12.4% in peg-interferon beta-1a 125 µg every 4 weeks, and 8.8% in placebo), with some indication of the differences in reasons: adverse events of 4.8% in peg-interferon beta-1a 125 µg every 2 weeks, 4.7% in peg-interferon beta-1a 125 µg every 4 weeks, and 1.0% in placebo.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	The study was sponsored by Biogen Idec, "*Biogen Idec collected, analysed, and contributed to the interpretation of the data*" (page 659), and 5 co-authors of the published paper were affiliated to the pharmaceutical company.

AFFIRM 2006

Study characteristics	
Methods	RCT
Participants	Age: 18 to 50 years; definite RRMS; median disease duration 5 years (range, 0 to 34 years); mean EDSS 2.3; prior use of DMT not reported
Interventions	Natalizumab 300 mg by intravenous infusion once every 4 weeks for up to 116 weeks (n = 627) Placebo (unspecified) (n = 315)
Outcomes	Relapse at 12 and 24 months. Disability worsening at 24 months
Notes	Funding: Biogen Idec, Inc. and Elan Pharmaceutica

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Patients were randomly assigned to treatment that was stratified according to study site in blocks of three (two active, one placebo) with the use of a computer-generated block randomization schedule*" (page 900).
Allocation concealment (selection bias)	Low risk	"*Amultidigit identification number, implemented by an interactive voice-response system was used*" (page 900).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*All study personnel, patients, sponsor personnel involved in the conduct of the study, and the investigator advisory committee were unaware of treatment assignments throughout the study*", and "*Treating neurologists were responsible for all aspects of patient care, including the management of adverse events and the treatment of relapsing disease*" (pages 900-1).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quoted: "*A list of predefined questions relating to signs or symptoms suggestive of vascular thrombosis will be presented to the subject".* *"Examining neurologists performed objective evaluation with use of the EDSS and neurologic examination during all study visits; they were not in contact with patients in any other capacity, so as to reduce the possibility of being unblinded by side effects or laboratory assessments*", (page 901).
Incomplete outcome data (attrition bias)	Low risk	Overall, 9.1% were lost-to follow-up (8.3% in natalizumab and 10.8% in placebo), without indication of the differences in reasons.

AFFIRM 2006 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	The study was sponsored by Biogen Idec and Elan Pharmaceuticals, "*Data were analyzed by Biogen Idec and Elan Pharmaceuticals*" (page 909) and 4 co-authors of the published paper were affiliated to the pharmaceutical company.

ALLEGRO 2012

Study characteristics	
Methods	RCT
Participants	Age: 18 to 55 years; definite RRMS; mean disease duration 9 years; mean EDSS 2.6; prior use of DMT at any time prior to the start of study: 39.0% (38.2% in laquinimod and 39.7% in placebo)
Interventions	Laquinimod 0.6 mg oral capsule once daily for 24 months (n = 550) Placebo oral capsule once daily for 24 months (n = 556)
Outcomes	Relapse at 24 months. Disability worsening at 24 months
Notes	Funding: Teva Pharmaceutical Industries

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*The randomization list, stratified according to study center, was computer-generated*" (page 1002).
Allocation concealment (selection bias)	Low risk	"*The subject was allocated a screening number by the investigator using an Interactive Voice Response System (IVRS)*" (page 44 of Protocol).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Patients and investigators were unaware of the study assignments*" (page 1002).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Neurologic assessments and general medical evaluations were conducted by two neurologists in order to minimize the possibility of unblinding: an examining neurologist assessed neurologic condition, and the treating neurologist determined whether a patient had a relapse*", and "*the treating neurologist was unaware of the study-group assignment*" (page 1002).
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 21.9% were lost-to follow-up (20.5% in laquinimod and 23.2% in placebo), with some indication of the differences in reasons: adverse event(s) in 7.6% in laquinimod and 5.0% in placebo.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes

ALLEGRO 2012 *(Continued)*

Other bias	High risk	"*The sponsor designed and monitored the study*" and "*The data were collected and analyzed by the sponsor*" (page 1001).

ASCLEPIOS I 2020

Study characteristics	
Methods	RCT
Participants	Age: 18-55 years; individuals with mainly relapsing forms of MS (mixed sample, 94% RMS); mean disease duration 8 years; mean EDSS 2.9; prior use of DMT: 59.8% (58.9% in ofatumumab, and 60.6% in teriflunomide).
Interventions	Ofatumumab 20 mg subcutaneously every 4 weeks for up to 30 months (n = 465) Teriflunomide 14 mg orally once daily for up to 30 months (n = 462)
Outcomes	Follow-up: 30 months ARR Disability worsening Numbers of gadolinium-enhancing lesions on T1-weighted magnetic resonance imaging Annualised rate of new or enlarging lesions on T2-weighted magnetic resonance imaging Cognitive decline
Notes	Private funding: Novartis Pharma

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was stratified by geographical region and by multiple sclerosis subtype (relapsing–remitting multiple sclerosis or secondary progressive multiple sclerosis. Randomization numbers were linked to the different treatment arms, which were linked to medication numbers. A separate medication list was produced by or under the responsibility of Novartis Drug Supply Management, using a validated system that automated the random assignment of medication numbers to packs containing each of the trial drugs."
Allocation concealment (selection bias)	Low risk	"Patient randomization list was produced by the Interactive Response Technology providerusing a validated system that automated the random assignment of patient numbers torandomization numbers".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigators, the sponsor, and the steering committee were unaware of treatment assignments throughout the trials. An independent data monitoring committee reviewed the safety of treatment using regular analyses performed by independent statisticians, who were not involved in the conduct of the trials."

ASCLEPIOS I 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	"Efficacy analyses were carried out according to the intention-to-treat principle". 98% of participants evaluated in both arms.
Selective reporting (reporting bias)	Low risk	The results for all the outcomes listed in the protocol have been reported.
Other bias	High risk	Supported by Novartis Pharma. Quote: "The investigators collected data, which were analyzed by the sponsor. All the authors, including those employed by Novartis, had full access to the data and were involved in the critical review of all drafts of the manuscript".

ASCLEPIOS II 2020

Study characteristics	
Methods	RCT
Participants	Age: 18-55 years; individuals with mainly relapsing forms of MS (mixed sample, 94% RMS); mean disease duration 8 years; mean EDSS 2.9; prior use of DMT: 60.6% (59.5% in ofatumumab, and 61.8% in teriflunomide)
Interventions	Ofatumumab 20 mg subcutaneously every 4 weeks for up to 30 months (n = 481) Teriflunomide 14 mg orally once daily for up to 30 months (n = 474)
Outcomes	Follow-up: 30 months ARR Disability worsening Numbers of gadolinium-enhancing lesions on T1-weighted magnetic resonance imaging Annualised rate of new or enlarging lesions on T2-weighted magnetic resonance imaging Cognitive decline
Notes	Supported by Novartis Pharma

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was stratified by geographical region and by multiple sclerosis subtype (relapsing–remitting multiple sclerosis or secondary progressive multiple sclerosis). Randomization numbers were linked to the different treatment arms, which were linked to medication numbers. A separate medication list was produced by or under the responsibility of Novartis Drug Supply Management, using a validated system that automated the random assignment of medication numbers to packs containing each of the trial drugs."
Allocation concealment (selection bias)	Low risk	"Patient randomization list was produced by the Interactive Response Technology provider using a validated system that automated the random assignment of patient numbers to randomization numbers".

ASCLEPIOS II 2020 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigators, the sponsor, and the steering committee were unaware of treatment assignments throughout the trials. An independent data monitoring committee reviewed the safety of treatment using regular analyses performed by independent statisticians, who were not involved in the conduct of the trials."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Efficacy analyses were carried out according to the intention-to-treat principle". 97.5% and 99% of participants evaluated in each arm.
Selective reporting (reporting bias)	Low risk	The results for all the outcomes listed in the protocol have been reported.
Other bias	High risk	Supported by Novartis Pharma. Quote: "The investigators collected data, which were analyzed by the sponsor. All the authors, including those employed by Novartis, had full access to the data and were involved in the critical review of all drafts of the manuscript".

ASSESS 2020

Study characteristics	
Methods	RCT
Participants	Age: 18-65 years; clinically definite relapsing forms of multiple sclerosis; mean disease duration 4.5 years; mean EDSS 2.7; prior use of DMT at any time prior to the start of study: 53.1% (51.7% in fingolimod 0.5 mg, 52.7% in fingolimod 0.25 mg, and 55.0% in glatiramer acetate)
Interventions	Fingolimod 0.5 mg orally once daily for 12 months (n = 352) Fingolimod 0.25 mg orally once daily for 12 months (n = 370) Glatiramer acetate 20 mg subcutaneously daily for 12 months (n = 342)
Outcomes	Follow-up: 12 months Reduction in ARR New or newly enlarging T2 and gadolinium-enhancing T1 lesions AE
Notes	Funded by Novartis Pharma AG, Basel, Switzerland

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A patient randomization list will be produced by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of PPD us-

ASSESS 2020 *(Continued)*

		ing a validated system that automates the random assignment of medication numbers to study drug packs containing each of the study drugs."
Allocation concealment (selection bias)	Low risk	"Participants were randomized (1:1:1) to receive fingolimod, 0.5 mg, or fingolimod, 0.25 mg, orally once per day or glatiramer acetate, 20 mg, subcutaneously once per day using an interactive voice response system. The randomization number will not be communicated to the caller."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and providers were not blind to treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Participant scores from the Expanded Disability Status Scale were evaluated by an independent Neurostatus-certified rater who was blinded to the clinical data. Data from magnetic resonance imaging (MRI) scans were analyzed independently by a blinded reader (D.L.A.) at a central reading site (NeuroRX Research)". "The independent evaluating physician will remain blinded until the database lock and data analysis has been completed. In order to maintain rater-blinding, all patients will be instructed to wear appropriate clothing to completely cover typical or actual injection sites before all scheduled visits and relapse-related neurologic examinations, and not to discuss their treatment or AEs (e.g. injection site reactions) with the independent evaluating physician".
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All efficacy analyses were conducted in the full analysis set, which comprised all randomized participants who received at least 1 dose of the study drug."
Selective reporting (reporting bias)	Low risk	The results for all the outcomes listed in the protocol have been reported.
Other bias	High risk	"The study was funded by Novartis Pharma AG, Basel, Switzerland". "Novartis Pharma AG participated in the design and conduct of the study, data collection, data management, data analysis and interpretation, and preparation, review, and approval of the manuscript."

BECOME 2009

Study characteristics	
Methods	RCT
Participants	Age: 18 to 55; definite RRMS or CIS; median time since MS onset 1 year; mean EDSS 2.0; all participants (except one) were previously untreated patients Mixed sample: 82% RRMS/18% CIS
Interventions	Interferon beta-1b (Betaseron) 250 µg subcutaneously every other day for 24 months (n = 36) Glatiramer acetate 20 mg subcutaneous daily for 24 months (n = 39)
Outcomes	Relapse at 12 and 24 months. Disability worsening at 24 months
Notes	Funding: Bayer Schering Pharma

BECOME 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Randomization was stratified by clinical site (Newark or Teaneck) and the presence of enhancement on screening MRI*" (page 1977).
Allocation concealment (selection bias)	Unclear risk	Nothing was said about allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Patients could not be blinded because of the characteristic injection reactions to IFN-1b or glatiramer acetate*" (page 1977).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Subjective relapses that were confirmed by a blinded examining neurologist using worsening scores on either the Scripps Neurological Rating Scale (SNRS) or the Expanded Disability Status Scale (EDSS) were considered objective relapses*" (page 1977). However, it is not clear how and when the examining neurologist evaluated subjective relapses and EDSS scores.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 14.7% were lost-to follow-up (19.4% in interferon beta-1b and 10.3% in glatiramer acetate), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	"*The BECOME study was supported by Bayer Schering Pharma, distributors of IFN-1b, but was investigator-initiated and remains the intellectual property of New Jersey Medical School/University of Medicine & Dentistry of New Jersey. The sponsor of the study was allowed to comment on data interpretation and had the opportunity to review and comment on the final manuscript prior to submission. The sponsor was not allowed to participate in any of the following phases of the study: conduct of the study, data collection, data management, data analysis, and preparation of the manuscript*" (page 1981).

BEYOND 2009

Study characteristics

Methods	RCT
Participants	Age: 18 to 55 years; definite RRMS; mean disease duration 5 years; mean EDSS 2.3; prior use of DMT not reported
Interventions	Interferon beta-1b (Betaseron) 250 µg subcutaneously every other day for 24 months (n = 897) Interferon beta-1b (Betaseron) 500 µg subcutaneous every other day for 24 months (n = 899) Glatiramer acetate 20 mg subcutaneously daily for 24 months (n = 448)
Outcomes	Relapse at 24 months. Disability worsening at 24 months
Notes	Funding: Bayer HealthCare Pharmaceuticals

BEYOND 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Use of SAS-based block randomisation with regional stratification*" (page 890)
Allocation concealment (selection bias)	Unclear risk	"*Patients were randomly assigned in a 2:2:1 ratio ... by the central randomisation group*..." (page 890).
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Physicians and patients were double-blind to comparisons between the two doses of IFNß-1b... Ibuprofen or acetaminophen were given at the same time as random assignment to IFNß-1b, at least during the first 3 months, to reduce flu-like symptoms. The treating physicians and the patients were therefore aware of treatment assignments*" (page 891).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The masked evaluating physicians did all neurological assessments and ascertained functional system and EDSS scores. The evaluating physicians were not involved in the care of patients and had no access to patient files or previous assessments*", and "*Patients covered their injection sites during neurological examination and did not discuss any adverse events with the evaluating physician*" (pages 891-2).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 16.0% were lost-to follow-up (19.2% in interferon beta-1b 500 µg, 12.6% in interferon beta-1b 250 µg, and 16.5% in glatiramer acetate), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	The study was funded by Bayer HealthCare Pharmaceuticals, and some co-authors of the published paper were affiliated to the pharmaceutical company or have received personal compensation from the company.

Bornstein 1987

Study characteristics	
Methods	RCT
Participants	Age: 20 to 35 years; definite RRMS; mean disease duration 6 years; mean EDSS 3.1; prior use of DMT not reported
Interventions	Glatiramer acetate 20 mg subcutaneously daily for 24 months (n = 25) Placebo bacteriostatic saline subcutaneously daily for 24 months (n = 25)
Outcomes	Relapse at 12 and 24 months. Disability worsening at 24 months
Notes	Funding: grants from the NINCDS and the NIH, Bethesda, Md

Risk of bias

Bias	Authors' judgement	Support for judgement

Bornstein 1987 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"*The random assignment of the first patient of a pair determined the assignment of both*" (page 409).
Allocation concealment (selection bias)	High risk	An open allocation schedule was used: "*Treatment assignments were made known to the clinical assistant responsible for the production, labelling and distribution of medication*" (page 409).
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*The patient's self evaluation of ... side effects was reported to the clinical assistant, who was not blinded to the treatment*" (page 409).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Patients visited the clinic every three months for two years. At each visit, a neurologist unaware of the patient's treatment group completed a neurologic examination and status evaluation*" and "*Patients were also seen at the time of suspected exacerbations ... the neurologist verified exacerbations on the basis of study criteria*" (page 409).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 4.0% were lost-to follow-up (0% in glatiramer acetate and 8.0% in placebo), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

BRAVO 2014

Study characteristics	
Methods	RCT
Participants	Age: 18 to 55 years; definite RRMS; median disease duration 5 years; median EDSS 2.5; prior use of DMT at any time prior to the start of study: 7.4% (6.9% in laquinimod, 9.4% in interferon beta-1a and 6.0% in placebo)
Interventions	Laquinimod 0.6 mg oral capsule once daily for 24 months (n = 434) Interferon beta-1a (Avonex) 30 µg intramuscular once a week for 24 months (n = 447) Placebo oral capsule once daily for 24 months (n = 450)
Outcomes	Relapse at 24 months. Disability worsening at 24 months
Notes	Funding: Teva Pharmaceutical Industries

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*The computer-generated randomization scheme prepared by the Teva Global Biostatistics Unit*" (page 775)

BRAVO 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	"*1:1:1 treatment assignment ratio stratified by study center, to laquinimod 0.6 mg capsule once-daily, matching oral placebo, or IFNß-1a IM 30 µg once-weekly injection*" (page 775)
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Patients and treating neurologists were blinded to oral treatment assignment (laquinimod or placebo), but not to IFNb-1a IM assignment*", and "*All patients, including those receiving oral treatment, wore clothing and/or a robe that ensured coverage of all potential IM injection sites during examination and were instructed not to discuss adverse events (AEs), routes of administration, or treatment assignments with the examining neurologist*" (page 775).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The examining neurologist was blinded to all treatments*", and "*The examining neurologist performed an EDSS assessment for relapse confirmation within 7 days of symptom onset*" (page 775).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 18.1% were lost-to follow-up (18.7% in laquinimod, 15.4% in interferon beta-1a, and 20.2% in placebo), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	"*N. Sasson of Teva Pharmaceutical Industries provided statistical support for the manuscript*" (page 773), and 2 co-authors of the published paper were affiliated to the pharmaceutical company.

CAMMS223 2008

Study characteristics	
Methods	RCT
Participants	Age: 18 to 50; definite RRMS; median time since first relapse 1 year; mean EDSS 1.9; all participants were previously untreated patients.
Interventions	Alemtuzumab 24 mg per day intravenously on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24 (n = 110) Alemtuzumab 12 mg per day intravenously on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24 (n = 113) Interferon beta-1a (Rebif) 44 µg subcutaneous 3 times a week for 36 months (n = 111) All participants received 1 g of intravenous methylprednisolone for 3 days at baseline and at months 12 and 24.
Outcomes	Relapse at 12, 24, and 36 months. Disability worsening at 24 and 36 months
Notes	Funding: Genzyme (a Sanofi company) and Bayer Schering Pharma

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Eligible patients were randomly assigned in a 1:1:1 ratio to receive alemtuzumab (at a dose of either 12 mg per day or 24 mg per day) or interferon beta-1a with the use of the Pocock and Simon minimization algorithm to balance the study*

CAMMS223 2008 *(Continued)*

		groups with regard to age (< 30 years or ≥ 30 years), sex, and baseline EDSS score (< 2.0 or ≥ 2.0)" (page 1787).
Allocation concealment (selection bias)	Low risk	"*Patients were allocated via an interactive voice response system (IVRS)*" (information provided on request by Genzyme).
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Patients wore clothing that covered injection sites*", and "*Safety was assessed quarterly by the treating neurologist, who was aware of study-group assignment*" (page 1787).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*EDSS scores were determined quarterly in a blinded fashion by a neurologist who also adjudicated possible relapses. Patients wore clothing that covered injection sites*" (page 1787). It is not clear how potential relapses were assessed.
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 25.1% were lost to follow-up (16.4% in alemtuzumab 24 mg, 18.6% in alemtuzumab 12 mg, and 40.5% in interferon beta-1a), with some indication of the differences in reasons: adverse events of 0.01% in alemtuzumab 24 mg, 1.8% in alemtuzumab 12 mg, and 11.7% in interferon beta-1a; and lack of benefit of 1.8% in alemtuzumab 24 mg, 1.8% in alemtuzumab 12 mg, and 14.4% in interferon beta-1a.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes. Missing data not reported in the published paper were provided on request by Genzyme.
Other bias	High risk	"*Genzyme employees analyzed the data*" (page 1789), and 5 co-authors of the published paper were affiliated to the pharmaceutical company.

CARE-MS I 2012

Study characteristics	
Methods	RCT
Participants	Age: 18 to 50 years; definite RRMS; mean disease duration 2 years; mean EDSS 2.0; all participants were previously untreated patients.
Interventions	Alemtuzumab 12 mg per day intravenously on 5 consecutive days at month 0 and 3 consecutive days at month 12 (n = 386) Interferon beta-1a (Rebif) 44 µg subcutaneously 3 times a week for 24 months (n = 195) Participants in both groups received 1 g per day of intravenous methylprednisolone on 3 consecutive days at baseline and at month 12. After a protocol amendment in January 2009, alemtuzumab patients received oral aciclovir 200 mg twice daily during alemtuzumab infusion and for 28 days thereafter as prophylaxis against herpes infection.
Outcomes	Relapse at 12 and 24 months. Disability worsening at 24 months
Notes	Funding: Genzyme (a Sanofi company)
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

CARE-MS I 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	"*We randomly allocated patients in a 2:1 ratio*" and "*Randomisation was stratified by site*" (page 1820).
Allocation concealment (selection bias)	Low risk	"*We randomly allocated patients using an interactive voice response system*" (page 1820).
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Because both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and because subcutaneous interferon beta 1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo...*" (page 1820)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*We secured clinical data integrity by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists. In the absence of a masked rater, unmasked raters could submit EDSS assessments*" (page 1820). Moreover, it is not clear how and when the committee evaluated potential relapses
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 7.1% were lost to follow-up (4.9% in alemtuzumab 12 mg and 11.3% in interferon beta-1a), with some indication of the differences in reasons: adverse events of 2.6% in alemtuzumab and 0% in interferon beta-1a
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	"*The study sponsor (Genzyme) was involved in the design and undertaking of the trial, data analysis and interpretation, writing of the manuscript, and the decision to submit the manuscript for publication. Bayer Schering Pharma participated in the design and oversight of the trial*", "*The sponsor did the statistical analyses*" (page 1822), and 4 co-authors of the published paper were affiliated to the pharmaceutical company.

CARE-MS II 2012

Study characteristics	
Methods	RCT
Participants	Age: 18 to 55 years; definite RRMS; mean disease duration 5 years; mean EDSS 2.7; all patients were previously treated: "*at least one relapse while on interferon beta or glatiramer after at least 6 months of treatment*"
Interventions	Alemtuzumab 24 mg per day intravenously on 5 consecutive days at month 0 and 3 consecutive days at month 12 (n = 170; data presented for safety assessment only) Alemtuzumab 12 mg per day intravenously on 5 consecutive days at month 0 and 3 consecutive days at month 12 (n = 436) Interferon beta-1a (Rebif) 44 µg subcutaneous 3 times a week for 24 months (n = 231) Participants in both groups received 1 g per day of intravenous methylprednisolone on 3 consecutive days at baseline and at month 12. After a protocol amendment in December 2008, alemtuzumab patients received oral aciclovir 200 mg twice daily during alemtuzumab infusion and for 28 days thereafter as prophylaxis against herpes infection.
Outcomes	Relapse at 12 and 24 months. Disability worsening at 24 months

CARE-MS II 2012 *(Continued)*

Notes	Funding: Genzyme (a Sanofi company)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*2:1 randomisation allocation stratified by site*" (pages 1830-1)
Allocation concealment (selection bias)	Low risk	"*We randomly allocated patients with an interactive voice response system*" (page 1830).
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Because both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo...*" (page 1831)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses. Raters, who were masked to treatment-group assignment, did the EDSS assessments every 3 months and when a relapse was suspected*" and "*In the absence of a masked rater, unmasked raters could submit EDSS assessments*" (page 1831). Moreover, it is not clear how and when the raters evaluated potential relapses.
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 11.4% were lost to follow-up (4.6% in alemtuzumab 12 mg and 24.2% in interferon beta-1a), with some indication of the differences in reasons: lack of benefit of 0% in alemtuzumab 12 mg and 2.6% in interferon beta-1a.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	"*Genzyme (Sanofi) was involved in the design and undertaking of the trial, data analysis and interpretation, writing of the manuscript, and the decision to submit the manuscript for publication*" (page 1833), and 4 co-authors of the published paper were affiliated to the pharmaceutical company.

CLARITY 2010

Study characteristics

Methods	RCT
Participants	Age: 18-65 years; clinically definite with relapsing forms of MS; mean disease duration 9 years; mean EDSS 2.9; prior use of DMT: 30.3% (26.1% in cladribine 3.5 mg, 32.2% in cladribine 5.25 mg and 32.5% in placebo)
Interventions	Cladribine 3.5 mg/kg of body weight orally in two short courses for the first 12 months and two short courses for the second 12 months (for a total of 8 to 20 days per year) (n = 433) Cladribine 5.25 mg/kg of body weight orally in four short courses for the first 12 months and two short courses for the second 12 months (for a total of 8 to 20 days per year) (n = 456) Placebo for 24 months (n = 437)
Outcomes	Follow-up: 24 months ARR

CLARITY 2010 *(Continued)*

	Relapse rate
	Disease progression
	Lesion count on magnetic resonance imaging
	Withdrawals due to AEs
	SAEs
Notes	Private funding: EMD Serono

Risk of bias

Bias	Authors' judgement	Support for judgement
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	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To maintain 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) All outcomes	Low risk	"An independent evaluating physician who was unaware of study-group assignments performed neurologic examinations and determined whether a clinical event fulfilled criteria consistent with a relapse. Evaluators at a central neuroradiology center assessed MRI evaluations in a blinded fashion".
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The intention-to-treat population included all patients who underwent randomization, and the safety population included all patients who received at least one dose of a study drug and for whom follow-up safety data were available".
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes submitted in Clinical Trials.gov after study completion
Other bias	High risk	"Data were gathered by an independent commercial research organization and analyzed by the sponsor (Merck Serono) in accordance with the statistical plan. The first draft of the manuscript was cowritten by the lead academic author and a representative of the sponsor, with the medical-writing services agency providing support as directed."

CombiRx 2013

Study characteristics

Methods	RCT
Participants	Age: 18 to 60 years; definite RRMS; mean disease duration 1 year; mean EDSS 2.0; all participants were previously untreated patients.

CombiRx 2013 *(Continued)*

Interventions	Interferon beta-1a (Avonex) 30 µg intramuscularly once a week with matched placebo preparation for 36 months (n = 250) Glatiramer acetate 20 mg subcutaneous daily with matched placebo preparation for 36 months (n = 259)
Outcomes	Relapse at 36 months. Disability worsening at 36 months
Notes	Funding: National Institutes of Health (NIH)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Participants were randomized via a computerized data entry system using a permuted block design within sites with block sizes of 6 and 12*" (page 328).
Allocation concealment (selection bias)	Low risk	"*Participants were randomized via a computerized data entry system that masked treatment arm allocation*" (page 328).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Participants were randomized via a computerized data entry system that masked drug dispensing to participants and all site personnel for the entire duration of the trial period*" (page 328).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Treating clinician and an examining clinician were both blinded to treatment assignment*", "*confirmed progression was assessed by the blinded EDSS examiner and confirmed centrally*", and "*The designation of the type of relapse was determined centrally according to data entered onto a relapse assessment form and the change in EDSS*" (pages 328-329). The blinding of the central commission was not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 18.1% were lost to follow-up (22.4% in interferon beta-1a and 13.9% in glatiramer acetate; P value for proportion terminating early = 0.029), with some indication of the differences in reasons: adverse event(s) of 7.2% in interferon beta-1a and 4.6% in glatiramer acetate.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

CONCERTO 2021

Study characteristics

Methods	RCT
Participants	Age: 18-55 years; clinically definite with relapsing forms of MS; mean disease duration 5.8 years; mean EDSS 2.7; prior use of DMT: 29.24% (27% in laquinimod 0.6 mg and 31.5% in placebo)
Interventions	Laquinimod 0.6 mg oral capsule once daily for 24 months (n = 727); placebo once daily for 24 months (n = 740) N = 732 patients were assigned to receive 1.2 mg of laquinimod daily; this arm was discontinued at 1 January 2016 due to findings of cardiovascular events.

CONCERTO 2021 *(Continued)*

Outcomes	Follow-up: 24 months Relapse Disability worsening Withdrawals due to AEs SAEs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, investigators, the sponsor, and designated personnel were blinded to treatment assignments".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Patients, investigators, the sponsor, and designated personnel were blinded to treatment assignments".
Incomplete outcome data (attrition bias) All outcomes	High risk	15% of participants in the laquinomod group and 20% of the placebo group dropped out of the study.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Low risk	"This study was sponsored by Teva Pharmaceutical Industries, Petach Tikva, Israel. The role of the sponsor included review for medical accuracy, providing funding for editorial services, and six co-authors of the published paper were affiliated to the pharmaceutical company".

CONFIRM 2012

Study characteristics

Methods	RCT
Participants	Age: 18 to 55 years; definite RRMS; mean disease duration (time since diagnosis) 5 years; mean EDSS 2.6; prior use of any MS medication at any time prior to the start of study: 40% to 41% across study groups
Interventions	Dimethyl fumarate 240 mg oral capsule 3 times daily for 24 months (n = 345) Dimethyl fumarate 240 mg oral capsule 2 times daily for 24 months (n = 362)

CONFIRM 2012 *(Continued)*

	Glatiramer acetate 20 mg subcutaneous daily for 24 months (n = 350) Placebo oral capsule 3 times daily for 24 months (n = 363)
Outcomes	Relapse at 12 and 24 months. Disability worsening at 24 months
Notes	Funding: Biogen Idec

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Patients were randomly assigned in a 1:1:1:1 ratio to receive oral placebo, BG-12 at a dose of 240 mg two times daily, BG-12 at a dose of 240 mg three times daily, or subcutaneous daily injections of 20 mg of glatiramer acetate for 96 weeks*" (page 1088); and "*The randomization was stratified by site*" (page 33 of Protocol).
Allocation concealment (selection bias)	Low risk	"*Randomization took place across all study sites using a centralized Interactive Voice Response System (IVRS)*" (page 33 of Protocol).
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Patients receiving glatiramer acetate were aware of their treatment assignment. All study management and site personnel, investigators, and patients were unaware of assignment to the BG-12 and placebo groups*", and "*To ensure that the assignments to the BG-12 and placebo groups would not be revealed, patients in those groups were instructed not to take the study medication within 4 hours before each study visit, since a flushing reaction is known to be more common with BG-12*" (page 1088). Since flushing is a known side effect of dimethyl fumarate, patients were possibly not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A*n independent neurologic evaluation committee, whose members were unaware of the study-group assignments, provided confirmation of relapses of multiple sclerosis*" and "*examining neurologists and members of the independent neurologic evaluation committee were unaware of all study-group assignments*" (page 1088).
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 20.3% were lost to follow-up (20.8% in dimethyl fumarate 240 mg 3 times daily, 20.7% in dimethyl fumarate 240 mg 2 times daily, 16.1% in glatiramer acetate, and 23.4% in placebo), with some indication of the differences in reasons: adverse events of 8.1% in dimethyl fumarate 240 mg 3 times daily, 6.1% in dimethyl fumarate 240 mg 2 times daily, 3.6% in glatiramer acetate, and 3.3% in placebo.
Selective reporting (reporting bias)	High risk	The published report included all prespecified primary benefit outcomes. However, disability confirmed at 6 months was not reported in the published report; it was reported by the FDA in terms of survival probabilities.
Other bias	High risk	The study was sponsored by Biogen Idec; "*data were analyzed by the sponsor*" (page 1088), and 6 co-authors of the published paper were affiliated to the pharmaceutical company.

DECIDE 2015

Study characteristics

Methods	RCT

DECIDE 2015 *(Continued)*

Participants	Age: 18-55 years; clinically definite RRMS; mean disease duration 7 years; mean EDSS 2.5; prior use of DMT at any time prior to the start of study: 41.1% (41.3% in daclizumab 150 mg and 40.8% in IFNc-1a 30 pg)
Interventions	Daclizumab 150 mg subcutaneously once every 4 weeks for 24 to 36 months Interferon beta-1a (Avonex) 30 µg intramuscularly once a week for 24 to 36 months
Outcomes	Primary outcome measures: • ARR at 3 years Secondary outcome measures (time frame: 2 years): • Number of new or newly enlarging T2 hyperintense lesions on brain MRI • Proportion of subjects with sustained (for 3 months) disability worsening • Proportion of subjects who are relapse-free • Proportion of subjects with a ≥ 7.5 point worsening from baseline in the MSIS-29 physical score
Notes	Sponsor: Biogen Idec ClinicalTrials.gov Identifier: NCT01064401

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was conducted with the use of a centralized interactive voice response system and stratified according to study site and prior use of interferon beta with the use of permuted-block randomization".
Allocation concealment (selection bias)	Low risk	"Randomization was conducted with the use of a centralized interactive voice response system".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All the patients and study personnel, including the treating neurologists, were unaware of the treatment assignments." "To prevent unblinding based on influenza-like symptoms following interferon beta-1a injection, patients were instructed to take nonsteroidal anti-inflammatory drugs (e.g. acetaminophen [paracetamol], ibuprofen, naproxen, aspirin) at the dose and frequency according to local labels before and for 24 hours after each injection of interferon beta-1a or matching placebo. To minimize unblinding that could potentially occur during routine clinical care, the study was designed so that there were separate study personnel who treated patients and who conducted efficacy assessments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All the efficacy assessments were performed by trained, certified, examining neurologists or technicians who were not involved in other aspects of care of the patients in the study". "Original data for MRI images were transferred from each site to the MRI reading center for blinded evaluation".
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All the patients who underwent randomization received a dose of the study drug and were included in the intention-to-treat population."
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	Supported by Biogen and AbbVie Biotherapeutics.

DECIDE 2015 *(Continued)*

	quote: "Data were collected by the investigators, were analyzed by the sponsors, and remained confidential during the study. All the authors were involved in each stage of the manuscript development, made the decision to submit the manuscript for publication, and take responsibility for the accuracy and completeness of the data and analyses. The sponsors reviewed and provided feedback on the manuscript to the authors, who had full editorial control of the manuscript". Four co-authors of the published paper were affiliated to the pharmaceutical company.

DEFINE 2012

Study characteristics	
Methods	RCT
Participants	Age: 18 to 55 years; clinically definite RRMS; mean disease duration (time since diagnosis) 6 years; mean EDSS 2.4; prior use of DMT at any time prior to the start of study: 40.7% (40.4% in dimethyl fumarate 240 mg 3 times daily, 39.5% in dimethyl fumarate 240 mg 2 times daily, and 42.2% in placebo)
Interventions	Dimethyl fumarate 240 mg oral capsule 3 times daily for 24 months (n = 416) Dimethyl fumarate 240 mg oral capsule 2 times daily for 24 months (n = 411) Placebo oral capsule 3 times daily for 24 months (n = 410)
Outcomes	Relapse at 12 and 24 months. Disability worsening at 24 months
Notes	Funding: Biogen Idec

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Patients were randomly assigned, in a 1:1:1 ratio, to receive BG-12 at a dose of 240 mg twice daily, BG-12 at a dose of 240 mg three times daily, or placebo. Randomization was performed centrally and was stratified according to site*" (page 1100).
Allocation concealment (selection bias)	Low risk	"*Randomization was performed centrally*" (page 1100), and "*Randomization took place across all study sites using a centralized Interactive Voice Response System (IVRS)*" (page 33 of Protocol).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*Double-blind*", and "*To ensure that the study-group assignments would not be revealed, patients were instructed to take the assigned study drug at least 4 hours before study visits, in case patients in the BG-12 groups had a side effect of flushing*" (page 1100). Since flushing is a known side effect of dimethyl fumarate, patients were possibly not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*To maintain concealment of the study-group assignments, each study center used separate examining and treating neurologists (all of whom remained unaware of the assignments throughout the trial). The examining neurologists conducted neurologic assessments, including assessment of the EDSS score, whereas the treating neurologists were responsible for all aspects of patient care, including the treatment of relapses and other disease symptoms*" and "*relapses were evaluated by an independent neurologic evaluation committee, whose*

DEFINE 2012 *(Continued)*

		members reviewed a standardized set of blinded clinical records (which did not include MRI data) from the treating and examining neurologists" (page 1100).
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 23.0% were lost to follow-up (23.1% in dimethyl fumarate 240 mg 3 times daily, 23.4% in dimethyl fumarate 240 mg 2 times daily, and 22.7% in placebo), with some indication of the differences in reasons: AEs of 8.7% in dimethyl fumarate 240 mg 3 times daily, 9.8% in dimethyl fumarate 240 mg 2 times daily, and 5.4% in placebo.
Selective reporting (reporting bias)	High risk	The published report included all prespecified primary benefit outcomes. However, disability confirmed at 6 months was not reported in the published report; it was reported by the FDA in terms of survival probabilities.
Other bias	High risk	The study was sponsored by Biogen Idec, "*data were analyzed by the sponsor*" (page 1099), and four co-authors of the published paper were affiliated to the pharmaceutical company.

Etemadifar 2006

Study characteristics	
Methods	RCT
Participants	Age: 15-50 years; clinically definite RRMS; mean disease duration 3 years; mean EDSS 2.0; all participants were previously untreated patients.
Interventions	IFNc-1b (Betaseron) 250 pg subcutaneously every other day for 24 months (n = 30) IFNc-1a (Avonex) 30 pg intramuscularly once a week for 24 months (n = 30) IFNc-1a (Rebif) 44 pg subcutaneously three times a week for 24 months (n = 30)
Outcomes	Relapse at 24 months
Notes	No information provided about funding and role of the sponsor

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The trial was single-blinded in that patients were aware but physicians who assessed the outcome were unaware of the treatment type that the patient had received".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"One physician who did not know which patients had received which treatment made clinical evaluation of all patients."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Statistical analysis was based on an intention-to treat principle". No dropouts from the study

Etemadifar 2006 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	No information provided about funding and role of the sponsor

Etemadifar 2007

Study characteristics	
Methods	RCT
Participants	Age: 13 to 50 years; clinically definite RRMS; mean disease duration not reported ("*short duration*"); mean EDSS 1.5; all participants were previously untreated patients.
Interventions	Azathioprine 3 mg/kg body weight oral daily for 12 months (n = 47) Interferons beta (Betaseron, Avonex, or Rebif) for 12 months (n = 47: 15 Betaseron 250 µg subcutaneously every other day, 19 Avonex 30 µg intramuscularly once a week, 13 Rebif 44 µg subcutaneously 3 times a week)
Outcomes	Relapse at 12 months and withdrawals due to AEs
Notes	No information provided about funding and role of the sponsor

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Patients were randomized according to a preexisting list produced by a computer program that differed from a random number generator only in that it assigned equal numbers of patients into each treatment group*" (page 1724).
Allocation concealment (selection bias)	Unclear risk	"*The first treatment group received $IFN\beta$ products regimen. The second group received AZA*" (page 1724).
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*The trial was single-blinded in that patients were aware but physicians who assessed the outcome were unaware of treatment type that the patient was receiving*" (page 1724).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The trial was single-blinded in that patients were aware but physicians who assessed the outcome were unaware of treatment type that the patient was receiving*", and "*Two neurologists (ME and VS) who did not know which patients had received which treatment clinically evaluated all patients*" (pages 1724-5).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 6.4% were lost to follow-up (6.4% in azathioprine and 6.4% in interferon beta), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Unclear risk	No information provided about funding and role of the sponsor

Fazekas 1997

Study characteristics	
Methods	RCT
Participants	Age: 15 to 64 years; clinically definite RRMS; mean disease duration 7 years; mean EDSS 3.3; prior use of DMT not reported
Interventions	Immunoglobulins 0.15 to 0.20 g/kg body weight intravenously monthly for 24 months (n = 75) Placebo intravenously monthly for 24 months (n = 75)
Outcomes	Relapse at 24 months. Disability worsening at 24 months
Notes	Funding: Sero-Merieux (Vienna, Austria)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Centralised computer-generated randomisation schedule with stratification by centre, age, sex, and deterioration rate*" (page 590)
Allocation concealment (selection bias)	Low risk	"*Randomly and centrally allocated*" and "*Infusions of IVIg and placebo were identical in appearance and were stored in plastic bags for concealment during administration*" (page 590).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*At each monthly visit a neurologist who was aware of treatment allocation (treating physician) administered the study medication and asked the patient about any side-effects*" (page 590).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Patients were assessed on the first day of treatment, every 6 months, and at the end of the 2-year study by a different neurologist (assessing physician) who was unaware of treatment allocation*", and "*All patients were told to contact their centre as soon as there was any change in their condition. In such cases, the assessing physician examined the patient to confirm a possible relapse and to assess the severity of the disability*" (page 590).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 1.3% were lost to follow-up (0% in immunoglobulins and 2.7% in placebo), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Unclear risk	The study was sponsored by Triton Biosciences and the role of the study sponsor was unclear.

FREEDOMS 2010

Study characteristics	
Methods	RCT

FREEDOMS 2010 *(Continued)*

Participants	Age: 18 to 55 years; clinicaly definite RRMS; mean disease duration 8 years; mean EDSS 2.4; prior use of DMT at any time prior to the start of study: 40.9% (39.6% in fingolimod 1.25 mg, 42.6% in fingolimod 0.5 mg, and 40.4% in placebo)
Interventions	Fingolimod 1.25 mg oral capsule once daily for 24 months (n = 429) Fingolimod 0.5 mg oral capsule once daily for 24 months (n = 425) Placebo oral capsule once daily for 24 months (n = 418)
Outcomes	Relapse at 12 and 24 months. Disability worsening at 24 months
Notes	Funding: Novartis Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Patients were randomly assigned, in a 1:1:1 ratio, to receive oral fingolimod capsules in a dose of 0.5 mg or 1.25 mg or matching placebo ... Randomization was performed ... with the use of stratification according to site, with a block size of six within each site*" (page 388).
Allocation concealment (selection bias)	Unclear risk	"*Randomization was performed centrally, with the use of a validated system*" (page 388).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*Double-blind*" (page 388)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*To ensure that all assessments remained unbiased regarding the study-group assignments (i.e. unaffected by awareness of them), an independent, specially trained and certified examining neurologist determined all the EDSS scores*" (page 388). "*Relapses were verified by the examining neurologist within 7 days after the onset of symptoms*" (page 389).
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 18.8% were lost to follow-up (22.6% in fingolimod 1.25 mg, 13.2% in fingolimod 0.5 mg, and 20.6% in placebo), with some indication of the differences in reasons: 3.0% unsatisfactory therapeutic effect in fingolimod 1.25 mg, 1.4% in fingolimod 0.5 mg, and 6.0% in placebo; and abnormal laboratory values(s) 4.7% in fingolimod 1.25 mg, 2.1% in fingolimod 0.5 mg, and 0.2% in placebo.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	The study was sponsored by Novartis Pharma: "*data were analyzed by the sponsor*" (page 388), and 4 co-authors of the published paper were affiliated to the pharmaceutical company.

FREEDOMS II 2014

Study characteristics

Methods	RCT

FREEDOMS II 2014 *(Continued)*

Participants	Age: 18 to 55 years; clinically definite RRMS; mean disease duration 11 years; mean EDSS 2.4; prior use of DMT at any time prior to the start of study: 74.8% (77.6% in fingolimod 1.25 mg, 73.7% in fingolimod 0.5 mg, and 73.0% in placebo)
Interventions	Fingolimod 1.25 mg oral capsule once daily for 24 months (n = 370) Fingolimod 0.5 mg oral capsule once daily for 24 months (n = 358) Placebo oral capsule once daily for 24 months (n = 355) "*After review of data from the FREEDOMS and TRANSFORMS phase 3 studies, completed on Nov 12, 2009, after consultation with and at the recommendation of the data and safety monitoring board, we decided to stop the 1·25 mg dose. Patients on the high dose were subsequently switched to the 0·5 mg dose in a blinded manner*" (page 546)
Outcomes	Relapse at 12 and 24 months. Disability worsening at 24 months
Notes	Funding: Novartis Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*We randomly allocated patients (1:1:1; stratified by study centre) to receive oral fingolimod capsules in a dose of 0.5 mg or 1.25 mg or matching placebo, once daily for 24 months. The randomisation sequence was generated with an automated system under the supervision of the Novartis Drug Supply Management team*" (page 546).
Allocation concealment (selection bias)	Unclear risk	"*To mask treatment allocation, both fingolimod and placebo were dispensed in hard gelatin capsules of identical colour and size and packed in identical bottles*" (page 546).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Patients, investigators, site personnel, independent evaluating physician, first dose administrator and all Novartis personnel were blinded to the study medication assignments from the time of randomisation until the database lock and data analysis for the double-blind Treatment Phase was completed*" (Appendix, page 2).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The efficacy assessments (i.e. confirmation of relapses, scheduled EDSS, ...) were done by an independent, specially trained, and certified assessor not otherwise involved in the treatment of patients)*" (page 546); "*Patients were instructed not to discuss adverse events with the independent evaluating physician*"; "*Another physician not otherwise involved in the care of the study patient monitored patients for 6 or more hours after administration of the first dose of the study drug to maintain blind for the known heart rate decrease with fingolimod upon first dose administration*"; "*Clinical assessments were performed at screening and at randomization (baseline), and study visits were scheduled at 2 weeks and 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24 months after randomization*"; and "*In the case of MS relapse EDSS assessment was required at every unscheduled visit to confirm relapse*" (Appendix, page 2).
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 28.2% were lost to follow-up (32.2% in fingolimod 1.25 mg, 24.0% in fingolimod 0.5 mg, and 28.2% in placebo), with some indication of the differences in reasons: unsatisfactory therapeutic effect 2.7% in fingolimod 1.25 mg, 1.7% in fingolimod 0.5 mg, and 4.8% in placebo; and adverse events or abnormal laboratory values(s): 12.7% in fingolimod 1.25 mg, 10.1% in fingolimod 0.5 mg, and 5.1% in placebo.

FREEDOMS II 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	The study was sponsored by Novartis Pharma: "*The study sponsor participated in the design of the study, conduct of the study, data collection, data management, data analysis and interpretation, and preparation, review, and approval of the paper*" (page 550), and 4 co-authors of the published paper were affiliated to the pharmaceutical company.

GALA 2013

Study characteristics		
Methods	RCT	
Participants	Age: 18 to 55 years; clinically definite RRMS; mean disease duration 8 years; mean EDSS 2.8; prior use of DMT at any time prior to the start of study: 13.6% (13.6% in glatiramer acetate and 13.7% in placebo)	
Interventions	Glatiramer acetate 40 mg subcutaneously 3 times a week for 12 months (n = 943) Placebo subcutaneously 3 times a week for 12 months (n = 461)	
Outcomes	Relapse at 12 months	
Notes	Funding: Teva Pharmaceutical Industries	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Eligible patients were assigned to treatment groups in a 2:1 ratio (GA 40 mg tiw or placebo) according to the randomization scheme produced. The randomization scheme used constrained blocks stratified by center*" (page 706).
Allocation concealment (selection bias)	Unclear risk	"*Study drugs were packaged and labeled in a way that maintained the masked nature of the study; the appearance, shape, color, and smell were identical*" (page 706).
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*The investigators, the sponsor, and any personnel involved in patients' assessments, monitoring, analysis, and data management were blinded to treatment assignment*" (page 706).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Patients' general medical assessments were performed separately from the neurological assessments by 2 neurologists or physicians. The examining neurologist/physician was responsible for all neurological assessments*" and "*All follow-up neurological examinations were performed by the blinded examining neurologist*" (pages 706-7).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 8.2% were lost to follow-up (8.9% in glatiramer acetate and 6.7% in placebo), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.

GALA 2013 *(Continued)*

Other bias	High risk	"*This study was funded by Teva Pharmaceutical Industries, Petah Tikva, Israel. All members of the clinical advisory board, the country principal investigators, the Data Monitoring Committee (DMC), and the MRI Reading Center were reimbursed for their specific services on a contractual basis by Teva Pharmaceutical Industries*" (page 711).

Gobbi 2013

Study characteristics	
Methods	RCT
Participants	Age: 20 to 60 years; clinically definite RRMS; mean disease duration 11 years; median EDSS 3; prior use of DMT (natalizumab) for at least 12 months
Interventions	Interferon beta-1b (Betaferon) 250 ug every other day subcutaneously (n = 9) Natalizumab 300 mg monthly intravenously (n = 10)
Outcomes	Relapse at 12 months, withdrawals due to AE, SAEs, quality of life, cognitive decline, new or enlarging T2-weighted magnetic resonance imaging (MRI) lesions
Notes	This clinical trial is an investigator-initiated study for which no external funding was received.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "prospective, controlled, randomized, rater blinded, parallel-group, monocentric pilot study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "prospective, controlled, randomized, rater blinded, parallel-group, monocentric pilot study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts from the study
Selective reporting (reporting bias)	High risk	Quality of life and cognitive function reported as secondary outcomes in the protocol but results not reported in the final publication
Other bias	Low risk	The study appears to be free of other sources of bias. Quote: "no external funding was received."

GOLDEN 2017

Study characteristics	
Methods	RCT
Participants	Age: 18-60 years; clinically definite RRMS; mean disease duration 5 years; mean EDSS 2.6; prior use of DMT at any time prior to the start of study: 50.9% (52.5% in fingolimod, and 46.4% in IFNß-1b).
Interventions	Fingolimod 0.5 mg orally once daily for 18 months (n = 106) IFNß-1b (Betaseron) 250 pg subcutaneously every other day for 18 months (n = 51)
Outcomes	Relapse at 12 months, withdrawals due to AEs, SAEs, cognitive decline
Notes	The study was funded by Novartis Pharm, the first author was paid by the sponsor and two co-authors were affiliated to the sponsor.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"At baseline, eligible patients were randomised (2:1) to receive oral fingolimod (0.5 mg/day) or subcutaneous IFN β-1b (250 µg every other day; Fig. 1)" (page 2438).
Allocation concealment (selection bias)	Unclear risk	"At baseline, eligible patients were randomised (2:1) to receive oral fingolimod (0.5 mg/day) or subcutaneous IFN β-1b (250 µg every other day; Fig. 1)" (page 2438).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Rater-blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 19.1% was lost-to follow-up (8.5% in fingolimod, and 23.4% in IFNβ-1b), with some indications of differences in reasons: unsatisfactory therapeutic effect of 0.9% in fingolimod, and 13.7% in IFNβ.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified outcomes.
Other bias	High risk	The study was funded by Novartis Pharm, the first author was paid by the sponsor and two co-authors were afiliated to the sponsor.

Goodkin 1991

Study characteristics	
Methods	RCT
Participants	Age: 18 to 65 years; definite RRMS; mean disease duration 6 years; mean EDSS 3.5; prior use of DMT not reported

Goodkin 1991 *(Continued)*

Interventions	Azathioprine 3.0 mg/kg body weight oral daily for 24 months (n = 30) Placebo oral daily for 24 months (n = 29)
Outcomes	Relapse at 12 and 24 months, disability worsening at 24 months, withdrawals due to AEs
Notes	Funding: Wellcome Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Randomised by the statistician using random number tables*" (page 21)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and personnel were blinded, "*group PLC received indistinguishable placebo*", and "*whenever the treating physician made a dose change for an AZA patient, a similar dose change was simultaneously made for a matched placebo patient to preserve the blind*" (pages 20-1).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Each patient had the same masked examining neurologist and unmasked treating neurologist for the duration of the study. Standardized neurologic examinations were recorded at study entry and at 6 month intervals by the examining neurologist unless the patient reported subjective worsening, in which case an examination was performed as soon as was practical*" (page 21).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 11.9% were lost to follow-up (10.0% in azathioprine and 13.8% in placebo), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Unclear risk	The study was sponsored by Wellcome company and the role of the study sponsor was unclear.

IFNB MS Group 1993

Study characteristics

Methods	RCT
Participants	Age: 18 to 50 years; clinically definite RRMS; mean disease duration (time since diagnosis) 4 years; mean EDSS 2.9; prior use of DMT not reported
Interventions	Interferon beta-1b (Betaseron) 250 µg subcutaneously every other day for 24 months (n = 124) Interferon beta-1b (Betaseron) 50 µg subcutaneously every other day for 24 months (n = 125) Placebo subcutaneously every other day for 24 months (n = 123)
Outcomes	Relapse at 24 and 36 months, disability worsening at 24 months, withdrawals due to AEs

IFNB MS Group 1993 *(Continued)*

Notes	Funding: Triton Biosciences, Inc., Alameda, CA and Berlex Laboratories Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*Each placebo vial contained only similar quantity of albumin and dextrose*"; "*All personnel were blinded to treatment categories*"; and "*One treating neurologist who knew about side effects, reviewed laboratory findings for toxicity, and was responsible for overall care*" (page 656).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*One neurologist who was not aware of drug side effects to do the periodic examinations*" (page 656). However, it is not clear how and when potential relapses and EDSS were assessed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall, 9.1% were lost to follow-up (7.3% in interferon beta-1b 250 µg, 11.2% in interferon beta-1b 50 µg, and 8.9% in placebo). Nothing was said about the reasons for study discontinuation.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Unclear risk	The study was sponsored by Triton Biosciences and the role of the study sponsor was unclear.

INCOMIN 2002

Study characteristics

Methods	RCT
Participants	Age: 18 to 50 years; definite RRMS; mean disease duration (time since diagnosis) 6 years; mean EDSS 2.0; all participants were previously untreated patients.
Interventions	Interferon beta-1b (Betaseron) 250 µg subcutaneously every other day for 24 months (n = 96) Interferon beta-1a (Avonex) 30 µg intramuscularly once a week for 24 months (n = 92)
Outcomes	Relapse at 24 months, disability worsening at 24 months, withdrawals due to AEs, new or enlarging T2-weighted MRI lesions, new gadolinium-enhancing positive T1-weighted MRI lesions
Notes	Funding: the Italian Ministry of Health and the Italian MS Society

Risk of bias

Bias	Authors' judgement	Support for judgement

INCOMIN 2002 *(Continued)*

Random sequence generation (selection bias)	Low risk	"*Randomisation followed computer-generated random sequences of digits that were different for each centre and for each sex, to achieve centre and sex stratification*" (page 1454).
Allocation concealment (selection bias)	Low risk	"*The codes were randomly assigned to treatments by an independent team of statisticians unaware of the patient's clinical characteristics*" (page 1454).
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*All clinical outcomes were assessed in an open-label manner*" (page 1454).
Blinding of outcome assessment (detection bias) All outcomes	High risk	"*All clinical outcomes were assessed in an open-label manner*" (page 1454).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall, 3.2% were lost to follow-up (2.1% in interferon beta-1b and 4.3% in interferon beta-1a). Nothing was said about the reasons for study discontinuation.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

Johnson 1995

Study characteristics		
Methods	RCT	
Participants	Age: 18 to 45 years; definite RRMS; mean disease duration 7 years; mean EDSS 2.6; prior use of DMT not reported	
Interventions	Glatiramer acetate 20 mg subcutaneous daily for 24 months (n = 125) Placebo (not described) (n = 126)	
Outcomes	Relapse at 24 months, disability worsening at 24 months, withdrawals due to AEs, SAEs	
Notes	Funding: Teva Pharmaceutical	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*A centralized randomization scheme was used*" (page 1270).
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	"*Treating neurologists were blinded*" (page 1270).

Johnson 1995 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Examining neurologists were blinded*" (page 1270).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 14.3% were lost to follow-up (15.2% in glatiramer acetate and 13.5% in placebo), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	The study was funded by Teva Pharmaceutical and some co-authors of the published paper were affiliated to the pharmaceutical company.

Knobler 1993

Study characteristics	
Methods	RCT
Participants	Age: 18-50 years; clinically definite RRMS; mean disease duration 7 years; mean EDSS 3.1; prior use of DMT not reported
Interventions	IFNc-1b (Betaseron) 25 pg subcutaneously three times weekly for 36 months (n = 6) IFNc-1b (Betaseron) 125 pg subcutaneously three times weekly for 36 months (n = 6) IFNc-1b (Betaseron) 250 pg subcutaneously three times weekly for 36 months (n = 6) IFNc-1b (Betaseron) 500 pg subcutaneously three times weekly for 36 months (n = 6) Placebo for 36 months (n = 7)
Outcomes	Relapse at 36 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Were randomized into five equal groups of 6 patients each, after signing an informed consent" (page 335)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and investigators had no prior knowledge of the relationship between the injection volume delivered and the dosage group to which patients were assigned" (page 334).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"To secure double-blinding, one neurologist at each center performed the neurological examination for each patient and verified clinical exacerbations. A second neurologist independently evaluated the battery of clinical laboratory tests of hematological, renal, and hepatic functions performed at regular 3-month intervals to identify adverse reactions" (page 335).

Knobler 1993 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	High risk	The published report did not report AEs. "A second neurologist independently evaluated the battery of clinical laboratory tests of hematological, renal, and hepatic functions performed at regular 3-month intervals to identify adverse reactions. At each patient visit, a nurse coordinator collected patient diaries of daily events and documented adverse events noted in these records" (page 335).
Other bias	High risk	The study was sponsored by Triton Biosciences, and 4 co-authors of the published paper were affiliated to the pharmaceutical company.

Koch-Henriksen 2006

Study characteristics		
Methods	RCT	
Participants	Age: 18 to 55 years; definite RRMS; mean disease duration 8 years; mean EDSS 2.9; prior use of DMT not reported	
Interventions	Interferon beta-1b (Betaseron) 250 µg subcutaneously every other day for 24 months (n = 158) Interferon beta-1a (Rebif) 22 µg subcutaneously once a week for 24 months (n = 143)	
Outcomes	Relapse at 24 months. Disability worsening at 24 months	
Notes	Funding: not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*The randomization algorithm was adjusted to reduce deviations from a 50/50 result in each center*" (page 1057).
Allocation concealment (selection bias)	Low risk	"*A central computerized randomization schedule assigned patients to treatment*" (page 1057).
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Blinding was abandoned because it could not be maintained owing to the different administration schemes of the two study drugs*" (page 1057).
Blinding of outcome assessment (detection bias) All outcomes	High risk	"*Open-label trial*" (page 1057)
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 25.6% were lost to follow-up (27.8% in interferon beta-1b and 23.1% in interferon beta-1a), with some indication of the differences in reasons: "*The main cause of withdrawal in the IFN-1b 250 g arm was side effects (24/158, 15.2%), and treatment failure was the most frequent cause in the IFN-1a arm (15/143, 10.5%)*" (page 1057).

Koch-Henriksen 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Unclear risk	It is unclear if the study was sponsored.

Lewanska 2002

Study characteristics		
Methods	RCT	
Participants	Age: 18 to 55 years; definite RRMS; mean disease duration 9 years; mean EDSS 3.0; prior use of DMT not reported	
Interventions	Immunoglobulins 0.2 g/kg body weight intravenously monthly for 12 months (n = 17) Immunoglobulins 0.4 g/kg body weight intravenously monthly for 12 months (n = 16) Placebo intravenously monthly for 12 months (n = 18)	
Outcomes	Relapse at 12 months, withdrawals due to AEs	
Notes	Funding: Supported by the KBN (State Research Committee)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*The generation of allocation sequence was based on random-number table*" (page 566).
Allocation concealment (selection bias)	Unclear risk	"*Infusions of intravenous immunoglobulins and placebo were stored in identical opaque plastic bags for concealment during administration*" (page 566).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Evaluating physician was unaware of the actual treatment allocation. Before entry to the study, and monthly thereafter during the study and 3 months after the end of the study, each patient was examined blindly by the same neurologist who was unaware of treatment allocation. Monitoring and recording of relapses, concomitant treatment, side-effects or other medical events were documented throughout the study*" (page 566).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 3.9% were lost to follow-up (6.3% in immunoglobulins 0.4 g/kg, 0% in immunoglobulins 0.2 g/kg, and 5.6% in placebo), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

MAIN 2014

Study characteristics	
Methods	RCT
Participants	Age: 18 to 55 years; definite RRMS; mean disease duration 6 years; mean EDSS 1.9; prior use of DMT at any time prior to the start of study: 6.0% (6.5% in azathioprine and 5.5% in interferon beta)
Interventions	Azathioprine 3 mg/kg body weight oral daily for 24 months (n = 77) Interferons beta (Betaseron, Avonex, or Rebif) for 24 months (n = 73: 5 Betaseron 250 µg subcutaneously every other day, 26 Avonex 30 µg intramuscularly once a week, 35 Rebif 22 µg subcutaneously 3 times a week, 7 Rebif 44 µg subcutaneously 3 times a week)
Outcomes	Relapse at 12 and 24 months, disability worsening at 24 months, withdrawals due to AEs
Notes	Funding: AIFA (Italian Medicines Agency)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Patients were selected for AZA or IFNs using a randomization list (1:1 ratio), in blocks of four and stratified by disability score (EDSS ≤ 3.5 or > 3.5)*".
Allocation concealment (selection bias)	Low risk	"*Patients were selected for AZA or IFNs using a computer generated central randomization list*".
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Single-masked*"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"*Patients were assessed by an un-masked treating and a masked examining neurologist at their centers*", and "*The masked examining neurologist was responsible for the neurological examination and EDSS scoring at scheduled (every six months) and unscheduled visits, requested by the treating neurologist to confirm relapses*". Relapse assessment was not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 15.3% were lost to follow-up (19.5% in azathioprine and 11.0% in interferon beta), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

Millefiorini 1997

Study characteristics	
Methods	RCT
Participants	Age: 18 to 45 years; definite RRMS; mean disease duration 5 years; mean EDSS 3.6; prior use of DMT not reported

Millefiorini 1997 *(Continued)*

Interventions	Mitoxantrone 8 mg/m² of body surface intravenously monthly for 12 months (total dosage of 96 mg/m² of body surface over 12 months) (n = 27) Placebo intravenously monthly for 12 months (n = 24)
Outcomes	Relapse at 12 and 24 months, disability worsening at 24 months, withdrawals due to AEs
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Patients were randomized to MTX or placebo using a scheme stratified on age, sex and EDSS which resulted in eight different age/sex/EDSS strata. According to the study protocol, within each stratum the allocation of patients to treatment or placebo was balanced by using a block design of size eight*" (page 154).
Allocation concealment (selection bias)	Low risk	"*Central allocation and the intravenous bag and tubing were black to ensure no differences between the treatment groups*" (page 154).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treating physicians were not blinded. Unclear blinding of patients
Blinding of outcome assessment (detection bias) All outcomes	High risk	"*Monitoring and recording of exacerbations, concomitant therapy or other medical events were documented throughout the study by a treating physician selected in each centre before the beginning of the study. The treating physician was not blinded to study treatment*", and "*In order to maintain blindness, the interaction of the EDSS physicians with the patient was strictly restricted to the neurological examination. The neurologist was not allowed to talk with the patient about adverse events, or any other issue which could potentially disclose the patient's treatment*" (page 154).
Incomplete outcome data (attrition bias) All outcomes	Low risk	None were lost to follow-up.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	Unclear risk	It is unclear if this study was sponsored.

Mokhber 2014

Study characteristics

Methods	RCT
Participants	Mean age 29 years; clinically definite RRMS; disease duration not reported; mean EDSS 2.0; all participants were previously untreated patients.
Interventions	IFNß-1a (Avonex) 30 pg intramuscularly once per week for 12 months (n = 23) IFNß-1a (Rebif) 44 pg subcutaneously three times per week for 12 months (n = 23) IFNß-1b (Betaseron) 250 pg subcutaneously every other day for 12 months (n = 23)

Mokhber 2014 *(Continued)*

Outcomes	Quality of life, cognitive decline
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The study neurologist (MRA) enrolled the participants and allocated the subjects using a computer-generated list of random numbers to the 3 treatment groups of three distinct commercially available forms of interferon beta" (page 17).
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Participants and all those assessing outcomes were blinded to the treatment groups"; "The study psychologist (MMG) and neuropsychiatrist (NM), both blinded to the treatment groups, evaluated the cognitive function before treatment, and 12 months after treatment" (page 18).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 5.8% was lost-to follow-up (13.0% in Avonex, 0% in Rebif, and 4.3% in Betaseron), without indications of differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

MSCRG 1996

Study characteristics

Methods	RCT
Participants	Age: 18 to 55 years; clinically definite RRMS; mean disease duration 7 years; mean EDSS 2.4; all participants were previously untreated patients.
Interventions	Interferon beta-1a (Avonex) 30 µg intramuscularly once a week for 24 months (n = 158) Placebo intramuscularly once a week for 24 months (n = 143)
Outcomes	Relapse at 12 and 24 months, disability worsening at 24 months, mortality
Notes	Funding: Biogen, Inc, Cambridge, MA

Risk of bias

Bias	Authors' judgement	Support for judgement

MSCRG 1996 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"*Randomisation performed at statistical centre of Buffalo General Hospital, one of the participating centres (biased coin assignment used for sequence generation)*" (page 286)
Allocation concealment (selection bias)	Unclear risk	"*Schedule sent to each clinical centre; included patients were sequentially assigned the next ID number from the schedule*" (page 286).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*Personnel and participants were blinded to treatment status*" (page 286).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Evaluating physicians were blinded to treatment status*" (page 286).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 42.9% were lost to follow-up (46.2% in interferon beta-1a and 39.2% in placebo). The study stopped early for benefit without a formal-stopping rule.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	The study was sponsored by Biogen and "*Personnel of the study sponsor (Biogen) were involved in the conduct and data analysis*" (page 293).

OPERA I 2017

Study characteristics	
Methods	RCT
Participants	Age: 18-55 years; clinically definite RRMS; mean disease duration 4 years; mean EDSS 2.8; prior use of DMT in the 2 years prior to the start of study: 27.4% (26.2% in ocrelizumab, and 28.6% in IFNc-1a)
Interventions	Ocrelizumab 600 mg intravenously every 6 months for 24 months, with a dual infusion of 300 mg on days 1 and 15 for the first dose and as a single 600 mg infusion thereafter (n = 410) IFNc-1a (Rebif) 44 pg subcutaneously three times weekly for 24 months (n = 411)
Outcomes	Disability worsening at 24 months, withdrawals due to AEs, SAEs, quality of life, new or enlarging T2-weighted MRI lesions, new gadolinium-enhancing positive T1-weighted MRI lesions, mortality
Notes	Sponsor: Hoffmann-La Roche ClinicalTrials.gov Identifier: NCT01247324

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization of patients was stratified by region (US/rest of the world) and baseline EDSS score (less than 4/greater than or equal to 4)" (Appendix, page 5).

OPERA I 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Randomization was performed centrally with the use of an independent interactive Web-response system" (page 223).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial" (page 223).
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 14.0% was lost-to follow-up (10.7% in ocrelizumab, and 17.3% in IFNβ-1a), with some indications of differences in reasons: unsatisfactory therapeutic effect of 2.0% in ocrelizumab, and 2.9% in IFNβ-1a; and adverse events of 3.2% in ocrelizumab, and 6.3% in IFNβ-1a.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified outcomes.
Other bias	High risk	The study was sponsored by Hoffmann-La Roche and data were analysed by the sponsor (page 222). Four co-authors of the published paper were affiliated to the pharmaceutical company and the last author was paid by the sponsor.

OPERA II 2017

Study characteristics	
Methods	RCT
Participants	Age: 18-55 years; clinically definite RRMS; mean disease duration 4 years; mean EDSS 2.8; prior use of DMT in the 2 years prior to the start of study: 25.9% (27.1% in ocrelizumab, and 24.7% in IFNc-1a)
Interventions	Ocrelizumab 600 mg intravenously every 6 months for 24 months, with a dual infusion of 300 mg on days 1 and 15 for the first dose and as a single 600 mg infusion thereafter (n = 417) IFNc-1a (Rebif) 44 pg subcutaneously three times weekly for 24 months (n = 418)
Outcomes	Disability worsening at 24 months, withdrawals due to AEs, SAEs, quality of life, new or enlarging T2-weighted MRI lesions, new gadolinium-enhancing positive T1-weighted MRI lesions, mortality
Notes	Sponsor: Hoffmann-La Roche ClinicalTrials.gov Identifier: NCT01412333

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization of patients was stratified by region (US/rest of the world) and baseline EDSS score (less than 4/greater than or equal to 4)" (Appendix, page 5).
Allocation concealment (selection bias)	Low risk	"Randomization was performed centrally with the use of an independent interactive Web-response system" (page 223).

OPERA II 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial" (page 223).
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 18.6% was lost-to follow-up (13.7% in ocrelizumab, and 23.4% in IFNβ-1a), with some indications of differences in reasons: unsatisfactory therapeutic effect of 1.4% in ocrelizumab, and 3.6% in IFNβ-1a; and adverse events of 4.1% in ocrelizumab, and 6.2% in IFNβ-1a.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified outcomes.
Other bias	High risk	The study was sponsored by Hoffmann-La Roche and data were analysed by the sponsor (page 222). Four co-authors of the published paper were affiliated to the pharmaceutical company and the last author was paid by the sponsor.

OPTIMUM 2021

Study characteristics	
Methods	RCT
Participants	Age: 18-55 years; clinically definite RRMS; mean disease duration 8 years; mean EDSS 2.57; prior use of DMT in the 2 years prior to the start of study: 37.42% (38% in ponesimod, and 37% in teriflunomide)
Interventions	Ponesimod 20 mg once daily for 9 months (n = 567) Teriflunomide 14 mg once daily for 9 months (n = 566)
Outcomes	Relapse at 24 months, disability worsening at 24 months, SAEs, withdrawals due to AEs, mortality
Notes	The study was sponsored by Actelion Pharmaceuticals, part of Janssen Pharmaceutical Companies.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Each of the study sites will be assigned a unique site number, and every subject will receive a unique screening number (= subject number), which identifies the subject throughout the study. After having confirmed the eligibility of the subject and prior to the start of study treatment, the investigator/delegate contacts the interactive response technology (IRT) at visit 3 to randomize the subject. The IRT assigns a randomization number to the subject and assigns the treatment kit number, which matches the treatment arm assigned by the randomization list to the randomization number of each subject. The randomization list is generated by an independent CRO (ALMAC Clinical technologies, see contact details in the IRT manual) and kept strictly confidential." (page 90 of Protocol)
Allocation concealment (selection bias)	Low risk	"Each of the study sites will be assigned a unique site number, and every subject will receive a unique screening number (= subject number), which identi-

OPTIMUM 2021 *(Continued)*

		fies the subject throughout the study. After having confirmed the eligibility of the subject and prior to the start of study treatment, the investigator/delegate contacts the interactive response technology (IRT) at visit 3 to randomize the subject. The IRT assigns a randomization number to the subject and assigns the treatment kit number, which matches the treatment arm assigned by the randomization list to the randomization number of each subject. The randomization list is generated by an independent CRO (ALMAC Clinical technologies, see contact details in the IRT manual) and kept strictly confidential." (Page 90 protocol).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"This study will be performed in a double-blind fashion. The investigator and study staff, the subjects, the monitors, all Clinical Trial Team (CTT) members at Actelion and CROs involved in the conduct of the study will remain blinded to the treatment until study closure" (page 90 of Protocol).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"This study will be performed in a double-blind fashion. The investigator and study staff, the subjects, the monitors, all Clinical Trial Team (CTT) members at Actelion and CROs involved in the conduct of the study will remain blinded to the treatment until study closure" (page 90 of Protocol).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 16.5% was lost-to follow-up (16.4% in teriflunomide, and 16.6% in ponesimod).
Selective reporting (reporting bias)	Low risk	The published report included all prespecified outcomes.
Other bias	High risk	The study was sponsored by Actelion Pharmaceuticals, part of Janssen Pharmaceutical Companies and the sponsor contributed to the analysis and manuscript preparation.

PRISMS 1998

Study characteristics	
Methods	RCT
Participants	Age: 18 to 50 years; definite RRMS; mean disease duration 7 years; mean EDSS 2.5; prior use of DMT: "*Only 3% of patients had received previous immunosuppressive therapy*".
Interventions	Interferon beta-1a (Rebif) 44 µg subcutaneously 3 times a week for 24 months (n = 184) Interferon beta-1a (Rebif) 22 µg subcutaneously 3 times a week for 24 months (n = 189) Placebo subcutaneously 3 times a week for 24 months (n = 187)
Outcomes	Relapse at 12 and 24 months, withdrawals due to AEs, mortality
Notes	Funding: Ares-Serono International SA, Geneva, Switzerland
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

PRISMS 1998 *(Continued)*

Random sequence generation (selection bias)	Low risk	"*Randomisation at Corporate Biometrics Department of Ares-Serono (computer-generated list, stratified by centre, equal allocation of the treatment groups by a block size of 6)*" (page 1499)
Allocation concealment (selection bias)	Low risk	"*The study drug was packed accordingly to the randomisation list and delivered to the centres so that treatment allocation remained concealed*" (page 1499).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*All personnel involved in the study were unaware of treatment allocation*", and "*All injection sites were covered up at neurological examinations to ensure that masking was not compromised because of local reactions*" (page 1499).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*All personnel involved in the study were unaware of treatment allocation*"; "*Patients were assessed by two physicians. A "treating" neurologist was responsible for overall medical management of the patient, including treatment of any side-effects, and an "assessing" neurologist was responsible for neurological assessments and follow-up of relapses*"; and "*All patients had a neurological assessment every 3 months. Additional assessments were done during relapses*" (page 1499).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 4.8% were lost to follow-up (2.7% in interferon beta-1a 44 µg, 6.3% in interferon beta-1a 22 µg, and 5.3% in placebo), without indication of the differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	The study was sponsored by Ares-Serono International SA, Geneva, Switzerland and 6 co-authors have received departmental funding from Ares-Serono to support the trial.

RADIANCE 2019

Study characteristics	
Methods	RCT
Participants	Age: 18-55 years; mixed sample: 98% RRMS and 2% PM; mean disease duration 7 years; mean EDSS 2.5; prior use of DMT in the 2 years prior to the start of study: 29% (28.6% Interferon beta-1a, 29.8% Ozanimod 0.5 mg, 28.4% Ozanimod 1.0 mg)
Interventions	Interferon beta-1a 30 µg weekly intramuscularly for 24 months (n =443) Ozanimod 0.5 mg daily orally for 24 months (n = 443) Ozanimod 1.0 mg daily orally for 24 months (n = 434)
Outcomes	Disability worsening at 24 months, withdrawals due to AEs, SAEs, quality of life, new or enlarging T2-weighted MRI lesions, new gadolinium-enhancing positive T1-weighted MRI lesions, mortality
Notes	The study was sponsored by Celgene International II.
Risk of bias	

Bias	Authors' judgement	Support for judgement

RADIANCE 2019 *(Continued)*

Random sequence generation (selection bias)	Low risk	"The randomisation sequence was generated by the contract research organisation and based on a blocked algorithm stratified by baseline EDSS score (≤ 3·5 vs > 3·5) and country" (page 1023).
Allocation concealment (selection bias)	Low risk	"Participants were randomised (1:1:1) via an interactive voice response system" (page 1023).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebos consisting of daily oral capsules identical in appearance to ozanimod were given to participants in the interferon beta-1a group and weekly intramuscular injections identical to interferon beta-1a were given to participants in the ozanimod group" and "Participants, investigators, EDSS assessors, study personnel, MRI reviewers (NeuroRx, Montreal, QC, Canada), and the funder were masked to treatment and total and differential white blood cell counts" (page 1023).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Placebos consisting of daily oral capsules identical in appearance to ozanimod were given to participants in the interferon beta-1a group and weekly intramuscular injections identical to interferon beta-1a were given to participants in the ozanimod group" and "Participants, investigators, EDSS assessors, study personnel, MRI reviewers (NeuroRx, Montreal, QC, Canada), and the funder were masked to treatment and total and differential white blood cell counts" (page 1023).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 13.3% was lost-to follow-up (10.4% in ozanimod 1 mg, 14.8% in ozanimod 0.5 mg, and 14.7% in IFNβ-1a), without indications of differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary outcomes.
Other bias	High risk	The study was sponsored by Celgene International II, "The funder of this study was involved in study design, data analysis, data interpretation, and writing of the report, but not data collection" (page 1027), and four co-authors of the published paper were affiliated to the pharmaceutical company.

REGARD 2008

Study characteristics	
Methods	RCT
Participants	Age: 18 to 60 years; definite RRMS; mean disease duration 6 years; mean EDSS 2.3; prior use of DMT not reported
Interventions	Interferon beta-1a (Rebif) 44 µg subcutaneously 3 times a week for 24 months (n = 386) Glatiramer acetate 20 mg subcutaneously daily for 24 months (n = 378)
Outcomes	Relapse at 24 months, disability worsening at 24 months, withdrawals due to AEs, SAEs, new or enlarging T2-weighted magnetic resonance imaging (MRI) lesions, new gadolinium-enhancing positive T1-weighted MRI lesions, mortality
Notes	Funding: EMD Serono and Pfizer
Risk of bias	

REGARD 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Computer-generated randomisation list stratified by centre*" (page 904)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Neither the patients nor the treating physicians were blinded to treatment*" (page 904).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The physicians who assessed patients ...were blinded to treatment and communicated with the patients only as needed to complete the EDSS, Kurtzke functional scale (KFS), and relapse assessments. Patients were asked not to discuss their treatment with the assessing physician and they covered their injection sites*" (page 904).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall, 3.3% were lost to follow-up (5.2% in interferon beta-1a and 1.3% in glatiramer acetate). Nothing was said about the reasons for study discontinuation.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	"*The study protocol was drafted and developed by the study sponsors, EMD Serono and Pfizer, in conjunction with the investigator steering committee. Data management and analysis were done by the study sponsors*" (page 907), and 2 co-authors of the published paper were affiliated to the pharmaceutical company.

SELECT 2013

Study characteristics	
Methods	RCT
Participants	Age: 18 to 55 years; definite RRMS; median disease duration (since diagnosis) 3 years; mean EDSS 2.7; prior use of DMT at any time prior to the start of study: 23.7% (22.5% in daclizumab 300 mg, 25.5% in daclizumab 150 mg, and 24.0% in placebo)
Interventions	Daclizumab 300 mg subcutaneously once every 4 weeks for 12 months (n = 209) Daclizumab 150 mg subcutaneously once every 4 weeks for 12 months (n = 208) Placebo subcutaneously once every 4 weeks for 12 months (n = 204)
Outcomes	Relapse at 12 months, withdrawals due to AEs, SAEs, quality of life, new or enlarging T2-weighted MRI lesions, new gadolinium-enhancing positive T1-weighted MRI lesions, mortality
Notes	Funding: Biogen Idec and AbbVie Biotherapeutics Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement

SELECT 2013 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"*Patients were randomly assigned in a 1:1:1 ratio*" (page 2168).
Allocation concealment (selection bias)	Low risk	"*Patients were randomly assigned via a centralised interactive voice response system*" (page 2168).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*All personnel and patients were masked to treatment assignment*" (page 2168).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Three members of an independent neurology assessment committee, consisting of multiple sclerosis neurologists who were masked to group assignment, adjudicated whether the protocol definition of relapse was satisfied*" (page 2168).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall, 7.1% were lost to follow-up (5.7% in daclizumab 300 mg, 7.7% in daclizumab 150 mg, and 7.8% in placebo). Nothing was said about the reasons for study discontinuation.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	The study was sponsored by Biogen Idec and AbbVie Biotherapeutics Inc, "*The sponsor of the study provided assistance in manuscript preparation. The study was designed by the sponsor; the sponsor held and analysed data*" (page 2169), and 5 co-authors of the published paper were affiliated to the pharmaceutical company.

SUNBEAM 2019

Study characteristics	
Methods	RCT
Participants	Age: 18 to 55 years; mixed samale 98% RRMS and 2% PMS ; median disease duration 7 years; mean EDSS 2.6; prior use of DMT at any time prior to the start of study: 31% (33.7% Interferon beta-1a, 29.3% Ozanimod 0.5 mg, 28.6% Ozanimod 1.0 mg)
Interventions	Interferon beta-1a 30 µg weekly intramuscularly for 12 months (n = 448) Ozanimod 0.5 mg orally daily for 12 months (n = 451) Ozanimod 1.0 mg orally daily for 12 months (n = 447)
Outcomes	Withdrawals due to AEs, SAEs, quality of life, new or enlarging T2-weighted magnetic resonance imaging (MRI) lesions, new gadolinium-enhancing positive T1-weighted MRI lesions, cognitive decline, mortality
Notes	The study was sponsored by Celgene International II.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was based on a blocked algorithm stratified by country and baseline EDSS score (≤ 3·5 vs > 3·5)" (page 1011).

SUNBEAM 2019 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Randomisation was...done through interactive voice and web-based response technology" (page 1011).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To maintain masking, participants assigned to interferon beta-1a received daily oral placebo capsules identical in appearance to ozanimod; those assigned to ozanimod received weekly intramuscular placebo injections" and "Treating investigators, EDSS assessors, study personnel, MRI reviewers, participants, and the sponsor were masked to treatment and total and differential white blood cell counts" (pages 1011-1012).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"To maintain masking, participants assigned to interferon beta-1a received daily oral placebo capsules identical in appearance to ozanimod; those assigned to ozanimod received weekly intramuscular placebo injections" and "Treating investigators, EDSS assessors, study personnel, MRI reviewers, participants, and the sponsor were masked to treatment and total and differential white blood cell counts" (pages 1011-1012).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 6.8% was lost-to follow-up (6.5% in ozanimod 1 mg, 5.8% in ozanimod 0.5 mg, and 8.0% in IFNβ-1a), without indications of differences in reasons.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary outcomes.
Other bias	High risk	The study was sponsored by Celgene International II, "The funders of this study were involved in study design, data analysis, data interpretation, and writing of the report, but not data collection" (page 1015), and four co-authors of the published paper were affiliated to the pharmaceutical company.

TEMSO 2011

Study characteristics	
Methods	RCT
Participants	Age: 18 to 55 years; mixed sample: 91% RRMS and 9% PMS; mean disease duration 9 years; mean EDSS 2.7; prior use of DMT in the previous 2 years: 27.0% (28.4% in teriflunomide 14 mg, 27.9% in teriflunomide 7 mg, and 24.8% in placebo)
Interventions	Teriflunomide 14 mg oral capsule once daily for 25 months (n = 359) Teriflunomide 7 mg oral capsule once daily for 25 months (n = 366) Placebo oral capsule once daily for 25 months (n = 363)
Outcomes	Relapse 12 and 24 months, disability worsening at 24 months, withdrawals due to AEs, SAEs
Notes	Funding: Sanofi-Aventis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Eligible patients were randomly assigned (in a 1:1:1 ratio) to receive a once-daily oral dose of placebo, 7 mg of teriflunomide, or 14 mg of teriflunomide for 108*

TEMSO 2011 *(Continued)*

		weeks. Randomization was stratified according to the baseline EDSS score (≤ 3.5 or >3.5) and according to trial site, with a block size of 6." (page 1294).
Allocation concealment (selection bias)	Low risk	"*The treatment allocation was determined according to the randomization code provided by an interactive voice response system (IVRS)*" (page 74 of Medical Review of FDA).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Double blind*" (page 1294), and at page 40 of the Protocol they described blinding, packaging and labeling ("*Each medication kit was labeled with a two-part tear-off label...*"). "*Unblinding of 40 patients in TEMSO study, and the reasons provided do not appear to justify the need of unblinding*" (page 230 of Statistical Review of FDA).
Blinding of outcome assessment (detection bias) All outcomes	High risk	"*A treating neurologist at each site was responsible for evaluating patient eligibility, supervising the administration of study medication, recording and managing adverse events, assessing relapses, and monitoring safety assessments. An independent, specially trained and certified examining neurologist determined all the EDSS scores and performed all assessments of functional systems. Both treating and examining neurologists were unaware of treatment assignments; only the treating neurologist was aware of any side effects that could potentially be related to active therapy*" (pages 1294-5), "*Each episode of relapse was to be confirmed by the treating neurologist (unblinded), based on the objective assessments by an independent examining neurologist (blinded)*" (page 207 of Statistical Review of FDA) and "*Patients were required to visit the study site within 7 days after the onset of a suspected relapse, for assessments by the examining neurologist*" (page 1295).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall, 20.1% were lost to follow-up (21.2% in teriflunomide 14 mg, 19.1% in teriflunomide 7 mg, and 20.1% in placebo). Nothing was said about the reasons for study discontinuation. "*Some patients discontinued study at the time of blind broken, although it is not clear whether or not the discontinuation was due to unblinding*" (page 208 of Statistical Review of FDA).
Selective reporting (reporting bias)	High risk	The published report included all prespecified primary benefit outcomes. However, disability confirmed at 6 months was not reported in the published report; it was reported by the FDA in terms of survival probabilities.
Other bias	High risk	The study was sponsored by Sanofi-Aventis, "*data were analyzed by the sponsor*" (page 1294), and 3 co-authors of the published paper were affiliated to the pharmaceutical company.

TOWER 2014

Study characteristics	
Methods	RCT
Participants	Age: 18 to 55 years; mixed sample: 97% RRMS and 3% PMS; mean disease duration 8 years; mean EDSS 2.7; prior use of DMT in the previous 2 years: 32.8% (33.9% in teriflunomide 14 mg, 30.1% in teriflunomide 7 mg, and 34.7% in placebo)
Interventions	Teriflunomide 14 mg oral capsule once daily for at least 12 months (n = 372) Teriflunomide 7 mg oral capsule once daily for at least 12 months (n = 408) Placebo oral capsule once daily for at least 12 months (n = 389)

TOWER 2014 *(Continued)*

	The study was completed 48 weeks after the last patient was randomised, resulting in a variable duration of follow-up.
Outcomes	Relapse at 12 months, withdrawals due to AEs, SAEs, quality of life, mortality
Notes	Funding: Genzyme (a Sanofi company)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Randomisation was done using a permuted-block randomisation schedule with stratification according to study site and baseline EDSS score (≤ 3.5 or > 3.5)*" (page 248).
Allocation concealment (selection bias)	Low risk	"*Randomisation was done centrally, via an interactive voice recognition system that generated an allocation sequence*" and "*investigators used the allocation sequence to randomly assign eligible patients in a 1:1:1 ratio to receive once-daily oral placebo, teriflunomide 7 mg, or teriflunomide 14 mg (identical in taste and appearance)*" (page 248).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Patients and individuals administering the interventions were masked to treatment assignment*" (page 248).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Those assessing the outcomes were masked to treatment assignment*" and "*A treating neurologist was responsible for recording of adverse events, and assessment of relapses. An examining neurologist assigned EDSS scores at screening, randomisation, and every 12 weeks until the last treatment visit, and on any unscheduled visits for assessment of suspected relapse or disability worsening*" (page 248).
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 29.8% were lost to follow-up (30.6% in teriflunomide 14 mg, 29.2% in teriflunomide 7 mg, and 29.6% in placebo), with some indication of the differences in reasons: adverse events of 15.6% in teriflunomide 14 mg, 13.2% in teriflunomide 7 mg, and 6.7% in placebo; and lack of benefit of 5.4% in teriflunomide 14 mg, 7.4% in teriflunomide 7 mg, and 9.5% in placebo.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes.
Other bias	High risk	The study was sponsored by Genzyme, "*data were analyzed by the sponsor*" (page 250), and 4 co-authors of the published paper were affiliated to the pharmaceutical company.

TRANSFORMS 2010

Study characteristics

Methods	RCT
Participants	Age: 18 to 55 years; definite RRMS; mean disease duration 7 years; mean EDSS 2.2; prior use of DMT at any time prior to the start of study: 56.7% (58.5% in fingolimod 1.25 mg, 55.2% in fingolimod 0.5 mg, and 56.3% in interferon beta-1a)

TRANSFORMS 2010 *(Continued)*

Interventions	Fingolimod 1.25 mg oral capsule once daily for 12 months (n = 426) Fingolimod 0.5 mg oral capsule once daily for 12 months (n = 431) Interferon beta-1a (Avonex) 30 µg intramuscularly once a week for 12 months (n = 435)
Outcomes	Relapse at 12 months, withdrawals due to AEs, SAEs, new or enlarging T2-weighted MRI lesions, new gadolinium-enhancing positive T1-weighted MRI lesions, mortality
Notes	Funding: Novartis Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*Randomization was performed in blocks of six within each site and was stratified according to site*" (page 403).
Allocation concealment (selection bias)	Low risk	"*Randomization was performed centrally*" and "*Study-group assignments were performed with the use of an interactive voice-response system*" (page 403).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Capsules, syringes and packaging materials for active and placebo treatments were indistinguishable*"; "*During the trial, patients, study personnel, steering-committee members, and the study statistician were unaware of study-group assignments and leukocyte counts*"; and "*An independent physician monitored patients after the first dose of the oral study drug was administered and was instructed not to discuss heart-rate changes with patients or study personnel*" (page 404).
Blinding of outcome assessment (detection bias) All outcomes	High risk	"*At each site, a treating neurologist supervised medical management*", "*Patients were instructed not to discuss adverse events with clinical evaluators*", and "*Potential relapses triggered an unscheduled visit and were confirmed by the treating neurologist on the basis of blinded examination by the examining neurologist*" (pages 403-4).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 10.8% were lost to follow-up (13.4% in fingolimod 1.25 mg, 7.7% in fingolimod 0.5 mg, and 11.3% in interferon beta-1a), with few indications of the differences in reasons: unsatisfactory therapeutic effect of 0.7% in fingolimod 1.25 mg, 0.7% in fingolimod 0.5 mg, and 1.6% in interferon beta-1a; adverse event(s) of 6.1% in fingolimod 1.25 mg, 2.1% in fingolimod 0.5 mg, and 2.1% in interferon beta-1a; and abnormal laboratory values(s) of 0.9% in fingolimod 1.25 mg, 1.4% in fingolimod 0.5 mg, and 0.2% in interferon beta-1a.
Selective reporting (reporting bias)	Low risk	The published report included all prespecified primary benefit outcomes. Missing data not reported in the published paper were provided on request by Novartis Pharma.
Other bias	High risk	The study was sponsored by Novartis Pharma, "*data were analyzed by the sponsor*" (page 403), and 5 co-authors of the published paper were affiliated to the pharmaceutical company.

AE: adverse event
ARR: annualised relapse rate
AZA: azathioprine
CIS: clinically isolated syndrome
CTT: clinical trial team
DMT: disease modifying therapy
EDSS: Expanded Disability Status Scale

FDA: (US) Food and Drug Administration
GA: glatiramer acetate
IFN: interferons
IM: intramuscular
IRT: interactive response technology
IV: intravenous
IVRS: *i*nteractive voice response system
KFS: Kurtzke functional scale
MRI: magnetic resonance imaging
MS: multiple sclerosis
MSIS-29: Multiple Sclerosis Impact Scale
MTX: mitoxantrone
PMS: progressive multiple sclerosis
PPD: Pharmaceutical Product Development
RCT: randomised controlled trial
RRMS: relapsing-remitting multiple sclerosis
SAE: serious adverse event
SAS: Statistical Analysis System
SNRS: Scripps Neurological Rating Scale
tiw: three times in a week
YER: yearly exacerbation rate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACT 2009	Study evaluating combination therapy (interferon beta-1a combined with methotrexate, methyl-prednisolone, or both)
Agius 2014	Pooled post hoc analysis
Ashtari 2011	Study on interferon beta-1a versus methotrexate; methotrexate is not relevant to the review
ATAMS 2014	Study on atacicept versus placebo; atacicept is not relevant to the review
Bar-Or 2017	Wrong duration
Boiko 2018	Wrong study design, non-randomised
Boyko 2016	Wrong duration
British and Dutch 1988	Mixed sample with < 80% of patients with relapsing forms of MS
Calabrese 2012	Non-randomised study
Cascione 2018	Wrong comparator
CHOICE 2010	Follow-up of 6 months
Cohen 2015	Wrong duration
Cohen 2016	Wrong duration
Comi 2001	Insufficient follow-up duration: 9 months
Coyle 2017	Wrong comparator
Cree 2018	Wrong comparator

Study	Reason for exclusion
EVIDENCE 2007	Wrong intervention: compared same drug (two routes)
Fazekas 2008	Insufficient follow-up duration: 48 weeks
FORTE 2011	Study evaluating 2 doses of glatiramer acetate (40 mg compared to 20 mg) without a control group
Fox 2014	Wrong comparator
Freedman 2012	Study evaluating combination therapy (interferon beta-1a alone and combined with teriflunomide), with a follow-up of 6 months
Ghezzi 1989	Wrong publication type: abstract
Havrdova 2009	Study evaluating combination therapy (interferon beta-1a alone and combined with low-dose azathioprine alone or low-dose azathioprine and low-dose corticosteroids)
IMPROVE 2010	Insufficient duration
Kappos 2006	Follow-up of 6 months The patients were possibly included in the FREEDOMS study.
Kappos 2008	Follow-up of 6 months
Kappos 2011	Follow-up of 6 months
Khoury 2010	Study evaluating combination therapy (glatiramer acetate alone and combined with albuterol)
Lampl 2013	Wrong comparator
Le Page 2015	Wrong duration/design
Milanese 1993	Mixed population, < 80% people with relapsing forms of MS
Newsome 2015	Insufficient duration
Ochi 2018	Wrong duration
OWIMS 1999	Insufficient follow-up duration: 48 weeks
Saida 2012	Follow-up of 6 months
Saida 2017	Wrong duration
SENTINEL 2006	Study evaluating combination therapy (natalizumab combined with interferon beta-1a versus interferon beta-1a alone)
Simaniv 2019	Wrong duration
Sorensen 2014	Follow-up of 6 months
TENERE 2014	Insufficient follow-up duration: 48 weeks
Ziemssen 2017	Wrong duration

MS: multiple sclerosis

Characteristics of studies awaiting classification *[ordered by study ID]*

ACTRN12621001502820

Methods	Randomised control trial
Participants	People with multiple sclerosis
Interventions	Rituximab
Outcomes	Adverse events
Notes	

Boyko 2022

Methods	RCT
Participants	People with relapsing multiple sclerosis
Interventions	Sampeginterferon β-1a
Outcomes	Efficacy & safety
Notes	

CLARITY

Methods	RCT
Participants	People with relapsing multiple sclerosis
Interventions	Cladribine
Outcomes	Efficacy
Notes	

CombiRx

Methods	RCT
Participants	People with relapsing multiple sclerosis
Interventions	Glatiramer acetate, interferon beta
Outcomes	Treatment failure DIsability worsening

CombiRx *(Continued)*

Notes	

EUCTR2017-000559-26-IT

Methods	RCT
Participants	People with relapsing multiple sclerosis
Interventions	Fingolimod and dimethyl-fumarate
Outcomes	Efficacy
Notes	

EUCTR2020-001205-23-SE

Methods	RCT
Participants	People with relapsing multiple sclerosis
Interventions	Ocrelizumab, rituximab
Outcomes	Efficacy, safety
Notes	

EUCTR2020-004505-32-FR

Methods	RCT
Participants	People with relapsing multiple sclerosis
Interventions	Ofatumumab
Outcomes	Efficacy and tolerability
Notes	

EVOLVE-MS-1 Study

Methods	RCT
Participants	People with relapsing multiple sclerosis
Interventions	Diroximel fumarate
Outcomes	Efficacy and safety

EVOLVE-MS-1 Study *(Continued)*

Notes	

Masjedi 2021

Methods	RCT
Participants	People with multiple sclerosis
Interventions	Fingolimod versus dimethyl fumarate
Outcomes	Efficacy
Notes	

NCT04695080

Methods	RCT
Participants	People with multiple sclerosis
Interventions	Cladribine
Outcomes	Efficacy and safety
Notes	

OPTIMUM

Methods	RCT
Participants	People with relapsing multiple sclerosis
Interventions	Ponesimod compared with teriflunomide
Outcomes	Efficacy
Notes	

RIFUND-MS

Methods	RCT
Participants	People with relapsing multiple sclerosis
Interventions	Rituximab, dimethyl fumarate
Outcomes	Efficacy and safety

RIFUND-MS *(Continued)*

Notes	

SUNBEAM/RADIANCE

Methods	RCT
Participants	People with relapsing multiple sclerosis
Interventions	Ozanimod
Outcomes	Clinical and radiologic outcomes
Notes	

RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2012-000540-10-PL

Study name	EUCTR2012-000540-10-PL
Methods	RCT
Participants	Patients with relapsing-remitting forms of MS and secondary progressive forms with super-imposed relapses
Interventions	Ponesimod Placebo
Outcomes	Primary end point(s): Annualised relapse rate defined as the number of confirmed relapses per subject-year. Secondary Objective: To assess the effect of ponesimod on disability accumulation and on other aspects of multiple sclerosis (MS) disease control; to assess the safety and tolerability of ponesimod in subjects with RMS. Time point(s) of evaluation of this end point: All relapses up to EOS will be included in the analysis, irrespective of any treatment discontinuations prior to study completion. SECONDARY OUTCOME: Secondary end point(s): 1. Time to 12-week confirmed disability accumulation (CDA) from baseline to EOS; 2. Percent change in brain volume (PCBV) from baseline to week 108; 3. Time to first confirmed relapse; 4. Cumulative number of combined unique active lesions (CUAL; defined as new Gd + T1 lesions plus new or enlarging T2 lesions [without double-counting of lesions]) from baseline to week 108; 5. Change from baseline to week 108 in fatigue-related symptoms as measured by the symptoms domain of the Fatigue Symptoms and Impact Questionnaire – Relapsing Multiple Sclerosis (FSIQ–RMS) Time point(s) of evaluation of this end point: 1: end of study; 2, 4, 5: week 108; 3: time to first confirmed relapse
Starting date	2015
Contact information	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000540-10
Notes	

EUCTR2012-003647-30-SK

Study name	EUCTR2012-003647-30-SK
Methods	
Participants	Patients with relapsing forms of MS
Interventions	Two oral doses of laquinimod either of 0.6 mg/day or 1.2 mg/day (experimental drug) as compared placebo
Outcomes	Time to Confirmed Disease Progression (CDP) during period 1: CDP is defined as an increase in EDSS of 1 point from baseline for subjects with baseline EDSS of 5.0, or an increase in EDSS of 0.5 points from baseline for subjects with baseline EDSS of 5.5. Analysis will be performed at the completion of period 1. Secondary end point(s): • Brain atrophy as defined by the percent change in brain volume from baseline to month 15 • The time to first confirmed relapse during period 1
Starting date	2012
Contact information	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2012%E2%80%90003647%E2%80%9030%E2%80%90SK
Notes	

EUCTR2013-002082-19-SE

Study name	EUCTR2013-002082-19-SE
Methods	Study withdrawn
Participants	Study withdrawn
Interventions	Study withdrawn
Outcomes	Study withdrawn
Starting date	Study withdrawn
Contact information	http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-002082-19-SE 2013.
Notes	Study withdrawn

EUCTR2013-003884-71-BE

Study name	EUCTR2013-003884-71-BE
Methods	RCT
Participants	Patients with relapsing-remitting forms of MS

EUCTR2013-003884-71-BE *(Continued)*

Interventions	Alemtuzumab Other DMTs
Outcomes	Patient-reported Quality of Life (QoL) outcomes and health resource utilisation of patients
Starting date	2015
Contact information	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-003884-71
Notes	

EUCTR2014-001012-19-NL

Study name	EUCTR2014-001012-19-NL
Methods	RCT
Participants	Patients with relapsing-remitting forms of MS
Interventions	Fingolimod Inteferon- beta 1A Inteferon- beta 1A Glatiramer acetate
Outcomes	MRI outcomes Disability Relapse
Starting date	2014
Contact information	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001012-19
Notes	

EUCTR2018-000284-93-BG

Study name	EUCTR2018-000284-93-BG
Methods	RCT
Participants	Patients with relapsing forms of MS
Interventions	Glatiramer acetate Placebo
Outcomes	Primary end point(s): Annualised Relapse Rate (ARR) during the 52 weeks of the PC period as derived from the total number of confirmed relapses

EUCTR2018-000284-93-BG *(Continued)*

	Secondary end point(s): 1. Cumulative number of new enhancing lesions on T1-weighted images as compared to baseline. 2. Cumulative number of new or newly enlarging hyperintense T2 lesions as compared to baseline. 3. Change from baseline to week 52 in hyperintense T2-lesion volume. 4. Change from baseline to week 52 in enhancing T1-lesion volume.
Starting date	2019
Contact information	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-000284-93
Notes	

EUCTR2018-005038-39-GB

Study name	EUCTR2018-005038-39-GB
Methods	Phase 2b study
Participants	Progressive and relapsing forms of MS
Interventions	Cladribine Placebo
Outcomes	Upper-limb function, 9-hole peg test (9HPT)
Starting date	2020
Contact information	https://trialsearch.who.int/Trial2.aspx?TrialID=EUC-TR2018%E2%80%90005038%E2%80%9039%E2%80%90GB
Notes	

EUCTR2019-001505-24-NO

Study name	EUCTR2019-001505-24-NO
Methods	Clinical study
Participants	Patients with relapsing forms of MS
Interventions	Rituximab Cladribine
Outcomes	Primary endpoint: the number of new or enlarging cerebral MRI T2 lesions per patient from week 12 to week 96 Secondary Objective: Blood samples and MRI biomarkers that may contribute to future personalised treatment for these patients Evaluate the health and economic consequences of the two therapies
Starting date	2019

EUCTR2019-001505-24-NO *(Continued)*

Contact information	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2019%E2%80%90001505%E2%80%9024%E2%80%90NO
Notes	

EUCTR2020-002981-15-DK

Study name	EUCTR2020-002981-15-DK
Methods	Randomised study
Participants	Patients with relapsin and progressive forms of MS
Interventions	Ocrelizumab Rituximab
Outcomes	Primary end point: Percentage of patients with no new or enlarging T2 white matter lesions Secondary Objective: Secondary aims include evaluation of other standard efficacy and safety end-points and tertiary, explorative endpoints related to assessment of efficacy and safety
Starting date	2020
Contact information	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02238444/full
Notes	

IRCT20130812014333N

Study name	IRCT20130812014333N
Methods	RCT
Participants	Patients with relapsing and progressive forms of MS
Interventions	Rituximab Fingolimod
Outcomes	EDSS
Starting date	2018
Contact information	https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20130812014333N125
Notes	

IRCT201404195280N

Study name	IRCT201404195280N

IRCT201404195280N *(Continued)*

Methods	RCT
Participants	Patients with relapsing and progressive forms of MS
Interventions	Interferon beta-1a Interferon beta-1a
Outcomes	EDSS MSQOL-54 questionnaire
Starting date	2006
Contact information	https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT201404195280N16
Notes	

NCT01404117

Study name	NCT01404117
Methods	Study withdrawn
Participants	Study withdrawn
Interventions	Study withdrawn
Outcomes	Study withdrawn
Starting date	Study withdrawn
Contact information	https://clinicaltrials.gov/ct2/show/NCT01404117
Notes	

NCT01941004

Study name	NCT01941004
Methods	Study withdrawn
Participants	Study withdrawn
Interventions	Study withdrawn
Outcomes	Study withdrawn
Starting date	Study withdrawn
Contact information	https://clinicaltrials.gov/ct2/show/NCT01941004

NCT01941004 *(Continued)*

Notes	

NCT01975298

Study name	NCT01975298
Methods	Study withdrawn
Participants	Study withdrawn
Interventions	Study withdrawn
Outcomes	Study withdrawn
Starting date	Study withdrawn
Contact information	https://clinicaltrials.gov/ct2/show/NCT01975298
Notes	

NCT04056897

Study name	NCT04056897
Methods	RCT
Participants	Patients with relapsing forms of MS
Interventions	Teriflunomide Placebo
Outcomes	MRI outcomes DIsability Quality of Life surveys
Starting date	2019
Contact information	https://clinicaltrials.gov/ct2/show/NCT04056897
Notes	

NCT04121221

Study name	NCT04121221
Methods	RCT
Participants	Relapsing forms of MS

NCT04121221 *(Continued)*

Interventions	Glatiramer acetate Placebo
Outcomes	Primary outcome measures: 1. Annualised Relapse Rate (ARR) Secondary outcome measures : 1. Cumulative number of new enhancing lesions on T1-weighted images as compared to baseline 2. Cumulative number of new or newly enlarging hyperintense T2 lesions as compared to baseline 3. Change from baseline to week 52 in hyperintense T2-lesion volume 4. Change from baseline to week 52 in enhancing T1-lesion volume
Starting date	2022
Contact information	https://clinicaltrials.gov/ct2/show/NCT04121221
Notes	

NCT04121403

Study name	NCT04121403
Methods	RCT
Participants	Patients with relapsing forms of MS
Interventions	Rituximab Cladribine
Outcomes	MRI outcomes Disability Relapse
Starting date	2019
Contact information	https://clinicaltrials.gov/ct2/show/NCT04121403
Notes	

NCT04578639

Study name	NCT04578639
Methods	RCT
Participants	Patients (male or female) with active relapsing-remitting multiple sclerosis aged 18-60 years.
Interventions	Rituximab

NCT04578639 *(Continued)*

	Ocrelizumab
Outcomes	Proportion of patients with no new or enlarging T2-weighted brain MRI lesions from month 6 to month 24
Starting date	2020
Contact information	https://clinicaltrials.gov/ct2/show/NCT04578639
Notes	

NCT04688788

Study name	NCT04688788
Methods	RCT
Participants	Patients with relapsing and progressive forms of MS
Interventions	Rituximab Ocrelizumab
Outcomes	Percentage of patients without new or enlarging T2 white matter lesions on brain MRI scans from month 6 to month 24
Starting date	2021
Contact information	https://clinicaltrials.gov/ct2/show/NCT04688788
Notes	

WHO-ICTRP 002519

Study name	Study to evaluate the safety and efficacy of NU100 in patients with relapsing forms of multiple sclerosis
Methods	RCT
Participants	Patients with relapsing forms of MS
Interventions	Recombinant human interferon beta-1b (rhIFN beta-1b) product Interferon beta-1b (Betaferon) Placebo
Outcomes	Number of new combined unique active lesions (CUALs; defined as new gadolinium T1-weighted lesions and non-enhancing new and newly enlarging T2-weighted lesions) on MRI ARR Incidence and severity of all drug-related flu-like symptoms Incidence of antibody formation against IFN beta-1b

WHO-ICTRP 002519 *(Continued)*

	Changes from baseline in the EDSS Sustained change in EDSS measured for at least 3 months
Starting date	2011
Contact information	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3897
Notes	

WHO-ICTRP PER-024-14

Study name	WHO-ICTRP PER-024-14
Methods	RCT
Participants	Patients with relapsing forms of MS
Interventions	Ocrelizumab Interferon beta-1A
Outcomes	ARR
Starting date	2014
Contact information	https://trialsearch.who.int/Trial2.aspx?TrialID=PER%E2%80%90024%E2%80%9014
Notes	

9HPT: 9-hole peg test
ARR: annualised relapse rate
CDA: confirmed disability accumulation
CDP: confirmed disease progression
CUAL: combined unique active lesions
DMT: disease modifying therapy
EOS: end of study
EDSS: Expanded Disability Status Scale
FSIQ-RMS: Fatigue Symptoms and Impact Questionnaire–Relapsing Multiple Sclerosis
MRI: magnetic resonance imaging
MS: multiple sclerosis
MSQOL-54: Multiple Sclerosis Quality of Life-54
PC: placebo-controlled period
PCBV: percent change in brain volume
QoL: quality of life
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Treatment efficacy (primary outcomes): pairwise comparisons

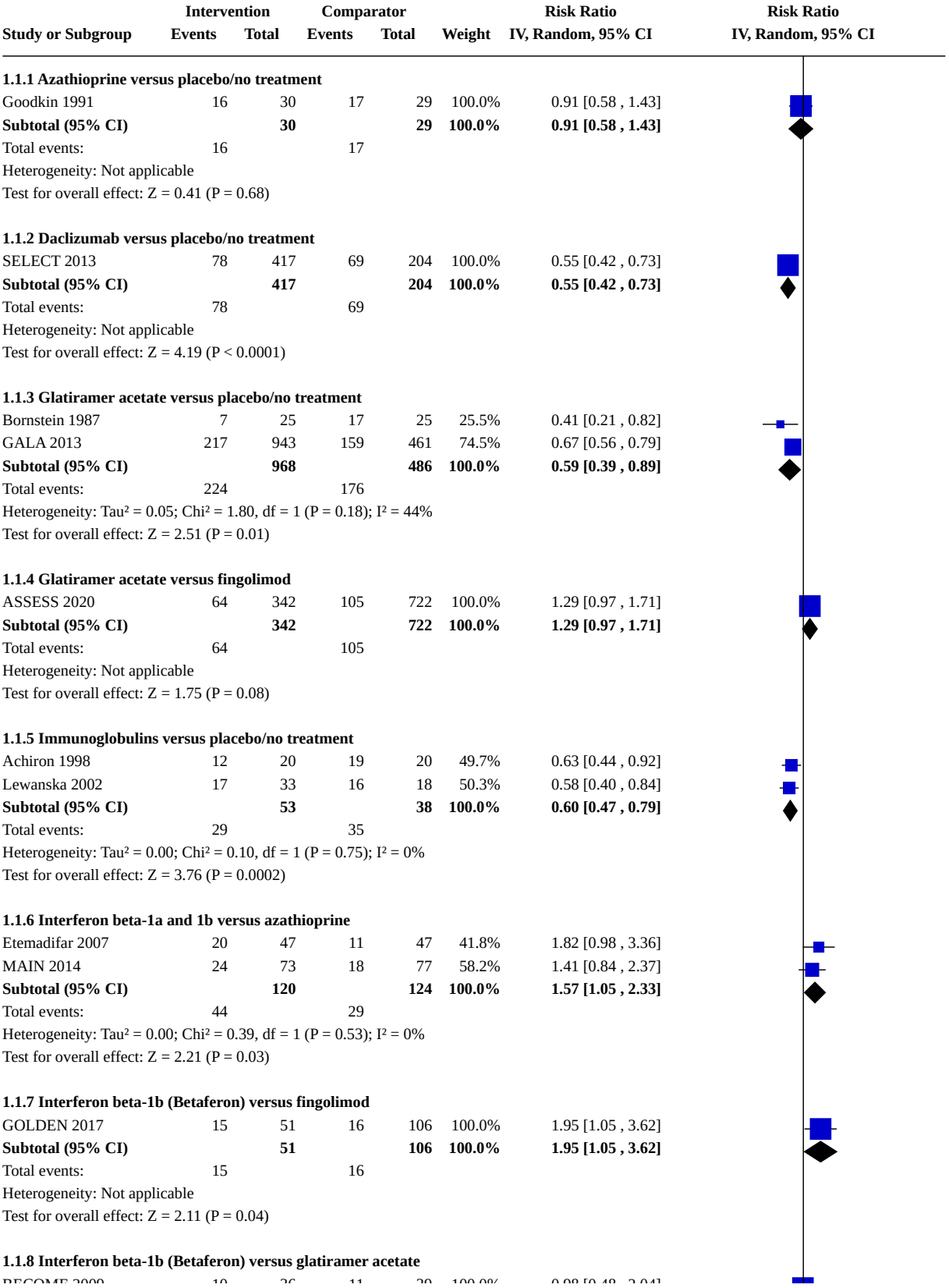
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Comparisons for relapse (12 months)	18		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1.1 Azathioprine versus placebo/no treatment	1	59	Risk Ratio (IV, Random, 95% CI)	0.91 [0.58, 1.43]
1.1.2 Daclizumab versus placebo/no treatment	1	621	Risk Ratio (IV, Random, 95% CI)	0.55 [0.42, 0.73]
1.1.3 Glatiramer acetate versus placebo/no treatment	2	1454	Risk Ratio (IV, Random, 95% CI)	0.59 [0.39, 0.89]
1.1.4 Glatiramer acetate versus fingolimod	1	1064	Risk Ratio (IV, Random, 95% CI)	1.29 [0.97, 1.71]
1.1.5 Immunoglobulins versus placebo/no treatment	2	91	Risk Ratio (IV, Random, 95% CI)	0.60 [0.47, 0.79]
1.1.6 Interferon beta-1a and 1b versus azathioprine	2	244	Risk Ratio (IV, Random, 95% CI)	1.57 [1.05, 2.33]
1.1.7 Interferon beta-1b (Betaferon) versus fingolimod	1	157	Risk Ratio (IV, Random, 95% CI)	1.95 [1.05, 3.62]
1.1.8 Interferon beta-1b (Betaferon) versus glatiramer acetate	1	75	Risk Ratio (IV, Random, 95% CI)	0.98 [0.48, 2.04]
1.1.9 Interferon beta-1a (Avonex, Rebif) versus placebo/no treatment	1	560	Risk Ratio (IV, Random, 95% CI)	0.76 [0.67, 0.85]
1.1.10 Interferon beta-1a (Avonex, Rebif) versus fingolimod	1	1292	Risk Ratio (IV, Random, 95% CI)	1.62 [1.32, 1.98]
1.1.11 Pegylated interferon beta-1a versus placebo/no treatment	1	1512	Risk Ratio (IV, Random, 95% CI)	0.68 [0.56, 0.82]
1.1.12 Mitoxantrone versus placebo/no treatment	1	51	Risk Ratio (IV, Random, 95% CI)	0.40 [0.21, 0.74]
1.1.13 Natalizumab versus placebo/no treatment	1	942	Risk Ratio (IV, Random, 95% CI)	0.52 [0.43, 0.63]
1.1.14 Natalizumab versus interferon beta-1b (Betaferon)	1	19	Risk Ratio (IV, Random, 95% CI)	0.18 [0.01, 3.35]
1.1.15 Teriflunomide versus placebo/no treatment	1	1169	Risk Ratio (IV, Random, 95% CI)	0.66 [0.55, 0.78]
1.2 Comparisons for relapse (24 months)	28		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.2.1 Azathioprine versus placebo/no treatment	1	59	Risk Ratio (IV, Random, 95% CI)	0.77 [0.51, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.2 Cladribine versus placebo/no treatment	1	1326	Risk Ratio (IV, Random, 95% CI)	0.53 [0.44, 0.63]
1.2.3 Dimethyl fumarate versus placebo/no treatment	2	2307	Risk Ratio (IV, Random, 95% CI)	0.61 [0.54, 0.68]
1.2.4 Fingolimod versus placebo/no treatment	2	2355	Risk Ratio (IV, Random, 95% CI)	0.54 [0.47, 0.62]
1.2.5 Glatiramer acetate versus placebo/no treatment	3	1014	Risk Ratio (IV, Random, 95% CI)	0.83 [0.72, 0.96]
1.2.6 Glatiramer acetate versus dimethyl fumurate	1	1057	Risk Ratio (IV, Random, 95% CI)	1.21 [0.99, 1.47]
1.2.7 Immunoglobulins versus placebo/no treatment	2	190	Risk Ratio (IV, Random, 95% CI)	0.73 [0.59, 0.89]
1.2.8 Interferon beta-1a and 1b versus azathioprine	1	150	Risk Ratio (IV, Random, 95% CI)	1.56 [1.02, 2.38]
1.2.9 Interferon beta-1b (Betaferon) versus placebo/no treatment	1	372	Risk Ratio (IV, Random, 95% CI)	0.89 [0.81, 0.99]
1.2.10 Interferon beta-1b (Betaferon) versus glatiramer acetate	2	2319	Risk Ratio (IV, Random, 95% CI)	1.18 [0.74, 1.90]
1.2.11 Interferon beta-1a (Avonex, Rebif) versus placebo/no treatment	3	1629	Risk Ratio (IV, Random, 95% CI)	0.83 [0.77, 0.90]
1.2.12 Interferon beta-1a (Avonex, Rebif) versus alemtuzumab	2	1248	Risk Ratio (IV, Random, 95% CI)	1.53 [1.14, 2.07]
1.2.13 Interferon beta-1a (Avonex, Rebif) versus glatiramer acetate	1	764	Risk Ratio (IV, Random, 95% CI)	0.93 [0.77, 1.14]
1.2.14 Interferon beta-1a (Avonex, Rebif) versus interferon beta-1b (Betaferon)	2	278	Risk Ratio (IV, Random, 95% CI)	1.23 [1.00, 1.52]
1.2.15 Laquinimod versus placebo/no treatment	3	3457	Risk Ratio (IV, Random, 95% CI)	0.82 [0.76, 0.89]
1.2.16 Laquinimod versus interferon beta-1a (Avonex, Rebif)	1	881	Risk Ratio (IV, Random, 95% CI)	1.10 [0.91, 1.33]
1.2.17 Mitoxantrone versus placebo/no treatment	1	51	Risk Ratio (IV, Random, 95% CI)	0.47 [0.27, 0.80]
1.2.18 Natalizumab versus placebo/no treatment	1	942	Risk Ratio (IV, Random, 95% CI)	0.56 [0.48, 0.65]
1.2.19 Teriflunomide versus placebo/no treatment	1	1088	Risk Ratio (IV, Random, 95% CI)	0.82 [0.73, 0.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.20 Teriflunomide versus ponesimod	1	1133	Risk Ratio (IV, Random, 95% CI)	1.42 [1.27, 1.60]
1.3 Comparisons for relapse (36 months)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.3.1 Interferon beta-1b (Betaferon) versus placebo/no treatment	2	403	Risk Ratio (IV, Random, 95% CI)	0.86 [0.67, 1.11]
1.3.2 Interferon beta-1b (Avonex, Rebif) versus alemtuzumab	1	334	Risk Ratio (IV, Random, 95% CI)	2.21 [1.54, 3.15]
1.3.3 Interferon beta-1b (Avonex, Rebif) versus daclizumab	1	1841	Risk Ratio (IV, Random, 95% CI)	1.49 [1.33, 1.67]
1.3.4 Interferon beta-1b (Avonex, Rebif) versus glatiramer acetate	1	509	Risk Ratio (IV, Random, 95% CI)	1.27 [0.92, 1.75]
1.4 Comparisons for disability worsening (24 months)	31		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.4.1 Azathioprine versus placebo/no treatment	1	59	Risk Ratio (IV, Random, 95% CI)	0.60 [0.22, 1.63]
1.4.2 Cladribine versus placebo/no treatment	1	1326	Risk Ratio (IV, Random, 95% CI)	0.72 [0.56, 0.91]
1.4.3 Dimethyl fumerate versus placebo/no treatment	2	2306	Risk Ratio (IV, Random, 95% CI)	0.67 [0.56, 0.80]
1.4.4 Fingolimod versus placebo/no treatment	2	2355	Risk Ratio (IV, Random, 95% CI)	0.68 [0.56, 0.83]
1.4.5 Glatiramer acetate versus placebo/no treatment	3	1014	Risk Ratio (IV, Random, 95% CI)	0.79 [0.58, 1.08]
1.4.6 Glatiramer acetate versus dimethyl fumerate	1	1057	Risk Ratio (IV, Random, 95% CI)	1.23 [0.90, 1.67]
1.4.7 Immunoglobulins versus placebo/no treatment	2	190	Risk Ratio (IV, Random, 95% CI)	0.75 [0.41, 1.37]
1.4.8 Interferon beta-1a and 1b versus azathioprine	1	150	Risk Ratio (IV, Random, 95% CI)	5.27 [0.63, 44.07]
1.4.9 Interferon beta-1a and 1b versus placebo/no treatment	1	372	Risk Ratio (IV, Random, 95% CI)	0.87 [0.61, 1.25]
1.4.10 Interferon beta-1a and 1b versus glatiramer acetate	1	2244	Risk Ratio (IV, Random, 95% CI)	1.07 [0.87, 1.31]
1.4.11 Interferon beta-1a (Avonex, Rebif) versus placebo/no treatment	2	1069	Risk Ratio (IV, Random, 95% CI)	0.71 [0.51, 0.98]

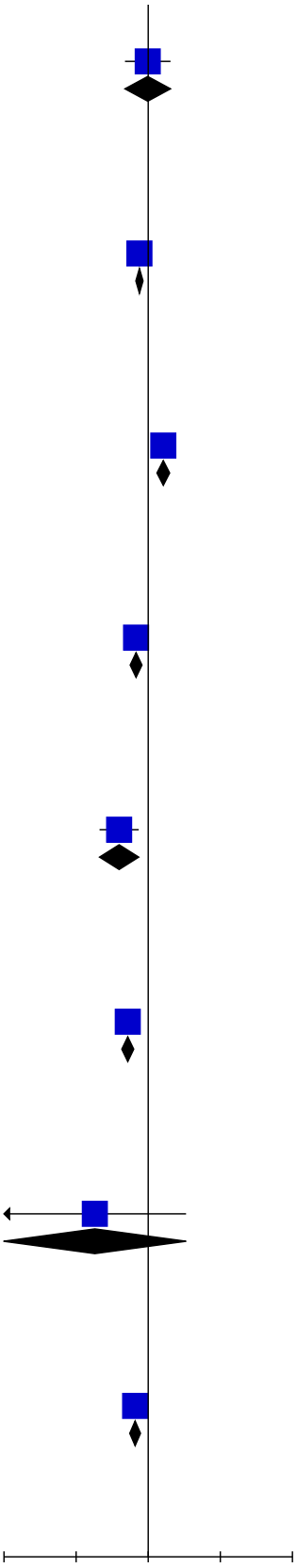
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4.12 Interferon beta-1a (Avonex, Rebif) versus alemtuzumab	2	1248	Risk Ratio (IV, Random, 95% CI)	1.37 [1.01, 1.87]
1.4.13 Interferon beta-1a (Avonex, Rebif) versus glatiramer acetate	1	764	Risk Ratio (IV, Random, 95% CI)	1.34 [0.87, 2.05]
1.4.14 Interferon beta-1a (Avonex, Rebif) versus interferon beta-1b (Betaferon)	2	489	Risk Ratio (IV, Random, 95% CI)	1.59 [0.86, 2.91]
1.4.15 Laquinimod versus placebo/no treatment	3	3457	Risk Ratio (IV, Random, 95% CI)	0.77 [0.59, 1.01]
1.4.16 Laquinimod versus interferon beta-1a (Avonex, Rebif)	1	881	Risk Ratio (IV, Random, 95% CI)	0.82 [0.51, 1.33]
1.4.17 Mitoxantrone versus placebo/no treatment	1	51	Risk Ratio (IV, Random, 95% CI)	0.20 [0.05, 0.83]
1.4.18 Natalizumab versus placebo/no treatment	1	942	Risk Ratio (IV, Random, 95% CI)	0.59 [0.46, 0.75]
1.4.19 Ocrelizumab versus interferon beta-1a (Avonex, Rebif)	2	1656	Risk Ratio (IV, Random, 95% CI)	0.66 [0.48, 0.90]
1.4.20 Ozanimod versus interferon beta-1a (Avonex, Rebif)	1	1320	Risk Ratio (IV, Random, 95% CI)	1.29 [0.85, 1.95]
1.4.21 Teriflunomide versus placebo/no treatment	1	1088	Risk Ratio (IV, Random, 95% CI)	0.76 [0.61, 0.95]
1.4.22 Teriflunomide versus ofatumumab	2	1882	Risk Ratio (IV, Random, 95% CI)	1.41 [1.08, 1.86]
1.4.23 Teriflunomide versus ponesimod	1	1133	Risk Ratio (IV, Random, 95% CI)	1.22 [0.84, 1.77]
1.5 Comparisons for disability worsening (36 months)	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.5.1 Interferon beta-1a (Avonex, Rebif) versus alemtuzumab	1	334	Risk Ratio (IV, Random, 95% CI)	2.68 [1.52, 4.72]
1.5.2 Interferon beta-1a (Avonex, Rebif) versus daclizumab	1	1841	Risk Ratio (IV, Random, 95% CI)	1.39 [1.12, 1.73]
1.5.3 Interferon beta-1a (Avonex, Rebif) versus glatiramer acetate	1	509	Risk Ratio (IV, Random, 95% CI)	0.88 [0.64, 1.22]

Analysis 1.1. Comparison 1: Treatment efficacy (primary outcomes): pairwise comparisons, Outcome 1: Comparisons for relapse (12 months)



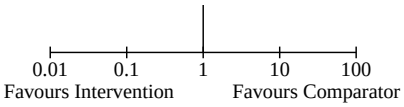
Analysis 1.1. (Continued)

1.1.8 Interferon beta-1b (Betaferon) versus glatiramer acetate						
BECOME 2009	10	36	11	39	100.0%	0.98 [0.48 , 2.04]
Subtotal (95% CI)		**36**		**39**	**100.0%**	**0.98 [0.48 , 2.04]**
Total events:	10		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.1.9 Interferon beta-1a (Avonex, Rebif) versus placebo/no treatment						
PRISMS 1998	220	373	146	187	100.0%	0.76 [0.67 , 0.85]
Subtotal (95% CI)		**373**		**187**	**100.0%**	**0.76 [0.67 , 0.85]**
Total events:	220		146			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.83 (P < 0.00001)						
1.1.10 Interferon beta-1a (Avonex, Rebif) versus fingolimod						
TRANSFORMS 2010	129	435	157	857	100.0%	1.62 [1.32 , 1.98]
Subtotal (95% CI)		**435**		**857**	**100.0%**	**1.62 [1.32 , 1.98]**
Total events:	129		157			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.67 (P < 0.00001)						
1.1.11 Pegylated interferon beta-1a versus placebo/no treatment						
ADVANCE 2014	195	1012	142	500	100.0%	0.68 [0.56 , 0.82]
Subtotal (95% CI)		**1012**		**500**	**100.0%**	**0.68 [0.56 , 0.82]**
Total events:	195		142			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.05 (P < 0.0001)						
1.1.12 Mitoxantrone versus placebo/no treatment						
Millefiorini 1997	8	27	18	24	100.0%	0.40 [0.21 , 0.74]
Subtotal (95% CI)		**27**		**24**	**100.0%**	**0.40 [0.21 , 0.74]**
Total events:	8		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.91 (P = 0.004)						
1.1.13 Natalizumab versus placebo/no treatment						
AFFIRM 2006	144	627	139	315	100.0%	0.52 [0.43 , 0.63]
Subtotal (95% CI)		**627**		**315**	**100.0%**	**0.52 [0.43 , 0.63]**
Total events:	144		139			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.75 (P < 0.00001)						
1.1.14 Natalizumab versus interferon beta-1b (Betaferon)						
Gobbi 2013	0	10	2	9	100.0%	0.18 [0.01 , 3.35]
Subtotal (95% CI)		**10**		**9**	**100.0%**	**0.18 [0.01 , 3.35]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
1.1.15 Teriflunomide versus placebo/no treatment						
TOWER 2014	202	780	153	389	100.0%	0.66 [0.55 , 0.78]
Subtotal (95% CI)		**780**		**389**	**100.0%**	**0.66 [0.55 , 0.78]**
Total events:	202		153			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.78 (P < 0.00001)						

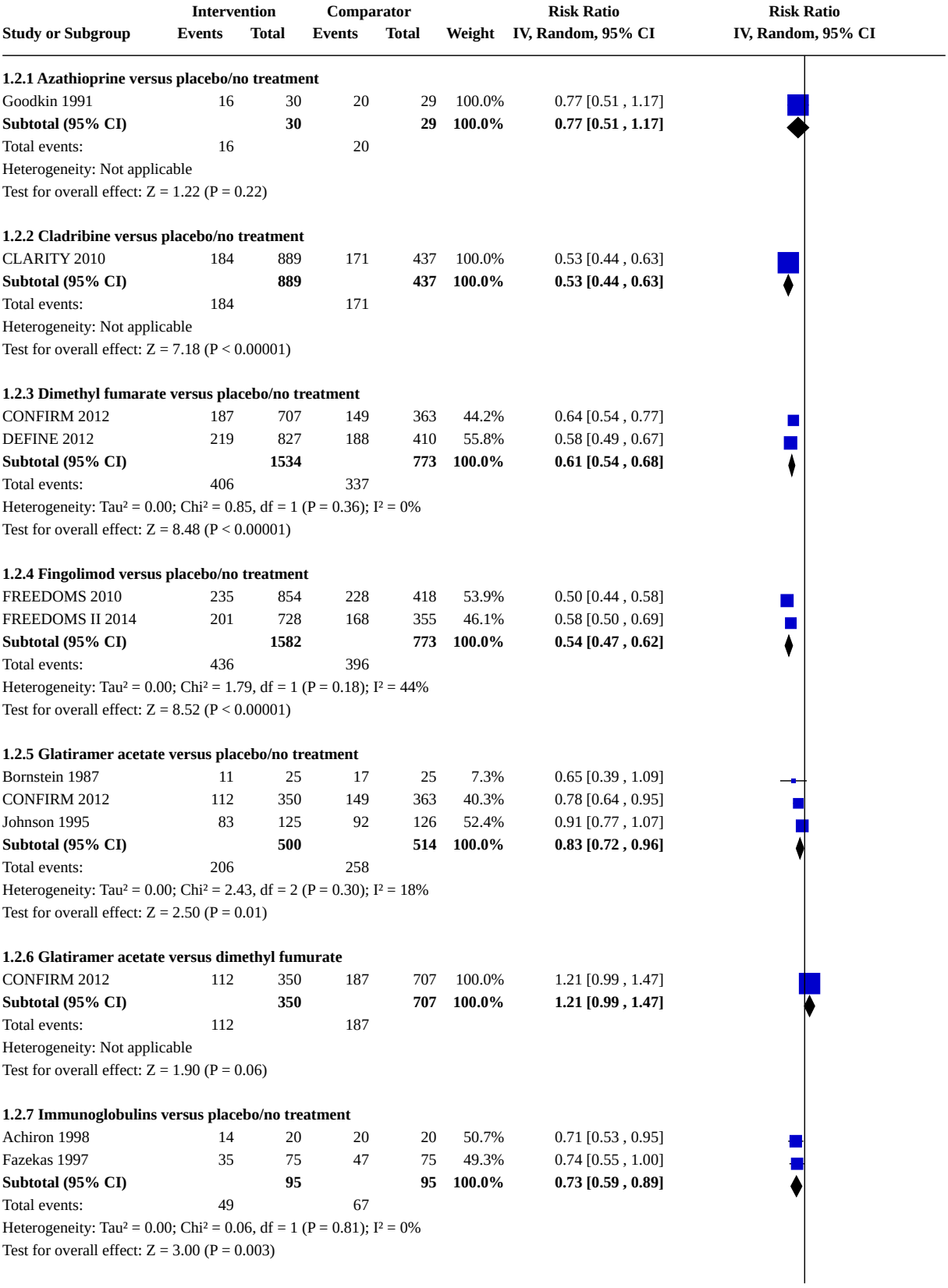


Analysis 1.1. (Continued)

Test for overall effect: Z = 4.76 (P < 0.00001)



Analysis 1.2. Comparison 1: Treatment efficacy (primary outcomes): pairwise comparisons, Outcome 2: Comparisons for relapse (24 months)



Analysis 1.2. (Continued)

Test for overall effect: Z = 3.00 (P = 0.003)

1.2.8 Interferon beta-1a and 1b versus azathioprine

MAIN 2014	34	73	23	77	100.0%	1.56 [1.02 , 2.38]
Subtotal (95% CI)		**73**		**77**	**100.0%**	**1.56 [1.02 , 2.38]**
Total events:	34		23			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.07 (P = 0.04)

1.2.9 Interferon beta-1b (Betaferon) versus placebo/no treatment

IFNB MS Group 1993	190	249	105	123	100.0%	0.89 [0.81 , 0.99]
Subtotal (95% CI)		**249**		**123**	**100.0%**	**0.89 [0.81 , 0.99]**
Total events:	190		105			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.18 (P = 0.03)

1.2.10 Interferon beta-1b (Betaferon) versus glatiramer acetate

BECOME 2009	17	36	11	39	32.7%	1.67 [0.91 , 3.08]
BEYOND 2009	737	1796	184	448	67.3%	1.00 [0.88 , 1.13]
Subtotal (95% CI)		**1832**		**487**	**100.0%**	**1.18 [0.74 , 1.90]**
Total events:	754		195			

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 2.66$, df = 1 (P = 0.10); $I^2 = 62\%$

Test for overall effect: Z = 0.69 (P = 0.49)

1.2.11 Interferon beta-1a (Avonex, Rebif) versus placebo/no treatment

BRAVO 2014	139	447	174	450	17.5%	0.80 [0.67 , 0.96]
MSCRG 1996	53	85	64	87	13.2%	0.85 [0.69 , 1.04]
PRISMS 1998	263	373	157	187	69.3%	0.84 [0.77 , 0.92]
Subtotal (95% CI)		**905**		**724**	**100.0%**	**0.83 [0.77 , 0.90]**
Total events:	455		395			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.20$, df = 2 (P = 0.90); $I^2 = 0\%$

Test for overall effect: Z = 4.70 (P < 0.00001)

1.2.12 Interferon beta-1a (Avonex, Rebif) versus alemtuzumab

CARE-MS I 2012	75	195	82	386	45.7%	1.81 [1.39 , 2.35]
CARE-MS II 2012	104	231	147	436	54.3%	1.34 [1.10 , 1.62]
Subtotal (95% CI)		**426**		**822**	**100.0%**	**1.53 [1.14 , 2.07]**
Total events:	179		229			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.36$, df = 1 (P = 0.07); $I^2 = 70\%$

Test for overall effect: Z = 2.82 (P = 0.005)

1.2.13 Interferon beta-1a (Avonex, Rebif) versus glatiramer acetate

REGARD 2008	126	386	132	378	100.0%	0.93 [0.77 , 1.14]
Subtotal (95% CI)		**386**		**378**	**100.0%**	**0.93 [0.77 , 1.14]**
Total events:	126		132			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.67 (P = 0.51)

1.2.14 Interferon beta-1a (Avonex, Rebif) versus interferon beta-1b (Betaferon)

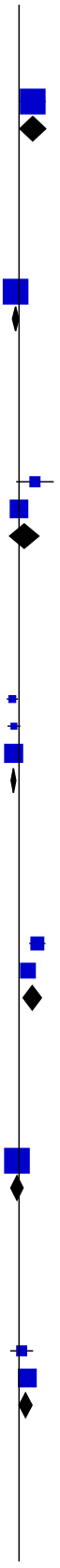
Etemadifar 2006	37	60	17	30	32.1%	1.09 [0.75 , 1.58]
INCOMIN 2002	59	92	47	96	67.9%	1.31 [1.01 , 1.69]
Subtotal (95% CI)		**152**		**126**	**100.0%**	**1.23 [1.00 , 1.52]**
Total events:	96		64			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.65$, df = 1 (P = 0.42); $I^2 = 0\%$

Test for overall effect: Z = 1.96 (P = 0.05)

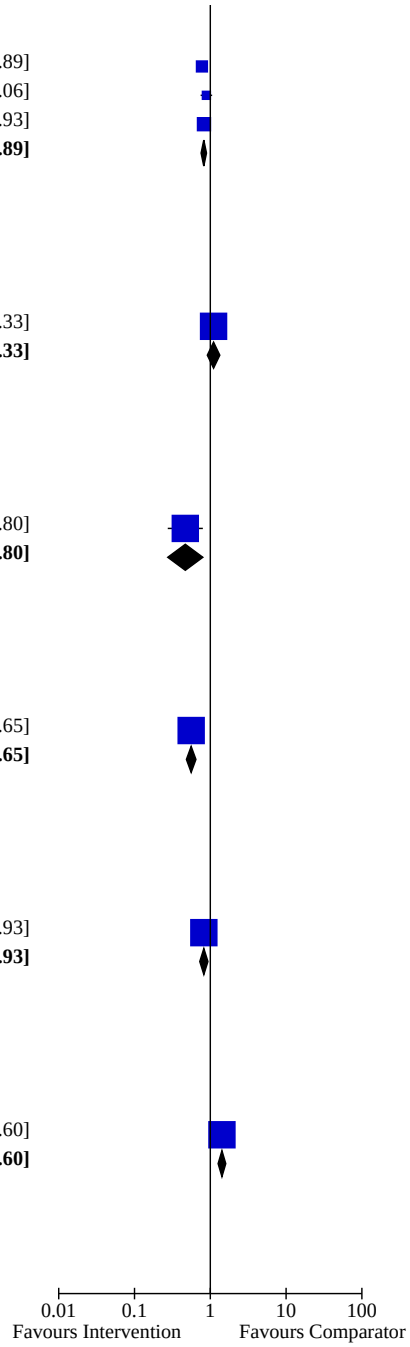
1.2.15 Laquinimod versus placebo/no treatment

ALLEGRO 2013 204 550 266 556 24.5% 0.78 [0.67 , 0.89]



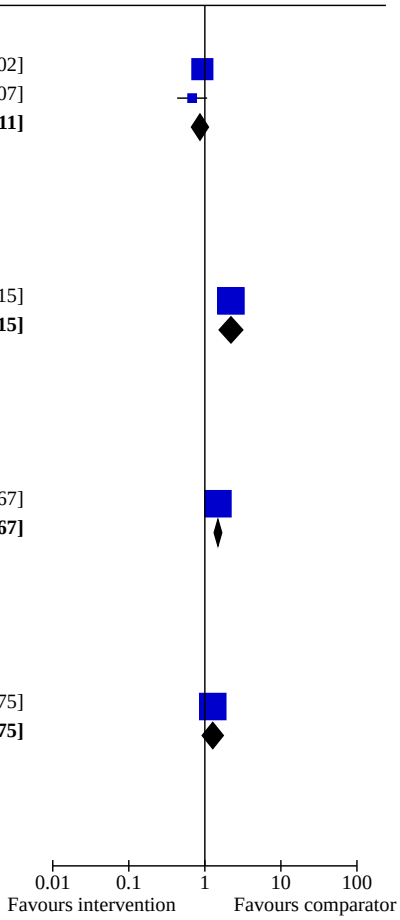
Analysis 1.2. (Continued)

1.2.15 Laquinimod versus placebo/no treatment						
ALLEGRO 2012	204	550	266	556	34.5%	0.78 [0.67 , 0.89]
BRAVO 2014	149	434	174	450	22.0%	0.89 [0.75 , 1.06]
CONCERTO 2021	269	727	332	740	43.5%	0.82 [0.73 , 0.93]
Subtotal (95% CI)		**1711**		**1746**	**100.0%**	**0.82 [0.76 , 0.89]**
Total events:	622		772			
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 4.74 (P < 0.00001)						
1.2.16 Laquinimod versus interferon beta-1a (Avonex, Rebif)						
BRAVO 2014	149	434	139	447	100.0%	1.10 [0.91 , 1.33]
Subtotal (95% CI)		**434**		**447**	**100.0%**	**1.10 [0.91 , 1.33]**
Total events:	149		139			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
1.2.17 Mitoxantrone versus placebo/no treatment						
Millefiorini 1997	10	27	19	24	100.0%	0.47 [0.27 , 0.80]
Subtotal (95% CI)		**27**		**24**	**100.0%**	**0.47 [0.27 , 0.80]**
Total events:	10		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.79 (P = 0.005)						
1.2.18 Natalizumab versus placebo/no treatment						
AFFIRM 2006	207	627	186	315	100.0%	0.56 [0.48 , 0.65]
Subtotal (95% CI)		**627**		**315**	**100.0%**	**0.56 [0.48 , 0.65]**
Total events:	207		186			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.88 (P < 0.00001)						
1.2.19 Teriflunomide versus placebo/no treatment						
TEMSO 2011	325	725	198	363	100.0%	0.82 [0.73 , 0.93]
Subtotal (95% CI)		**725**		**363**	**100.0%**	**0.82 [0.73 , 0.93]**
Total events:	325		198			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.10 (P = 0.002)						
1.2.20 Teriflunomide versus ponesimod						
OPTIMUM 2021	344	566	242	567	100.0%	1.42 [1.27 , 1.60]
Subtotal (95% CI)		**566**		**567**	**100.0%**	**1.42 [1.27 , 1.60]**
Total events:	344		242			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.97 (P < 0.00001)						

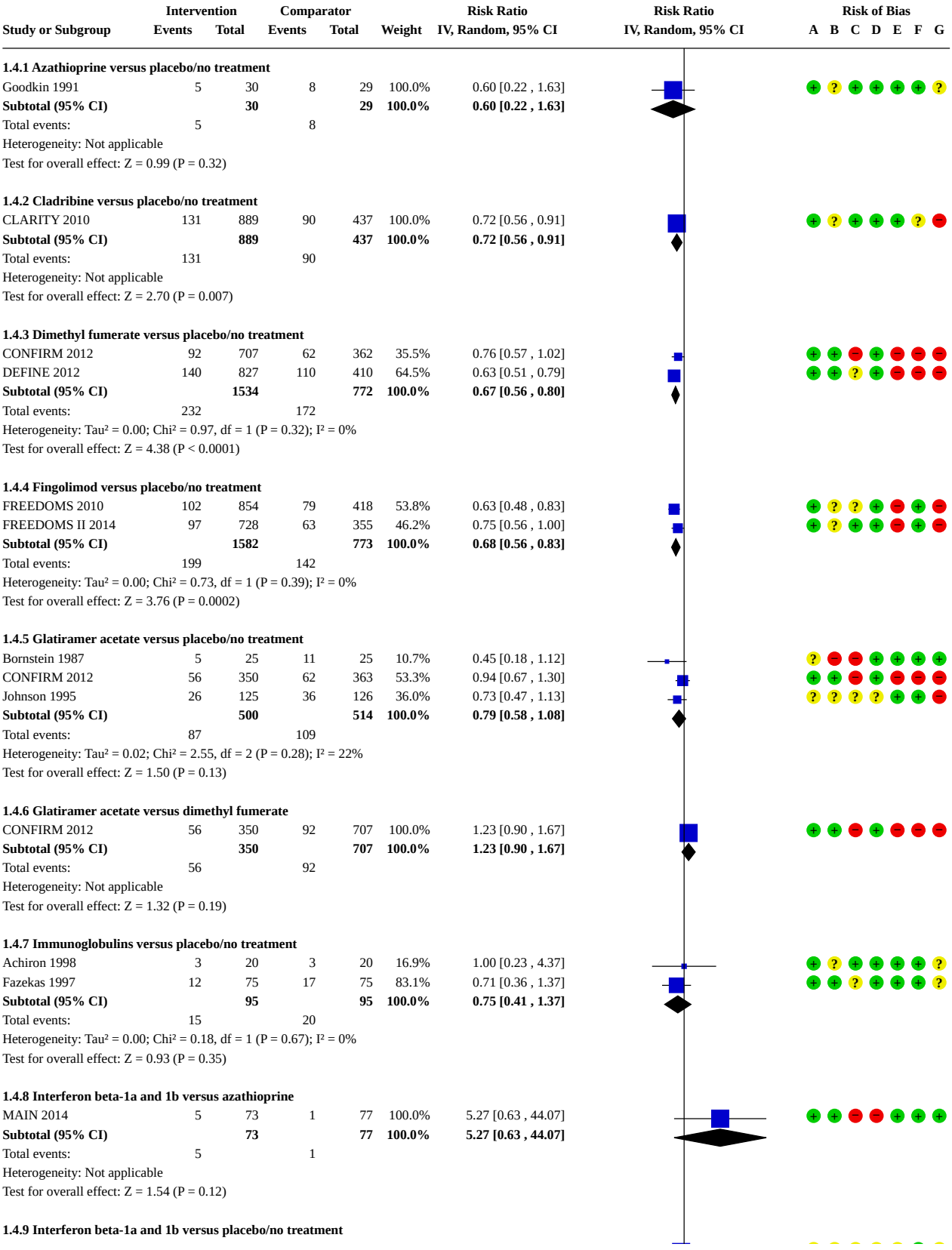


Analysis 1.3. Comparison 1: Treatment efficacy (primary outcomes): pairwise comparisons, Outcome 3: Comparisons for relapse (36 months)

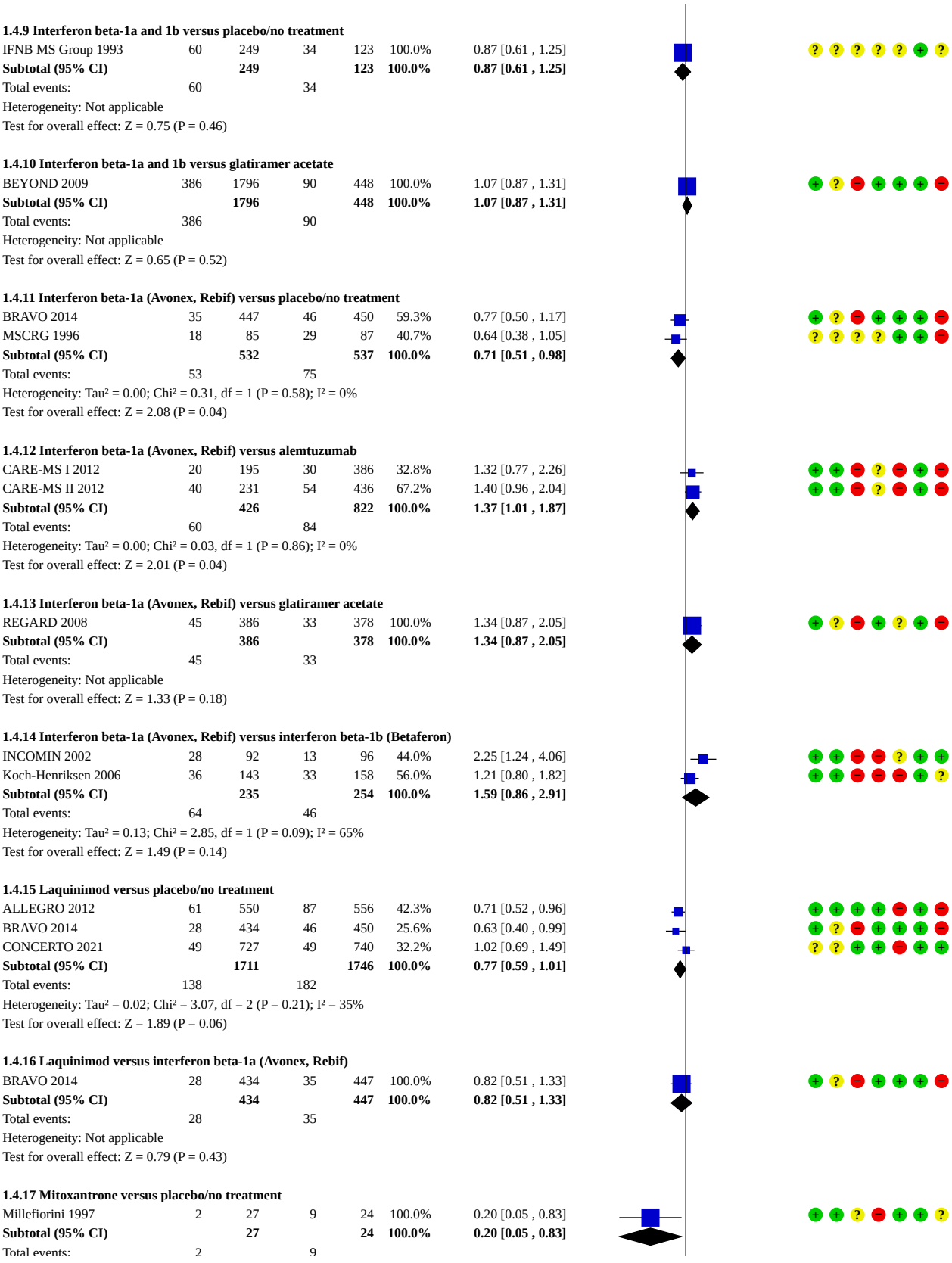
Study or Subgroup	Intervention Events	Intervention Total	Comparator Events	Comparator Total	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 Interferon beta-1b (Betaferon) versus placebo/no treatment						
IFNB MS Group 1993	199	249	106	123	76.8%	0.93 [0.84 , 1.02]
Knobler 1993	14	24	6	7	23.2%	0.68 [0.43 , 1.07]
Subtotal (95% CI)		**273**		**130**	**100.0%**	**0.86 [0.67 , 1.11]**
Total events:	213		112			
Heterogeneity: Tau² = 0.02; Chi² = 1.71, df = 1 (P = 0.19); I² = 42%						
Test for overall effect: Z = 1.13 (P = 0.26)						
1.3.2 Interferon beta-1b (Avonex, Rebif) versus alemtuzumab						
CAMMS223 2008	45	111	41	223	100.0%	2.21 [1.54 , 3.15]
Subtotal (95% CI)		**111**		**223**	**100.0%**	**2.21 [1.54 , 3.15]**
Total events:	45		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.34 (P < 0.0001)						
1.3.3 Interferon beta-1b (Avonex, Rebif) versus daclizumab						
DECIDE 2015	452	922	303	919	100.0%	1.49 [1.33 , 1.67]
Subtotal (95% CI)		**922**		**919**	**100.0%**	**1.49 [1.33 , 1.67]**
Total events:	452		303			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.86 (P < 0.00001)						
1.3.4 Interferon beta-1b (Avonex, Rebif) versus glatiramer acetate						
CombiRx 2013	65	250	53	259	100.0%	1.27 [0.92 , 1.75]
Subtotal (95% CI)		**250**		**259**	**100.0%**	**1.27 [0.92 , 1.75]**
Total events:	65		53			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						



Analysis 1.4. Comparison 1: Treatment efficacy (primary outcomes): pairwise comparisons, Outcome 4: Comparisons for disability worsening (24 months)



Analysis 1.4. (Continued)



1.4.9 Interferon beta-1a and 1b versus placebo/no treatment

IFNB MS Group 1993	60	249	34	123	100.0%	0.87 [0.61 , 1.25]
Subtotal (95% CI)		**249**		**123**	**100.0%**	**0.87 [0.61 , 1.25]**
Total events:	60		34			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.46)

1.4.10 Interferon beta-1a and 1b versus glatiramer acetate

BEYOND 2009	386	1796	90	448	100.0%	1.07 [0.87 , 1.31]
Subtotal (95% CI)		**1796**		**448**	**100.0%**	**1.07 [0.87 , 1.31]**
Total events:	386		90			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)

1.4.11 Interferon beta-1a (Avonex, Rebif) versus placebo/no treatment

BRAVO 2014	35	447	46	450	59.3%	0.77 [0.50 , 1.17]
MSCRG 1996	18	85	29	87	40.7%	0.64 [0.38 , 1.05]
Subtotal (95% CI)		**532**		**537**	**100.0%**	**0.71 [0.51 , 0.98]**
Total events:	53		75			

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)

1.4.12 Interferon beta-1a (Avonex, Rebif) versus alemtuzumab

CARE-MS I 2012	20	195	30	386	32.8%	1.32 [0.77 , 2.26]
CARE-MS II 2012	40	231	54	436	67.2%	1.40 [0.96 , 2.04]
Subtotal (95% CI)		**426**		**822**	**100.0%**	**1.37 [1.01 , 1.87]**
Total events:	60		84			

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)

1.4.13 Interferon beta-1a (Avonex, Rebif) versus glatiramer acetate

REGARD 2008	45	386	33	378	100.0%	1.34 [0.87 , 2.05]
Subtotal (95% CI)		**386**		**378**	**100.0%**	**1.34 [0.87 , 2.05]**
Total events:	45		33			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.33 (P = 0.18)

1.4.14 Interferon beta-1a (Avonex, Rebif) versus interferon beta-1b (Betaferon)

INCOMIN 2002	28	92	13	96	44.0%	2.25 [1.24 , 4.06]
Koch-Henriksen 2006	36	143	33	158	56.0%	1.21 [0.80 , 1.82]
Subtotal (95% CI)		**235**		**254**	**100.0%**	**1.59 [0.86 , 2.91]**
Total events:	64		46			

Heterogeneity: Tau² = 0.13; Chi² = 2.85, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 1.49 (P = 0.14)

1.4.15 Laquinimod versus placebo/no treatment

ALLEGRO 2012	61	550	87	556	42.3%	0.71 [0.52 , 0.96]
BRAVO 2014	28	434	46	450	25.6%	0.63 [0.40 , 0.99]
CONCERTO 2021	49	727	49	740	32.2%	1.02 [0.69 , 1.49]
Subtotal (95% CI)		**1711**		**1746**	**100.0%**	**0.77 [0.59 , 1.01]**
Total events:	138		182			

Heterogeneity: Tau² = 0.02; Chi² = 3.07, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 1.89 (P = 0.06)

1.4.16 Laquinimod versus interferon beta-1a (Avonex, Rebif)

BRAVO 2014	28	434	35	447	100.0%	0.82 [0.51 , 1.33]
Subtotal (95% CI)		**434**		**447**	**100.0%**	**0.82 [0.51 , 1.33]**
Total events:	28		35			

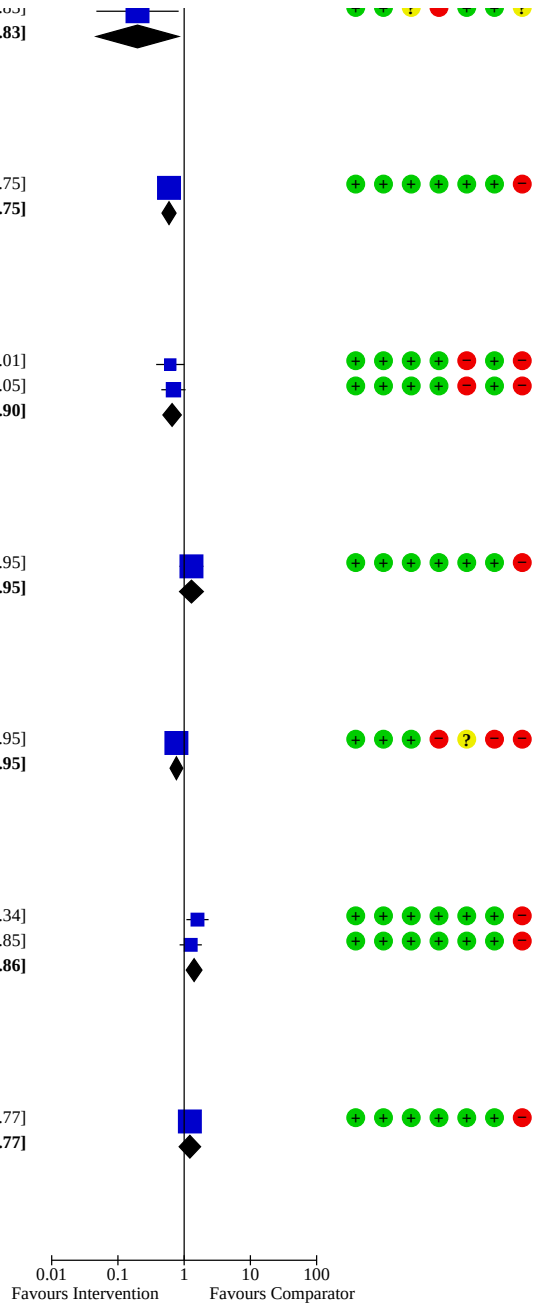
Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)

1.4.17 Mitoxantrone versus placebo/no treatment

Millefiorini 1997	2	27	9	24	100.0%	0.20 [0.05 , 0.83]
Subtotal (95% CI)		**27**		**24**	**100.0%**	**0.20 [0.05 , 0.83]**
Total events:	2		9			

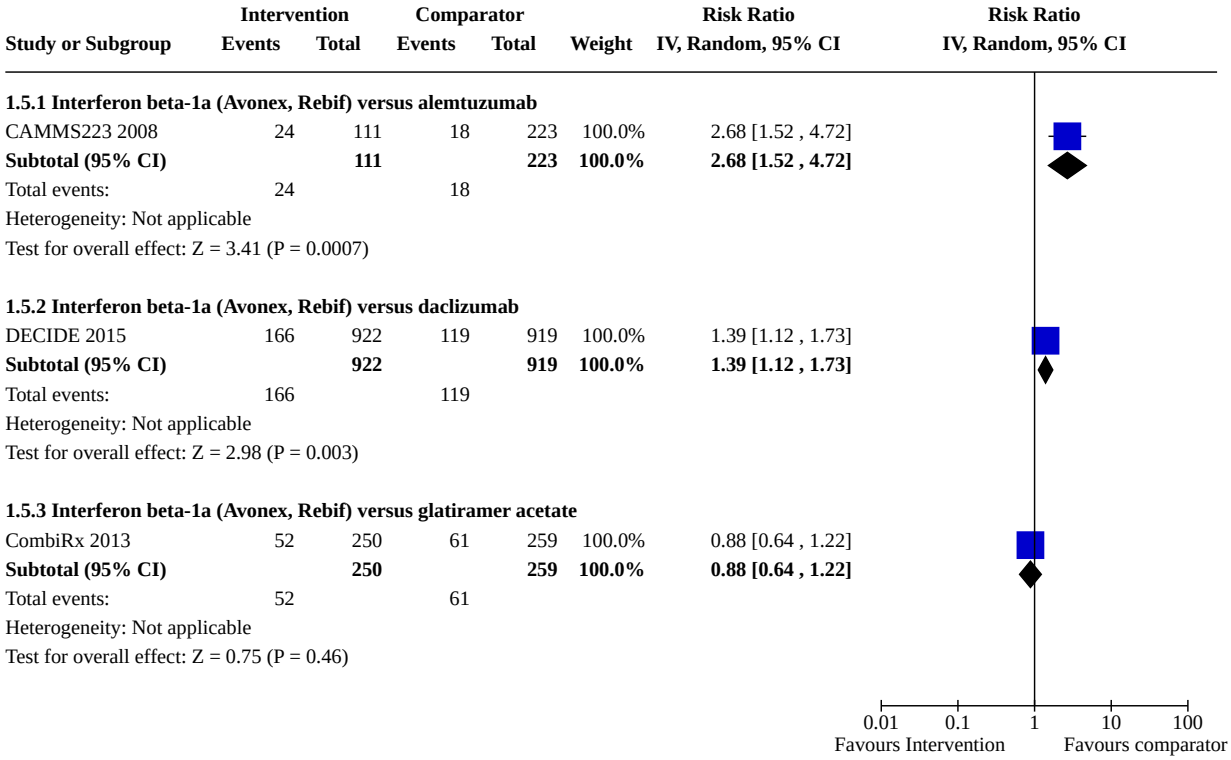
Analysis 1.4. (Continued)

Minerohrin 1997	2	27	9	24	100.0%	0.20 [0.05 , 0.83]
Subtotal (95% CI)		**27**		**24**	**100.0%**	**0.20 [0.05 , 0.83]**
Total events:	2		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.22 (P = 0.03)						
1.4.18 Natalizumab versus placebo/no treatment						
AFFIRM 2006	107	627	91	315	100.0%	0.59 [0.46 , 0.75]
Subtotal (95% CI)		**627**		**315**	**100.0%**	**0.59 [0.46 , 0.75]**
Total events:	107		91			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.22 (P < 0.0001)						
1.4.19 Ocrelizumab versus interferon beta-1a (Avonex, Rebif)						
OPERA I 2017	24	410	39	411	42.6%	0.62 [0.38 , 1.01]
OPERA II 2017	33	417	48	418	57.4%	0.69 [0.45 , 1.05]
Subtotal (95% CI)		**827**		**829**	**100.0%**	**0.66 [0.48 , 0.90]**
Total events:	57		87			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 2.57 (P = 0.01)						
1.4.20 Ozanimod versus interferon beta-1a (Avonex, Rebif)						
RADIANCE 2019	74	877	29	443	100.0%	1.29 [0.85 , 1.95]
Subtotal (95% CI)		**877**		**443**	**100.0%**	**1.29 [0.85 , 1.95]**
Total events:	74		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
1.4.21 Teriflunomide versus placebo/no treatment						
TEMSO 2011	151	725	99	363	100.0%	0.76 [0.61 , 0.95]
Subtotal (95% CI)		**725**		**363**	**100.0%**	**0.76 [0.61 , 0.95]**
Total events:	151		99			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.40 (P = 0.02)						
1.4.22 Teriflunomide versus ofatumumab						
ASCLEPIOS I 2020	60	462	38	465	50.1%	1.59 [1.08 , 2.34]
ASCLEPIOS II 2020	52	474	42	481	49.9%	1.26 [0.85 , 1.85]
Subtotal (95% CI)		**936**		**946**	**100.0%**	**1.41 [1.08 , 1.86]**
Total events:	112		80			
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 2.49 (P = 0.01)						
1.4.23 Teriflunomide versus ponesimod						
OPTIMUM 2021	56	566	46	567	100.0%	1.22 [0.84 , 1.77]
Subtotal (95% CI)		**566**		**567**	**100.0%**	**1.22 [0.84 , 1.77]**
Total events:	56		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Treatment efficacy (primary outcomes): pairwise comparisons, Outcome 5: Comparisons for disability worsening (36 months)



Comparison 2. Treatment safety (primary outcomes): pairwise comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Number of patients who discontinued treatment due to adverse effects	42		Odds Ratio (IV, Random, 95% CI)	Subtotals only
2.1.1 Azathioprine versus placebo/no treatment	1	54	Odds Ratio (IV, Random, 95% CI)	6.26 [0.70, 56.10]
2.1.2 Cladribine versus placebo/no treatment	1	1326	Odds Ratio (IV, Random, 95% CI)	1.38 [0.49, 3.86]
2.1.3 Daclizumab versus placebo/no treatment	1	600	Odds Ratio (IV, Random, 95% CI)	3.74 [0.85, 16.52]
2.1.4 Dimethyl fumarate versus placebo/no treatment	2	2300	Odds Ratio (IV, Random, 95% CI)	1.21 [0.93, 1.57]
2.1.5 Fingolimod versus placebo/no treatment	2	2355	Odds Ratio (IV, Random, 95% CI)	1.74 [1.29, 2.36]
2.1.6 Glatiramer acetate versus placebo/no treatment	4	2417	Odds Ratio (IV, Random, 95% CI)	1.66 [0.77, 3.55]

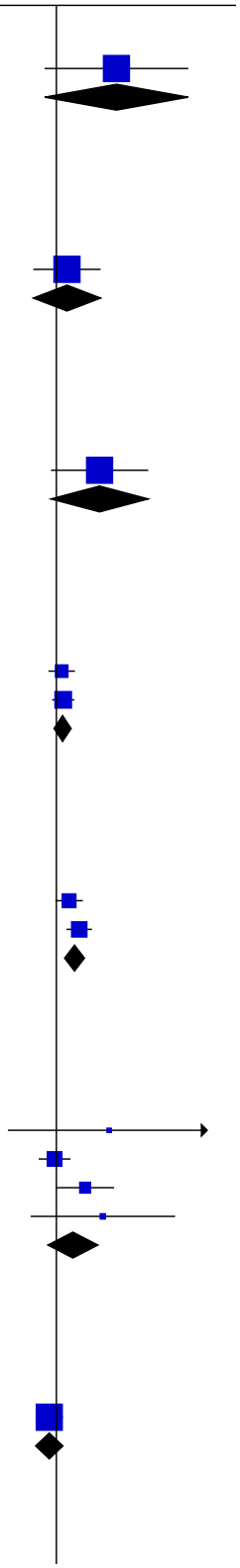
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.7 Glatiramer acetate versus dimethyl fumarate	1	1054	Odds Ratio (IV, Random, 95% CI)	0.81 [0.53, 1.22]
2.1.8 Glatiramer acetate versus fingolimod	1	1064	Odds Ratio (IV, Random, 95% CI)	1.26 [0.71, 2.22]
2.1.9 Immunoglobulins versus placebo/no treatment	2	199	Odds Ratio (IV, Random, 95% CI)	2.49 [0.38, 16.16]
2.1.10 Interferon beta-1a and 1b versus azathioprine	2	235	Odds Ratio (IV, Random, 95% CI)	0.48 [0.19, 1.21]
2.1.11 Interferon beta-1b (Betaferon) versus placebo/no treatment	1	372	Odds Ratio (IV, Random, 95% CI)	7.82 [1.02, 59.91]
2.1.12 Interferon beta-1b (Betaferon) versus fingolimod	1	151	Odds Ratio (IV, Random, 95% CI)	0.73 [0.07, 7.23]
2.1.13 Interferon beta-1b (Betaferon) versus glatiramer acetate	1	2220	Odds Ratio (IV, Random, 95% CI)	1.03 [0.47, 2.26]
2.1.14 Interferon beta-1a (Avonex, Rebif) versus placebo/no treatment	2	1457	Odds Ratio (IV, Random, 95% CI)	1.46 [0.82, 2.62]
2.1.15 Interferon beta-1a (Avonex, Rebif) versus alemtuzumab	3	1514	Odds Ratio (IV, Random, 95% CI)	4.18 [1.87, 9.33]
2.1.16 Interferon beta-1a (Avonex, Rebif) versus daclizumab	1	1841	Odds Ratio (IV, Random, 95% CI)	0.60 [0.45, 0.81]
2.1.17 Interferon beta-1a (Avonex, Rebif) versus fingolimod	1	1280	Odds Ratio (IV, Random, 95% CI)	0.46 [0.26, 0.80]
2.1.18 Interferon beta-1a (Avonex, Rebif) versus glatiramer acetate	2	1265	Odds Ratio (IV, Random, 95% CI)	1.36 [0.84, 2.22]
2.1.19 Interferon beta-1a (Avonex, Rebif) versus interferon beta-1b (Betaferon)	1	188	Odds Ratio (IV, Random, 95% CI)	0.20 [0.02, 1.75]
2.1.20 Laquinimod versus placebo/no treatment	3	3457	Odds Ratio (IV, Random, 95% CI)	1.49 [1.08, 2.06]
2.1.21 Laquinimod versus interferon beta-1a (Avonex, Rebif)	1	881	Odds Ratio (IV, Random, 95% CI)	0.82 [0.46, 1.49]
2.1.22 Pegylated interferon beta-1a versus placebo/no treatment	1	1512	Odds Ratio (IV, Random, 95% CI)	3.58 [1.61, 7.97]
2.1.23 Natalizumab versus placebo/no treatment	1	939	Odds Ratio (IV, Random, 95% CI)	1.63 [0.94, 2.83]
2.1.24 Natalizumab versus interferon beta-1b (Betaferon)	1	19	Odds Ratio (IV, Random, 95% CI)	0.27 [0.01, 7.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.25 Ocrelizumab versus interferon beta-1a (Avonex, Rebif)	2	1651	Odds Ratio (IV, Random, 95% CI)	0.55 [0.35, 0.89]
2.1.26 Ozanimod versus interferon beta-1a (Avonex, Rebif)	2	2659	Odds Ratio (IV, Random, 95% CI)	0.68 [0.44, 1.07]
2.1.27 Teriflunomide versus placebo/no treatment	2	2253	Odds Ratio (IV, Random, 95% CI)	1.83 [0.97, 3.43]
2.1.28 Teriflunomide versus ofatumumab	2	1882	Odds Ratio (IV, Random, 95% CI)	0.91 [0.61, 1.36]
2.1.29 Teriflunomide versus ponesimod	1	1131	Odds Ratio (IV, Random, 95% CI)	0.36 [0.19, 0.68]
2.2 Number of patients with any serious adverse effect	34		Odds Ratio (IV, Random, 95% CI)	Subtotals only
2.2.1 Cladribine versus placebo/no treatment	1	1326	Odds Ratio (IV, Random, 95% CI)	1.39 [0.88, 2.17]
2.2.2 Daclizumab versus placebo/no treatment	1	600	Odds Ratio (IV, Random, 95% CI)	1.41 [0.71, 2.79]
2.2.3 Dimethyl fumarate versus placebo/no treatment	2	2300	Odds Ratio (IV, Random, 95% CI)	1.06 [0.68, 1.65]
2.2.4 Fingolimod versus placebo/no treatment	2	2355	Odds Ratio (IV, Random, 95% CI)	0.98 [0.69, 1.39]
2.2.5 Glatiramer acetate versus placebo/no treatment	3	2369	Odds Ratio (IV, Random, 95% CI)	0.96 [0.65, 1.41]
2.2.6 Glatiramer acetate versus dimethyl fumarate	1	1054	Odds Ratio (IV, Random, 95% CI)	1.05 [0.63, 1.75]
2.2.7 Glatiramer acetate versus fingolimod	1	1064	Odds Ratio (IV, Random, 95% CI)	0.91 [0.53, 1.57]
2.2.8 Interferon beta-1b (Betaferon) versus fingolimod	1	151	Odds Ratio (IV, Random, 95% CI)	0.23 [0.03, 1.87]
2.2.9 Interferon beta-1b (Betaferon) versus glatiramer acetate	2	2295	Odds Ratio (IV, Random, 95% CI)	1.06 [0.78, 1.43]
2.2.10 Interferon beta-1b (Avonex, Rebif) versus placebo/no treatment	1	897	Odds Ratio (IV, Random, 95% CI)	0.72 [0.43, 1.24]
2.2.11 Interferon beta-1b (Avonex, Rebif) versus alemtuzumab	3	1514	Odds Ratio (IV, Random, 95% CI)	0.79 [0.55, 1.14]
2.2.12 Interferon beta-1b (Avonex, Rebif) versus daclizumab	1	1841	Odds Ratio (IV, Random, 95% CI)	0.58 [0.43, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.13 Interferon beta-1b (Avonex, Rebif) versus fingolimod	1	1280	Odds Ratio (IV, Random, 95% CI)	2.17 [1.54, 3.07]
2.2.14 Interferon beta-1b (Avonex, Rebif) versus glatiramer acetate	2	1265	Odds Ratio (IV, Random, 95% CI)	1.21 [0.84, 1.76]
2.2.15 Laquinimod versus placebo/no treatment	3	3457	Odds Ratio (IV, Random, 95% CI)	1.19 [0.86, 1.65]
2.2.16 Laquinimod versus interferon beta-1b (Avonex, Rebif)	1	881	Odds Ratio (IV, Random, 95% CI)	1.16 [0.67, 2.03]
2.2.17 Pegylated interferon beta-1a versus placebo/no treatment	1	1512	Odds Ratio (IV, Random, 95% CI)	1.08 [0.65, 1.79]
2.2.18 Natalizumab versus placebo/no treatment	1	939	Odds Ratio (IV, Random, 95% CI)	1.21 [0.79, 1.86]
2.2.19 Natalizumab versus interferon beta-1b (Betaferon)	1	19	Odds Ratio (IV, Random, 95% CI)	3.00 [0.11, 83.36]
2.2.20 Ocrelizumab versus interferon beta-1b (Avonex, Rebif)	2	1651	Odds Ratio (IV, Random, 95% CI)	0.83 [0.57, 1.19]
2.2.21 Ozanimod versus interferon beta-1b (Avonex, Rebif)	2	2659	Odds Ratio (IV, Random, 95% CI)	1.22 [0.82, 1.82]
2.2.22 Teriflunomide versus placebo/no treatment	2	2253	Odds Ratio (IV, Random, 95% CI)	1.16 [0.88, 1.51]
2.2.23 Teriflunomide versus ofatumumab	2	1882	Odds Ratio (IV, Random, 95% CI)	0.76 [0.55, 1.05]
2.2.24 Teriflunomide versus ponesimod	1	1131	Odds Ratio (IV, Random, 95% CI)	0.93 [0.61, 1.42]

Analysis 2.1. Comparison 2: Treatment safety (primary outcomes): pairwise comparisons, Outcome 1: Number of patients who discontinued treatment due to adverse effects

Study or Subgroup	Intervention Events	Intervention Total	Comparator Events	Comparator Total	Weight	Odds Ratio IV, Random, 95% CI
2.1.1 Azathioprine versus placebo/no treatment						
Goodkin 1991	6	29	1	25	100.0%	6.26 [0.70 , 56.10]
Subtotal (95% CI)		**29**		**25**	**100.0%**	**6.26 [0.70 , 56.10]**
Total events:	6		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						
2.1.2 Cladribine versus placebo/no treatment						
CLARITY 2010	14	889	5	437	100.0%	1.38 [0.49 , 3.86]
Subtotal (95% CI)		**889**		**437**	**100.0%**	**1.38 [0.49 , 3.86]**
Total events:	14		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
2.1.3 Daclizumab versus placebo/no treatment						
SELECT 2013	15	404	2	196	100.0%	3.74 [0.85 , 16.52]
Subtotal (95% CI)		**404**		**196**	**100.0%**	**3.74 [0.85 , 16.52]**
Total events:	15		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.74 (P = 0.08)						
2.1.4 Dimethyl fumarate versus placebo/no treatment						
CONFIRM 2012	85	703	38	363	41.2%	1.18 [0.78 , 1.76]
DEFINE 2012	133	826	55	408	58.8%	1.23 [0.88 , 1.73]
Subtotal (95% CI)		**1529**		**771**	**100.0%**	**1.21 [0.93 , 1.57]**
Total events:	218		93			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0\%$						
Test for overall effect: Z = 1.43 (P = 0.15)						
2.1.5 Fingolimod versus placebo/no treatment						
FREEDOMS 2010	93	854	32	418	46.5%	1.47 [0.97 , 2.24]
FREEDOMS II 2014	138	728	37	355	53.5%	2.01 [1.36 , 2.96]
Subtotal (95% CI)		**1582**		**773**	**100.0%**	**1.74 [1.29 , 2.36]**
Total events:	231		69			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.13$, df = 1 (P = 0.29); $I^2 = 12\%$						
Test for overall effect: Z = 3.58 (P = 0.0003)						
2.1.6 Glatiramer acetate versus placebo/no treatment						
Bornstein 1987	2	25	0	23	5.6%	5.00 [0.23 , 109.86]
CONFIRM 2012	35	351	38	363	50.3%	0.95 [0.58 , 1.54]
GALA 2013	29	943	6	461	34.1%	2.41 [0.99 , 5.84]
Johnson 1995	4	125	1	126	10.0%	4.13 [0.46 , 37.50]
Subtotal (95% CI)		**1444**		**973**	**100.0%**	**1.66 [0.77 , 3.55]**
Total events:	70		45			
Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 5.26$, df = 3 (P = 0.15); $I^2 = 43\%$						
Test for overall effect: Z = 1.30 (P = 0.20)						
2.1.7 Glatiramer acetate versus dimethyl fumarate						
CONFIRM 2012	35	351	85	703	100.0%	0.81 [0.53 , 1.22]
Subtotal (95% CI)		**351**		**703**	**100.0%**	**0.81 [0.53 , 1.22]**
Total events:	35		85			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						



Analysis 2.1. (Continued)

Test for overall effect: Z = 1.02 (P = 0.31)

2.1.8 Glatiramer acetate versus fingolimod

ASSESS 2020	20	342	34	722	100.0%	1.26 [0.71 , 2.22]
Subtotal (95% CI)		**342**		**722**	**100.0%**	**1.26 [0.71 , 2.22]**
Total events:	20		34			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)

2.1.9 Immunoglobulins versus placebo/no treatment

Fazekas 1997	3	75	1	73	66.9%	3.00 [0.30 , 29.52]
Lewanska 2002	1	33	0	18	33.1%	1.71 [0.07 , 44.09]
Subtotal (95% CI)		**108**		**91**	**100.0%**	**2.49 [0.38 , 16.16]**
Total events:	4		1			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 1 (P = 0.78); $I^2 = 0\%$
Test for overall effect: Z = 0.96 (P = 0.34)

2.1.10 Interferon beta-1a and 1b versus azathioprine

Etemadifar 2007	3	47	3	47	29.2%	1.00 [0.19 , 5.23]
MAIN 2014	6	72	14	69	70.8%	0.36 [0.13 , 0.99]
Subtotal (95% CI)		**119**		**116**	**100.0%**	**0.48 [0.19 , 1.21]**
Total events:	9		17			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.08$, df = 1 (P = 0.30); $I^2 = 7\%$
Test for overall effect: Z = 1.56 (P = 0.12)

2.1.11 Interferon beta-1b (Betaferon) versus placebo/no treatment

IFNB MS Group 1993	15	249	1	123	100.0%	7.82 [1.02 , 59.91]
Subtotal (95% CI)		**249**		**123**	**100.0%**	**7.82 [1.02 , 59.91]**
Total events:	15		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.98 (P = 0.05)

2.1.12 Interferon beta-1b (Betaferon) versus fingolimod

GOLDEN 2017	1	47	3	104	100.0%	0.73 [0.07 , 7.23]
Subtotal (95% CI)		**47**		**104**	**100.0%**	**0.73 [0.07 , 7.23]**
Total events:	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)

2.1.13 Interferon beta-1b (Betaferon) versus glatiramer acetate

BEYOND 2009	33	1775	8	445	100.0%	1.03 [0.47 , 2.26]
Subtotal (95% CI)		**1775**		**445**	**100.0%**	**1.03 [0.47 , 2.26]**
Total events:	33		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)

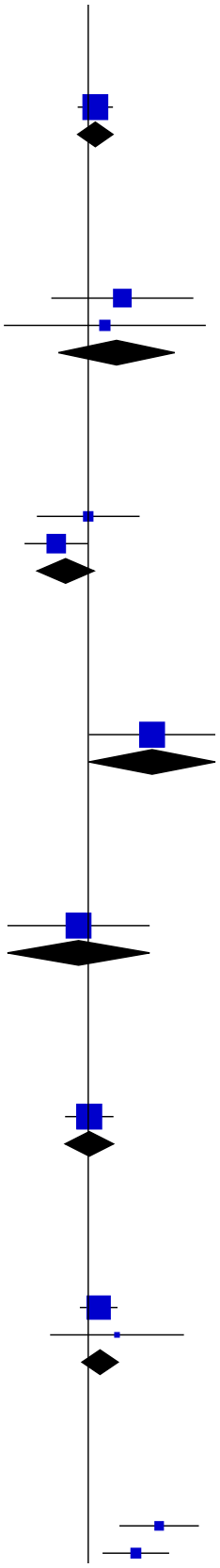
2.1.14 Interferon beta-1a (Avonex, Rebif) versus placebo/no treatment

BRAVO 2014	26	447	19	450	92.7%	1.40 [0.76 , 2.57]
PRISMS 1998	5	373	1	187	7.3%	2.53 [0.29 , 21.79]
Subtotal (95% CI)		**820**		**637**	**100.0%**	**1.46 [0.82 , 2.62]**
Total events:	31		20			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.27$, df = 1 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 1.28 (P = 0.20)

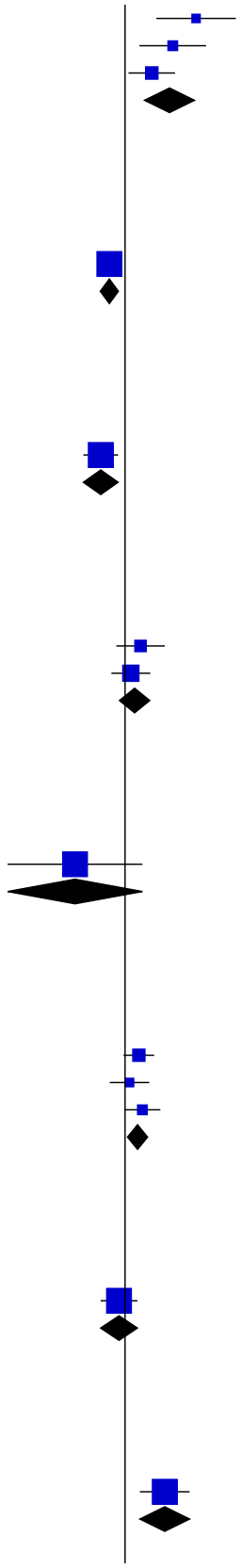
2.1.15 Interferon beta-1a (Avonex, Rebif) versus alemtuzumab

CAMMS223 2008	13	107	3	216	25.3%	9.82 [2.73 , 35.27]
CARE-MS I 2012	11	187	5	376	31.2%	4.64 [1.59 , 13.55]



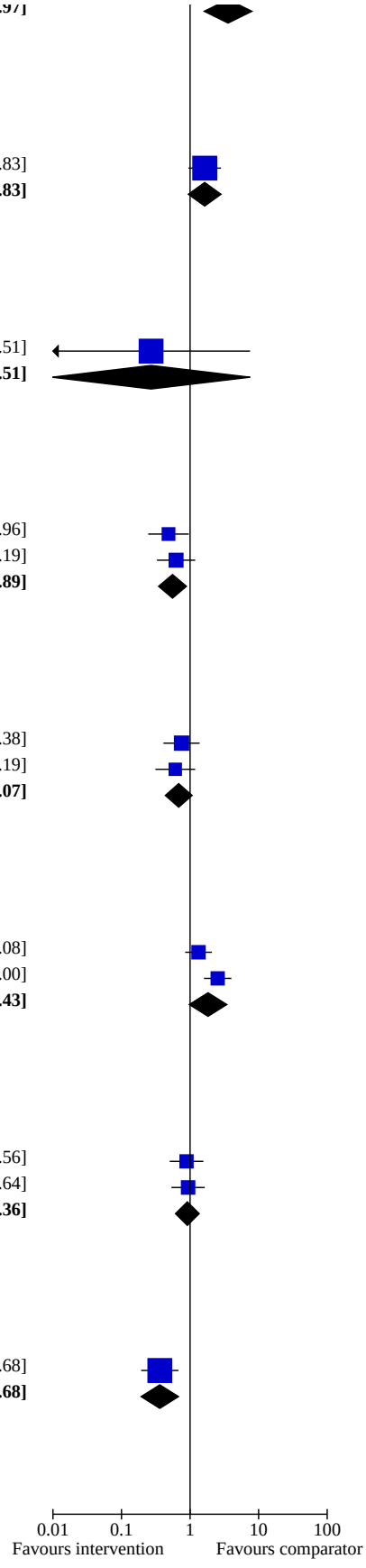
Analysis 2.1. (Continued)

CAMMS223 2008	13	107	3	216	25.3%	9.82 [2.73 , 35.27]
CARE-MS I 2012	11	187	5	376	31.2%	4.64 [1.59 , 13.55]
CARE-MS II 2012	15	202	14	426	43.6%	2.36 [1.12 , 4.99]
Subtotal (95% CI)		**496**		**1018**	**100.0%**	**4.18 [1.87 , 9.33]**
Total events:	39		22			
Heterogeneity: Tau² = 0.24; Chi² = 3.79, df = 2 (P = 0.15); I² = 47%						
Test for overall effect: Z = 3.49 (P = 0.0005)						
2.1.16 Interferon beta-1a (Avonex, Rebif) versus daclizumab						
DECIDE 2015	84	922	131	919	100.0%	0.60 [0.45 , 0.81]
Subtotal (95% CI)		**922**		**919**	**100.0%**	**0.60 [0.45 , 0.81]**
Total events:	84		131			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.41 (P = 0.0006)						
2.1.17 Interferon beta-1a (Avonex, Rebif) versus fingolimod						
TRANSFORMS 2010	16	431	66	849	100.0%	0.46 [0.26 , 0.80]
Subtotal (95% CI)		**431**		**849**	**100.0%**	**0.46 [0.26 , 0.80]**
Total events:	16		66			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.74 (P = 0.006)						
2.1.18 Interferon beta-1a (Avonex, Rebif) versus glatiramer acetate						
CombiRx 2013	17	250	11	259	39.2%	1.64 [0.75 , 3.59]
REGARD 2008	23	381	19	375	60.8%	1.20 [0.64 , 2.25]
Subtotal (95% CI)		**631**		**634**	**100.0%**	**1.36 [0.84 , 2.22]**
Total events:	40		30			
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.22)						
2.1.19 Interferon beta-1a (Avonex, Rebif) versus interferon beta-1b (Betaferon)						
INCOMIN 2002	1	92	5	96	100.0%	0.20 [0.02 , 1.75]
Subtotal (95% CI)		**92**		**96**	**100.0%**	**0.20 [0.02 , 1.75]**
Total events:	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.15)						
2.1.20 Laquinimod versus placebo/no treatment						
ALLEGRO 2012	42	550	28	556	42.8%	1.56 [0.95 , 2.55]
BRAVO 2014	21	434	19	450	25.9%	1.15 [0.61 , 2.18]
CONCERTO 2021	32	727	19	740	31.3%	1.75 [0.98 , 3.11]
Subtotal (95% CI)		**1711**		**1746**	**100.0%**	**1.49 [1.08 , 2.06]**
Total events:	95		66			
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 2.44 (P = 0.01)						
2.1.21 Laquinimod versus interferon beta-1a (Avonex, Rebif)						
BRAVO 2014	21	434	26	447	100.0%	0.82 [0.46 , 1.49]
Subtotal (95% CI)		**434**		**447**	**100.0%**	**0.82 [0.46 , 1.49]**
Total events:	21		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
2.1.22 Pegylated interferon beta-1a versus placebo/no treatment						
ADVANCE 2014	49	1012	7	500	100.0%	3.58 [1.61 , 7.97]
Subtotal (95% CI)		**1012**		**500**	**100.0%**	**3.58 [1.61 , 7.97]**
Total events:	49		7			



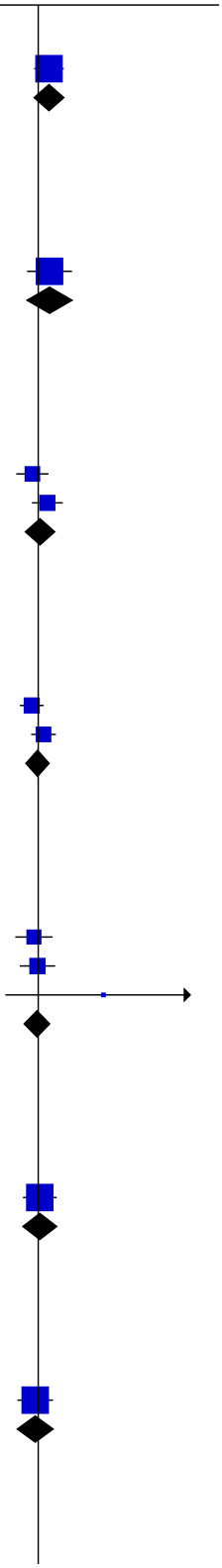
Analysis 2.1. (Continued)

Subtotal (95% CI)		**1012**		**500**	**100.0%**	**3.58 [1.61 , 7.97]**
Total events:	49		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.13 (P = 0.002)						
2.1.23 Natalizumab versus placebo/no treatment						
AFFIRM 2006	57	627	18	312	100.0%	1.63 [0.94 , 2.83]
Subtotal (95% CI)		**627**		**312**	**100.0%**	**1.63 [0.94 , 2.83]**
Total events:	57		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
2.1.24 Natalizumab versus interferon beta-1b (Betaferon)						
Gobbi 2013	0	10	1	9	100.0%	0.27 [0.01 , 7.51]
Subtotal (95% CI)		**10**		**9**	**100.0%**	**0.27 [0.01 , 7.51]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
2.1.25 Ocrelizumab versus interferon beta-1a (Avonex, Rebif)						
OPERA I 2017	13	408	26	409	47.2%	0.48 [0.25 , 0.96]
OPERA II 2017	16	417	25	417	52.8%	0.63 [0.33 , 1.19]
Subtotal (95% CI)		**825**		**826**	**100.0%**	**0.55 [0.35 , 0.89]**
Total events:	29		51			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.29$, df = 1 (P = 0.59); $I^2 = 0\%$						
Test for overall effect: Z = 2.47 (P = 0.01)						
2.1.26 Ozanimod versus interferon beta-1a (Avonex, Rebif)						
RADIANCE 2019	27	872	18	441	54.7%	0.75 [0.41 , 1.38]
SUNBEAM 2019	20	901	16	445	45.3%	0.61 [0.31 , 1.19]
Subtotal (95% CI)		**1773**		**886**	**100.0%**	**0.68 [0.44 , 1.07]**
Total events:	47		34			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.21$, df = 1 (P = 0.65); $I^2 = 0\%$						
Test for overall effect: Z = 1.66 (P = 0.10)						
2.1.27 Teriflunomide versus placebo/no treatment						
Achiron 1998	75	725	29	363	50.3%	1.33 [0.85 , 2.08]
TOWER 2014	111	777	24	388	49.7%	2.53 [1.60 , 4.00]
Subtotal (95% CI)		**1502**		**751**	**100.0%**	**1.83 [0.97 , 3.43]**
Total events:	186		53			
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 3.85$, df = 1 (P = 0.05); $I^2 = 74\%$						
Test for overall effect: Z = 1.88 (P = 0.06)						
2.1.28 Teriflunomide versus ofatumumab						
ASCLEPIOS I 2020	24	462	27	465	49.5%	0.89 [0.50 , 1.56]
ASCLEPIOS II 2020	25	474	27	481	50.5%	0.94 [0.54 , 1.64]
Subtotal (95% CI)		**936**		**946**	**100.0%**	**0.91 [0.61 , 1.36]**
Total events:	49		54			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.90); $I^2 = 0\%$						
Test for overall effect: Z = 0.45 (P = 0.65)						
2.1.29 Teriflunomide versus ponesimod						
OPTIMUM 2021	14	566	37	565	100.0%	0.36 [0.19 , 0.68]
Subtotal (95% CI)		**566**		**565**	**100.0%**	**0.36 [0.19 , 0.68]**
Total events:	14		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.18 (P = 0.001)						



Analysis 2.2. Comparison 2: Treatment safety (primary outcomes): pairwise comparisons, Outcome 2: Number of patients with any serious adverse effect

Study or Subgroup	Intervention Events	Intervention Total	Comparator Events	Comparator Total	Weight	Odds Ratio IV, Random, 95% CI
2.2.1 Cladribine versus placebo/no treatment						
CLARITY 2010	77	889	28	437	100.0%	1.39 [0.88 , 2.17]
Subtotal (95% CI)		**889**		**437**	**100.0%**	**1.39 [0.88 , 2.17]**
Total events:	77		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.15)						
2.2.2 Daclizumab versus placebo/no treatment						
SELECT 2013	34	404	12	196	100.0%	1.41 [0.71 , 2.79]
Subtotal (95% CI)		**404**		**196**	**100.0%**	**1.41 [0.71 , 2.79]**
Total events:	34		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
2.2.3 Dimethyl fumarate versus placebo/no treatment						
CONFIRM 2012	46	703	28	363	48.8%	0.84 [0.51 , 1.36]
DEFINE 2012	68	826	26	408	51.2%	1.32 [0.83 , 2.11]
Subtotal (95% CI)		**1529**		**771**	**100.0%**	**1.06 [0.68 , 1.65]**
Total events:	114		54			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.73$, df = 1 (P = 0.19); $I^2 = 42\%$						
Test for overall effect: Z = 0.24 (P = 0.81)						
2.2.4 Fingolimod versus placebo/no treatment						
FREEDOMS 2010	91	854	53	418	51.0%	0.82 [0.57 , 1.18]
FREEDOMS II 2014	106	728	45	355	49.0%	1.17 [0.81 , 1.71]
Subtotal (95% CI)		**1582**		**773**	**100.0%**	**0.98 [0.69 , 1.39]**
Total events:	197		98			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 1.81$, df = 1 (P = 0.18); $I^2 = 45\%$						
Test for overall effect: Z = 0.12 (P = 0.90)						
2.2.5 Glatiramer acetate versus placebo/no treatment						
CONFIRM 2012	24	351	28	363	46.5%	0.88 [0.50 , 1.55]
GALA 2013	42	943	21	461	51.8%	0.98 [0.57 , 1.67]
Johnson 1995	3	125	0	126	1.7%	7.23 [0.37 , 141.40]
Subtotal (95% CI)		**1419**		**950**	**100.0%**	**0.96 [0.65 , 1.41]**
Total events:	69		49			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.87$, df = 2 (P = 0.39); $I^2 = 0\%$						
Test for overall effect: Z = 0.20 (P = 0.84)						
2.2.6 Glatiramer acetate versus dimethyl fumarate						
CONFIRM 2012	24	351	46	703	100.0%	1.05 [0.63 , 1.75]
Subtotal (95% CI)		**351**		**703**	**100.0%**	**1.05 [0.63 , 1.75]**
Total events:	24		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						
2.2.7 Glatiramer acetate versus fingolimod						
ASSESS 2020	20	342	46	722	100.0%	0.91 [0.53 , 1.57]
Subtotal (95% CI)		**342**		**722**	**100.0%**	**0.91 [0.53 , 1.57]**
Total events:	20		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						



Analysis 2.2. (Continued)

Test for overall effect: Z = 0.33 (P = 0.74)

2.2.8 Interferon beta-1b (Betaferon) versus fingolimod

GOLDEN 2017	1	47	9	104	100.0%	0.23 [0.03 , 1.87]
Subtotal (95% CI)		**47**		**104**	**100.0%**	**0.23 [0.03 , 1.87]**
Total events:	1		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

2.2.9 Interferon beta-1b (Betaferon) versus glatiramer acetate

BECOME 2009	7	36	7	39	6.6%	1.10 [0.35 , 3.53]
BEYOND 2009	238	1775	57	445	93.4%	1.05 [0.77 , 1.44]
Subtotal (95% CI)		**1811**		**484**	**100.0%**	**1.06 [0.78 , 1.43]**
Total events:	245		64			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)

2.2.10 Interferon beta-1b (Avonex, Rebif) versus placebo/no treatment

BRAVO 2014	25	447	34	450	100.0%	0.72 [0.43 , 1.24]
Subtotal (95% CI)		**447**		**450**	**100.0%**	**0.72 [0.43 , 1.24]**
Total events:	25		34			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)

2.2.11 Interferon beta-1b (Avonex, Rebif) versus alemtuzumab

CAMMS223 2008	24	107	51	216	33.3%	0.94 [0.54 , 1.63]
CARE-MS I 2012	14	187	51	376	27.8%	0.52 [0.28 , 0.96]
CARE-MS II 2012	26	202	58	426	38.9%	0.94 [0.57 , 1.54]
Subtotal (95% CI)		**496**		**1018**	**100.0%**	**0.79 [0.55 , 1.14]**
Total events:	64		160			

Heterogeneity: Tau² = 0.03; Chi² = 2.63, df = 2 (P = 0.27); I² = 24%
Test for overall effect: Z = 1.24 (P = 0.21)

2.2.12 Interferon beta-1b (Avonex, Rebif) versus daclizumab

DECIDE 2015	88	922	142	919	100.0%	0.58 [0.43 , 0.77]
Subtotal (95% CI)		**922**		**919**	**100.0%**	**0.58 [0.43 , 0.77]**
Total events:	88		142			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.80 (P = 0.0001)

2.2.13 Interferon beta-1b (Avonex, Rebif) versus fingolimod

TRANSFORMS 2010	74	431	74	849	100.0%	2.17 [1.54 , 3.07]
Subtotal (95% CI)		**431**		**849**	**100.0%**	**2.17 [1.54 , 3.07]**
Total events:	74		74			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.39 (P < 0.0001)

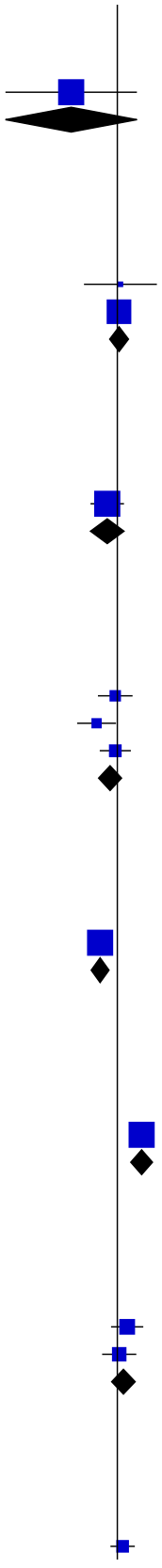
2.2.14 Interferon beta-1b (Avonex, Rebif) versus glatiramer acetate

CombiRx 2013	38	250	30	259	52.9%	1.37 [0.82 , 2.29]
REGARD 2008	29	381	27	375	47.1%	1.06 [0.62 , 1.83]
Subtotal (95% CI)		**631**		**634**	**100.0%**	**1.21 [0.84 , 1.76]**
Total events:	67		57			

Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)

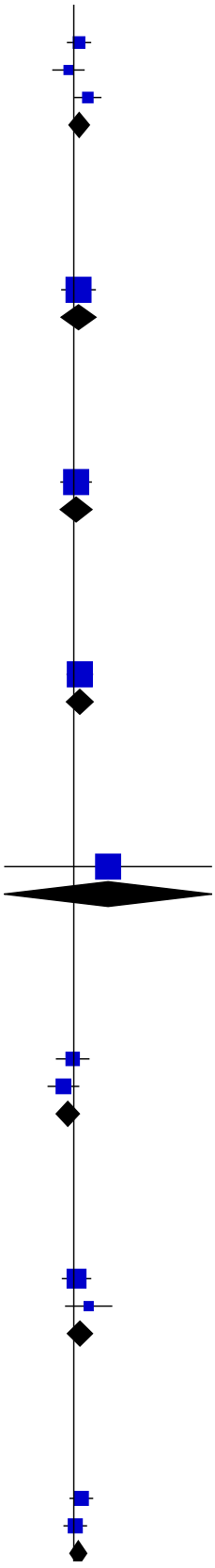
2.2.15 Laquinimod versus placebo/no treatment

ALLEGRO 2012	61	550	53	556	38.8%	1.18 [0.80 , 1.75]



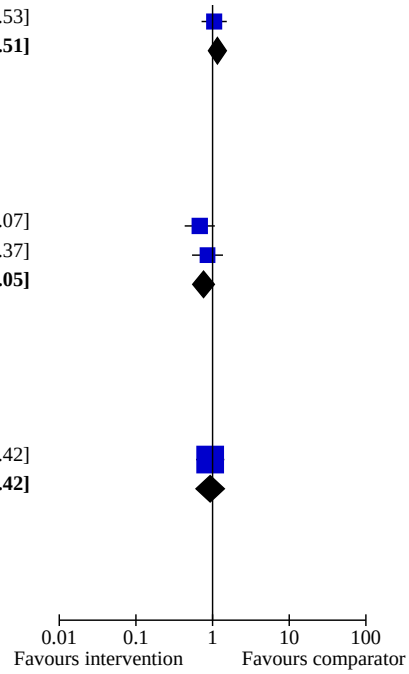
Analysis 2.2. (Continued)

2.2.15 Laquinimod versus placebo/no treatment						
ALLEGRO 2012	61	550	53	556	38.8%	1.18 [0.80 , 1.75]
BRAVO 2014	28	434	34	450	27.1%	0.84 [0.50 , 1.42]
CONCERTO 2021	54	727	36	740	34.1%	1.57 [1.02 , 2.42]
Subtotal (95% CI)		**1711**		**1746**	**100.0%**	**1.19 [0.86 , 1.65]**
Total events:	143		123			
Heterogeneity: Tau² = 0.03; Chi² = 3.24, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 1.04 (P = 0.30)						
2.2.16 Laquinimod versus interferon beta-1b (Avonex, Rebif)						
BRAVO 2014	28	434	25	447	100.0%	1.16 [0.67 , 2.03]
Subtotal (95% CI)		**434**		**447**	**100.0%**	**1.16 [0.67 , 2.03]**
Total events:	28		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
2.2.17 Pegylated interferon beta-1a versus placebo/no treatment						
ADVANCE 2014	50	1012	23	500	100.0%	1.08 [0.65 , 1.79]
Subtotal (95% CI)		**1012**		**500**	**100.0%**	**1.08 [0.65 , 1.79]**
Total events:	50		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
2.2.18 Natalizumab versus placebo/no treatment						
AFFIRM 2006	81	627	34	312	100.0%	1.21 [0.79 , 1.86]
Subtotal (95% CI)		**627**		**312**	**100.0%**	**1.21 [0.79 , 1.86]**
Total events:	81		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
2.2.19 Natalizumab versus interferon beta-1b (Betaferon)						
Gobbi 2013	1	10	0	9	100.0%	3.00 [0.11 , 83.36]
Subtotal (95% CI)		**10**		**9**	**100.0%**	**3.00 [0.11 , 83.36]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
2.2.20 Ocrelizumab versus interferon beta-1b (Avonex, Rebif)						
OPERA I 2017	28	408	29	409	47.1%	0.97 [0.56 , 1.65]
OPERA II 2017	28	417	38	417	52.9%	0.72 [0.43 , 1.19]
Subtotal (95% CI)		**825**		**826**	**100.0%**	**0.83 [0.57 , 1.19]**
Total events:	56		67			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
2.2.21 Ozanimod versus interferon beta-1b (Avonex, Rebif)						
RADIANCE 2019	58	872	27	441	72.0%	1.09 [0.68 , 1.75]
SUNBEAM 2019	29	901	9	445	28.0%	1.61 [0.76 , 3.43]
Subtotal (95% CI)		**1773**		**886**	**100.0%**	**1.22 [0.82 , 1.82]**
Total events:	87		36			
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
2.2.22 Teriflunomide versus placebo/no treatment						
TEMSO 2011	106	725	43	363	49.9%	1.27 [0.87 , 1.86]
TOWER 2014	94	777	45	388	50.1%	1.05 [0.72 , 1.53]
Subtotal (95% CI)		**1502**		**751**	**100.0%**	**1.16 [0.88 , 1.51]**



Analysis 2.2. (Continued)

TOWER 2014	94	777	45	388	50.1%	1.05 [0.72 , 1.53]
Subtotal (95% CI)		**1502**		**751**	**100.0%**	**1.16 [0.88 , 1.51]**
Total events:	200		88			
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.06 (P = 0.29)						
2.2.23 Teriflunomide versus ofatumumab						
ASCLEPIOS I 2020	35	462	50	465	51.3%	0.68 [0.43 , 1.07]
ASCLEPIOS II 2020	36	474	42	481	48.7%	0.86 [0.54 , 1.37]
Subtotal (95% CI)		**936**		**946**	**100.0%**	**0.76 [0.55 , 1.05]**
Total events:	71		92			
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
2.2.24 Teriflunomide versus ponesimod						
OPTIMUM 2021	45	566	48	565	100.0%	0.93 [0.61 , 1.42]
Subtotal (95% CI)		**566**		**565**	**100.0%**	**0.93 [0.61 , 1.42]**
Total events:	45		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						



Comparison 3. Treatment efficacy and safety (secondary outcomes): pairwise comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Comparisons for new gadolinium-enhancing positive T1-weighted MRI lesions (12 months)	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1.1 Daclizumab versus placebo/no treatment	1	621	Risk Ratio (IV, Random, 95% CI)	1.00 [0.97, 1.04]
3.1.2 Glatiramer acetate versus fingolimod	1	1035	Risk Ratio (IV, Random, 95% CI)	1.48 [1.23, 1.79]
3.1.3 Interferon beta-1b (Avonex, Rebif) versus fingolimod	1	1080	Risk Ratio (IV, Random, 95% CI)	2.05 [1.50, 2.80]
3.1.4 Interferon beta-1b (Avonex, Rebif) versus interferon beta-1b (Betaferon)	1	188	Risk Ratio (IV, Random, 95% CI)	2.39 [1.03, 5.53]
3.1.5 Natalizumab versus placebo/no treatment	1	942	Risk Ratio (IV, Random, 95% CI)	0.11 [0.07, 0.17]
3.1.6 Ozanimod versus interferon beta-1b (Avonex, Rebif)	1	1346	Risk Ratio (IV, Random, 95% CI)	0.49 [0.43, 0.55]
3.2 Comparisons for new gadolinium-enhancing positive T1-weighted MRI lesions (24 months)	11		Risk Ratio (IV, Random, 95% CI)	Subtotals only

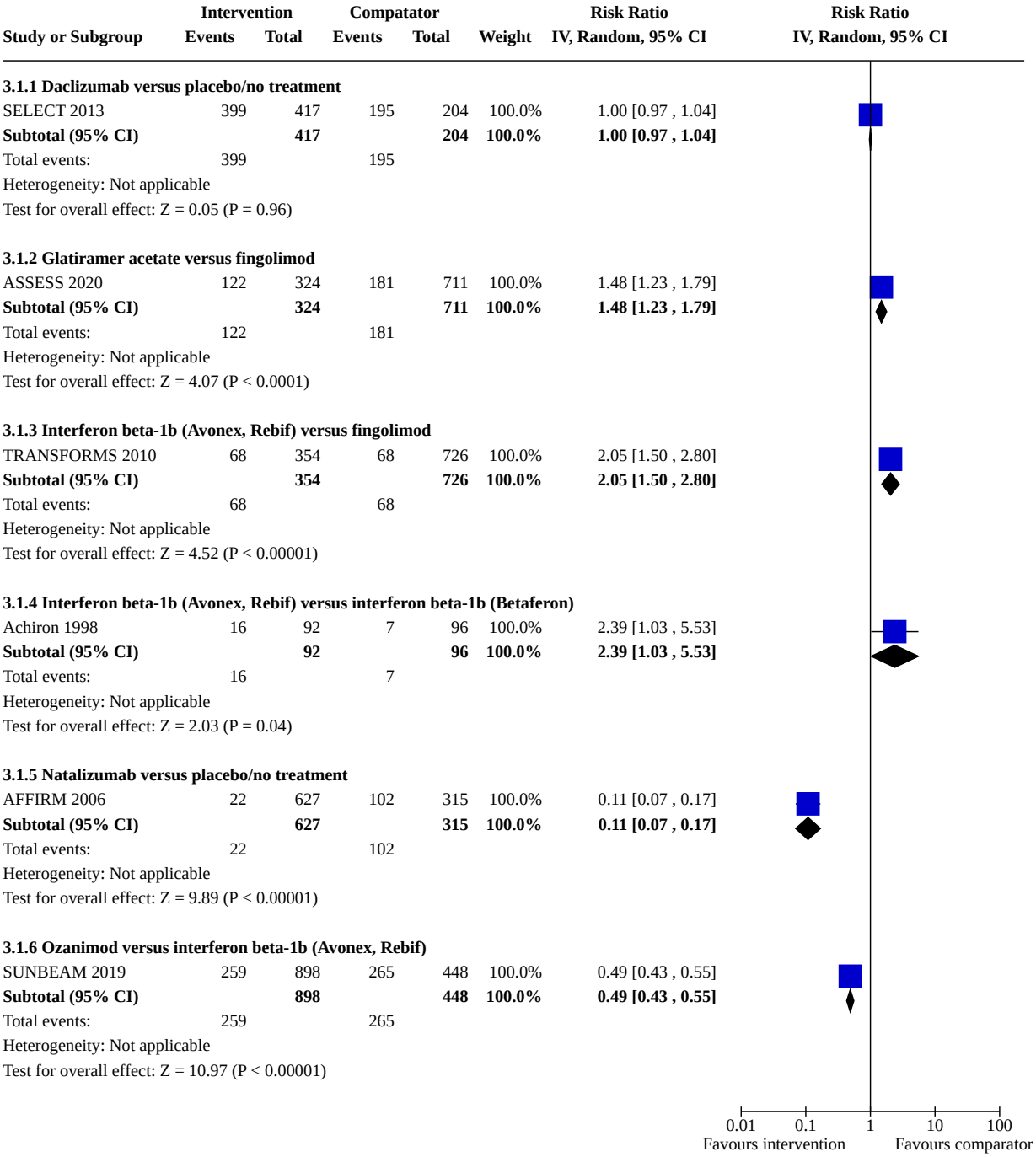
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2.1 Dimethyl fumarate versus placebo/no treatment	1	435	Risk Ratio (IV, Random, 95% CI)	0.50 [0.37, 0.69]
3.2.2 Fingolimod versus placebo/no treatment	1	1044	Risk Ratio (IV, Random, 95% CI)	0.29 [0.23, 0.38]
3.2.3 Glatiramer acetate versus placebo/no treatment	1	305	Risk Ratio (IV, Random, 95% CI)	0.59 [0.42, 0.84]
3.2.4 Glatiramer acetate versus dimethyl fumarate	1	452	Risk Ratio (IV, Random, 95% CI)	1.17 [0.81, 1.69]
3.2.5 Interferon beta-1a and 1b versus azathioprine	1	150	Risk Ratio (IV, Random, 95% CI)	0.53 [0.17, 1.68]
3.2.6 Interferon beta-1a (Avonex, Rebif) versus alemtuzumab	2	1144	Risk Ratio (IV, Random, 95% CI)	2.57 [1.90, 3.50]
3.2.7 Interferon beta-1a (Avonex, Rebif) versus glatiramer acetate	1	460	Risk Ratio (IV, Random, 95% CI)	0.58 [0.42, 0.80]
3.2.8 Interferon beta-1a (Avonex, Rebif) versus interferon beta-1b (Betaferon)	1	188	Risk Ratio (IV, Random, 95% CI)	2.14 [1.32, 3.48]
3.2.9 Natalizumab versus placebo/no treatment	1	942	Risk Ratio (IV, Random, 95% CI)	0.11 [0.07, 0.17]
3.2.10 Ocrelizumab versus interferon beta-1a (Avonex, Rebif)	2	1656	Risk Ratio (IV, Random, 95% CI)	0.27 [0.22, 0.35]
3.2.11 Ozanimod versus interferon beta-1a (Avonex, Rebif)	1	1320	Risk Ratio (IV, Random, 95% CI)	0.88 [0.77, 1.00]
3.3 Comparisons for new or enlarging T2-weighted MRI lesions (12 months)	7		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.3.1 Daclizumab versus placebo/no treatment	1	621	Risk Ratio (IV, Random, 95% CI)	1.00 [0.97, 1.04]
3.3.2 Glatiramer acetate versus fingolimod	1	1035	Risk Ratio (IV, Random, 95% CI)	1.25 [1.14, 1.38]
3.3.3 Interferon beta-1b (Betaferon) versus fingolimod	1	1083	Risk Ratio (IV, Random, 95% CI)	1.12 [0.99, 1.26]
3.3.4 Interferon beta-1b (Betaferon) versus immunoglobulins	1	188	Risk Ratio (IV, Random, 95% CI)	2.15 [1.27, 3.64]
3.3.5 Interferon beta-1a (Avonex, Rebif) versus placebo/no treatment	1	942	Risk Ratio (IV, Random, 95% CI)	0.51 [0.45, 0.57]
3.3.6 Interferon beta-1a (Avonex, Rebif) versus immunoglobulins	1	19	Risk Ratio (IV, Random, 95% CI)	0.51 [0.22, 1.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.7 Natalizumab versus interferon beta-1b (Betaferon)	1	1346	Risk Ratio (IV, Random, 95% CI)	0.95 [0.89, 1.02]
3.4 Comparisons for new or enlarging T2-weighted MRI lesions (24 months)	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.4.1 Fingolimod versus placebo/ no treatment	1	1046	Risk Ratio (IV, Random, 95% CI)	0.62 [0.56, 0.68]
3.4.2 Interferon beta 1a and 1b versus azathioprine	1	150	Risk Ratio (IV, Random, 95% CI)	1.19 [0.75, 1.89]
3.4.3 Interferon beta 1a (Avonex, Rebif) versus alemtuzumab	2	1131	Risk Ratio (IV, Random, 95% CI)	1.30 [1.02, 1.66]
3.4.4 Interferon beta 1a (Avonex, Rebif) versus glatiramer acetate	1	460	Risk Ratio (IV, Random, 95% CI)	0.95 [0.82, 1.10]
3.4.5 Interferon beta 1a (Avonex, Rebif) versus interferon beta 1b (Betaferon)	1	188	Risk Ratio (IV, Random, 95% CI)	1.66 [1.20, 2.28]
3.4.6 Natalizumab versus placebo/ no treatment	1	942	Risk Ratio (IV, Random, 95% CI)	0.50 [0.45, 0.55]
3.4.7 Ocrelizumab versus interferon beta 1a (Avonex, Rebif)	2	1656	Risk Ratio (IV, Random, 95% CI)	0.63 [0.57, 0.69]
3.4.8 Ozanimod versus interferon beta 1a (Avonex, Rebif)	1	1320	Risk Ratio (IV, Random, 95% CI)	0.93 [0.88, 0.99]
3.5 Comparisons for quality of life total (non-MS related: EQ-5D VAS)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.5.1 Cladribine versus Placebo/no treatment	1	1042	Std. Mean Difference (IV, Fixed, 95% CI)	0.19 [0.06, 0.32]
3.6 Comparisons for quality of life total (non-MS related) (INDEX)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.7 Comparisons for quality of life - physical (non-MS related: SF-36)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.7.1 Teriflunomide versus Placebo/ no treatment	1	1169	Std. Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.02, 0.22]
3.8 Comparisons for quality of life - physical (MS related: MSQOL-54 PH; MSQoL-54; MSIS29 Psychological)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.8.1 Interferon beta 1a Avonex/Rebif versus Daclizumab	1	1064	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.23, 0.03]
3.8.2 Interferon beta 1b Betaferon versus Interferon beta 1a Avonex Rebif	1	69	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.55, 0.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.8.3 Interferon beta 1a Avonex Rebif versus Ozanimod	2	2666	Std. Mean Difference (IV, Random, 95% CI)	0.14 [0.06, 0.23]
3.8.4 Daclizumab versus Placebo/No treatment	1	621	Std. Mean Difference (IV, Random, 95% CI)	0.22 [0.05, 0.38]
3.9 Comparisons for quality of life - mental (Non-MS related: SF-36)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.9.1 Teriflunomide versus Placebo/ no treatment	1	1169	Std. Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.02, 0.22]
3.10 Comparisons for quality of life - mental (MS related: MSQOL-54 PH; MSQoL-54; MSIS29 Psychological)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.10.1 Interferon beta 1a Avonex/Rebif versus Daclizumab	1	1841	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.18, 0.00]
3.10.2 Interferon beta 1b Betaferon versus Interferon beta 1a Avonex Rebif	1	69	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.78, 0.23]
3.10.3 Interferon beta 1a Avonex Rebif versus Ozanimod	2	2666	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.05, 0.11]
3.10.4 Daclizumab versus Placebo/No treatment	1	621	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.05, 0.28]
3.11 Mortality	28		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.11.1 Cladribine versus placebo/ no treatment	1	1326	Risk Ratio (IV, Random, 95% CI)	0.98 [0.18, 5.35]
3.11.2 Daclizumab versus placebo/ no treatment	1	621	Risk Ratio (IV, Random, 95% CI)	1.47 [0.06, 35.96]
3.11.3 Dimethyl fumarate versus placebo/ no treatment	2	2307	Risk Ratio (IV, Random, 95% CI)	1.05 [0.14, 8.12]
3.11.4 Fingolimod versus placebo/ no treatment	2	2355	Risk Ratio (IV, Random, 95% CI)	0.21 [0.03, 1.44]
3.11.5 Glatiramer acetate versus placebo/ no treatment	2	2117	Risk Ratio (IV, Random, 95% CI)	0.47 [0.06, 3.81]
3.11.6 Glatiramer acetate versus dimethyl fumarate	1	1057	Risk Ratio (IV, Random, 95% CI)	2.02 [0.13, 32.20]
3.11.7 Interferon beta 1b (Betaferon) versus glatiramer acetate	1	2244	Risk Ratio (IV, Random, 95% CI)	0.75 [0.08, 7.18]
3.11.8 Interferon beta 1a (Avonex, Rebif) versus placebo/ no treatment	3	1629	Risk Ratio (IV, Random, 95% CI)	0.76 [0.13, 4.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.11.9 Interferon beta 1a (Avonex, Rebif) versus alemtuzumab	3	1582	Risk Ratio (IV, Random, 95% CI)	0.46 [0.08, 2.71]
3.11.10 Interferon beta 1a (Avonex, Rebif) versus daclizumab	1	1841	Risk Ratio (IV, Random, 95% CI)	3.99 [0.45, 35.60]
3.11.11 Interferon beta 1a (Avonex, Rebif) versus fingolimod	1	1292	Risk Ratio (IV, Random, 95% CI)	0.39 [0.02, 8.18]
3.11.12 Interferon beta 1a (Avonex, Rebif) versus glatiramer acetate	2	1273	Risk Ratio (IV, Random, 95% CI)	1.62 [0.20, 13.11]
3.11.13 Laquinimod versus placebo/ no treatment	3	3457	Risk Ratio (IV, Random, 95% CI)	0.55 [0.11, 2.78]
3.11.14 Laquinimod versus interferon beta 1a (Avonex, Rebif)	1	881	Risk Ratio (IV, Random, 95% CI)	1.03 [0.06, 16.41]
3.11.15 Laquinimod versus placebo/ no treatment	1	1512	Risk Ratio (IV, Random, 95% CI)	0.49 [0.07, 3.50]
3.11.16 Natalizumab versus placebo/ no treatment	1	942	Risk Ratio (IV, Random, 95% CI)	2.52 [0.12, 52.25]
3.11.17 Ocrelizumab versus interferon beta 1a (Avonex, Rebif)	2	1656	Risk Ratio (IV, Random, 95% CI)	0.63 [0.08, 5.08]
3.11.18 Ozanimod versus interferon beta 1a (Avonex, Rebif)	1	1320	Risk Ratio (IV, Random, 95% CI)	1.52 [0.06, 37.16]
3.11.19 Teriflunomide versus placebo/ no treatment	1	1169	Risk Ratio (IV, Random, 95% CI)	1.50 [0.16, 14.34]
3.11.20 Teriflunomide versus ofatumumab	1	955	Risk Ratio (IV, Random, 95% CI)	3.04 [0.12, 74.54]
3.11.21 Teriflunomide versus ponesimod	1	1133	Risk Ratio (IV, Random, 95% CI)	5.01 [0.24, 104.10]

Analysis 3.1. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 1: Comparisons for new gadolinium-enhancing positive T1-weighted MRI lesions (12 months)

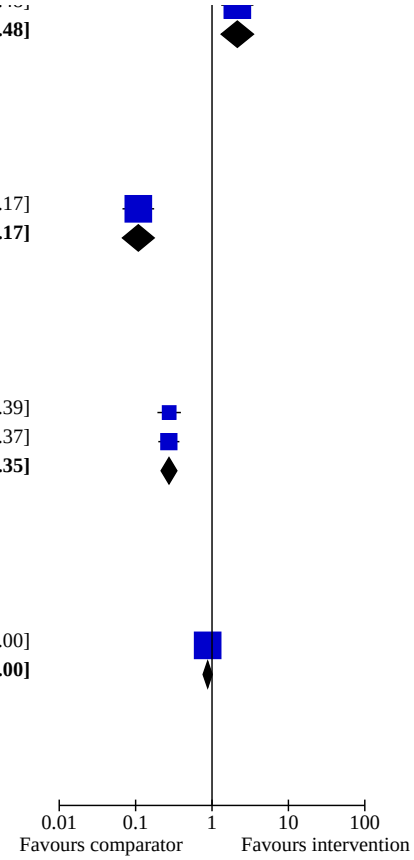


Analysis 3.2. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 2: Comparisons for new gadolinium-enhancing positive T1-weighted MRI lesions (24 months)

Study or Subgroup	Intervention Events	Intervention Total	Comparator Events	Comparator Total	Weight	Risk Ratio IV, Random, 95% CI
3.2.1 Dimethyl fumarate versus placebo/no treatment						
CONFIRM 2012	57	291	56	144	100.0%	0.50 [0.37 , 0.69]
Subtotal (95% CI)		**291**		**144**	**100.0%**	**0.50 [0.37 , 0.69]**
Total events:	57		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.34 (P < 0.0001)						
3.2.2 Fingolimod versus placebo/no treatment						
FREEDOMS 2010	73	712	116	332	100.0%	0.29 [0.23 , 0.38]
Subtotal (95% CI)		**712**		**332**	**100.0%**	**0.29 [0.23 , 0.38]**
Total events:	73		116			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.16 (P < 0.00001)						
3.2.3 Glatiramer acetate versus placebo/no treatment						
CONFIRM 2012	37	161	56	144	100.0%	0.59 [0.42 , 0.84]
Subtotal (95% CI)		**161**		**144**	**100.0%**	**0.59 [0.42 , 0.84]**
Total events:	37		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.95 (P = 0.003)						
3.2.4 Glatiramer acetate versus dimethyl fumarate						
CONFIRM 2012	37	161	57	291	100.0%	1.17 [0.81 , 1.69]
Subtotal (95% CI)		**161**		**291**	**100.0%**	**1.17 [0.81 , 1.69]**
Total events:	37		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
3.2.5 Interferon beta-1a and 1b versus azathioprine						
MAIN 2014	4	73	8	77	100.0%	0.53 [0.17 , 1.68]
Subtotal (95% CI)		**73**		**77**	**100.0%**	**0.53 [0.17 , 1.68]**
Total events:	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
3.2.6 Interferon beta-1a (Avonex, Rebif) versus alemtuzumab						
CARE-MS I 2012	34	178	26	366	41.0%	2.69 [1.67 , 4.34]
CARE-MS II 2012	44	190	38	410	59.0%	2.50 [1.68 , 3.72]
Subtotal (95% CI)		**368**		**776**	**100.0%**	**2.57 [1.90 , 3.50]**
Total events:	78		64			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0\%$						
Test for overall effect: Z = 6.06 (P < 0.00001)						
3.2.7 Interferon beta-1a (Avonex, Rebif) versus glatiramer acetate						
REGARD 2008	44	230	76	230	100.0%	0.58 [0.42 , 0.80]
Subtotal (95% CI)		**230**		**230**	**100.0%**	**0.58 [0.42 , 0.80]**
Total events:	44		76			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.31 (P = 0.0009)						
3.2.8 Interferon beta-1a (Avonex, Rebif) versus interferon beta-1b (Betaferon)						
INCOMIN 2002	37	92	18	96	100.0%	2.14 [1.32 , 3.48]
Subtotal (95% CI)		**92**		**96**	**100.0%**	**2.14 [1.32 , 3.48]**
Total events:	37		18			

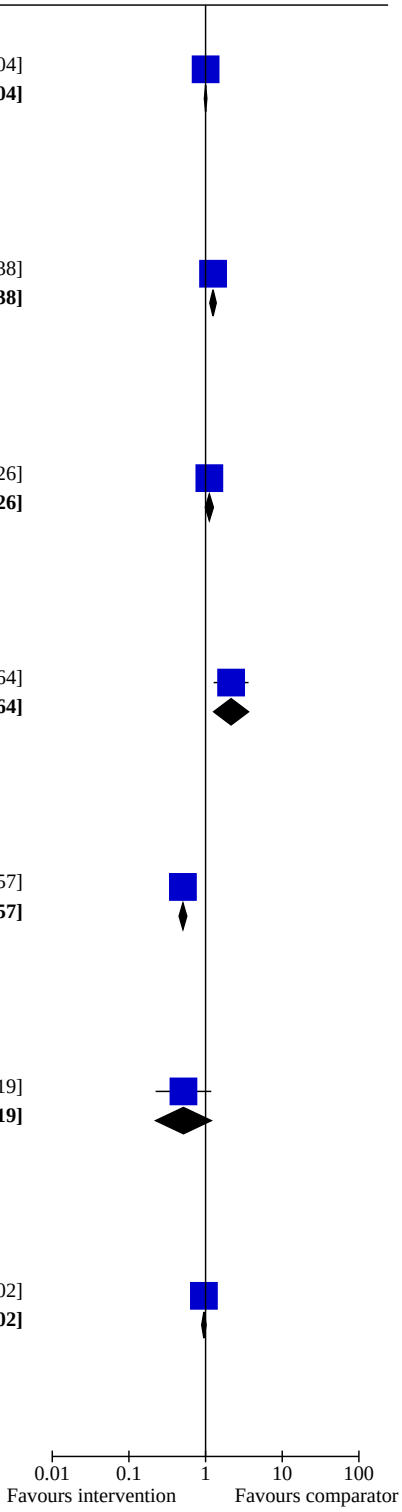
Analysis 3.2. (Continued)

Subtotal (95% CI)		**92**		**96**	**100.0%**	**2.14 [1.32 , 3.48]**
Total events:	37		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.08 (P = 0.002)						
3.2.9 Natalizumab versus placebo/no treatment						
AFFIRM 2006	19	627	88	315	100.0%	0.11 [0.07 , 0.17]
Subtotal (95% CI)		**627**		**315**	**100.0%**	**0.11 [0.07 , 0.17]**
Total events:	19		88			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.13 (P < 0.00001)						
3.2.10 Ocrelizumab versus interferon beta-1a (Avonex, Rebif)						
OPERA I 2017	34	410	124	411	44.6%	0.27 [0.19 , 0.39]
OPERA II 2017	41	417	151	418	55.4%	0.27 [0.20 , 0.37]
Subtotal (95% CI)		**827**		**829**	**100.0%**	**0.27 [0.22 , 0.35]**
Total events:	75		275			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 10.76 (P < 0.00001)						
3.2.11 Ozanimod versus interferon beta-1a (Avonex, Rebif)						
RADIANCE 2019	335	877	193	443	100.0%	0.88 [0.77 , 1.00]
Subtotal (95% CI)		**877**		**443**	**100.0%**	**0.88 [0.77 , 1.00]**
Total events:	335		193			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.90 (P = 0.06)						



Analysis 3.3. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 3: Comparisons for new or enlarging T2-weighted MRI lesions (12 months)

Study or Subgroup	Intervention Events	Intervention Total	Comparator Events	Comparator Total	Weight	Risk Ratio IV, Random, 95% CI
3.3.1 Daclizumab versus placebo/no treatment						
SELECT 2013	399	417	195	204	100.0%	1.00 [0.97 , 1.04]
Subtotal (95% CI)		**417**		**204**	**100.0%**	**1.00 [0.97 , 1.04]**
Total events:	399		195			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
3.3.2 Glatiramer acetate versus fingolimod						
ASSESS 2020	228	324	400	711	100.0%	1.25 [1.14 , 1.38]
Subtotal (95% CI)		**324**		**711**	**100.0%**	**1.25 [1.14 , 1.38]**
Total events:	228		400			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.58 (P < 0.00001)						
3.3.3 Interferon beta-1b (Betaferon) versus fingolimod						
TRANSFORMS 2010	196	361	350	722	100.0%	1.12 [0.99 , 1.26]
Subtotal (95% CI)		**361**		**722**	**100.0%**	**1.12 [0.99 , 1.26]**
Total events:	196		350			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
3.3.4 Interferon beta-1b (Betaferon) versus immunoglobulins						
INCOMIN 2002	33	92	16	96	100.0%	2.15 [1.27 , 3.64]
Subtotal (95% CI)		**92**		**96**	**100.0%**	**2.15 [1.27 , 3.64]**
Total events:	33		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.87 (P = 0.004)						
3.3.5 Interferon beta-1a (Avonex, Rebif) versus placebo/no treatment						
AFFIRM 2006	245	627	243	315	100.0%	0.51 [0.45 , 0.57]
Subtotal (95% CI)		**627**		**315**	**100.0%**	**0.51 [0.45 , 0.57]**
Total events:	245		243			
Heterogeneity: Not applicable						
Test for overall effect: Z = 11.62 (P < 0.00001)						
3.3.6 Interferon beta-1a (Avonex, Rebif) versus immunoglobulins						
Gobbi 2013	4	10	7	9	100.0%	0.51 [0.22 , 1.19]
Subtotal (95% CI)		**10**		**9**	**100.0%**	**0.51 [0.22 , 1.19]**
Total events:	4		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.56 (P = 0.12)						
3.3.7 Natalizumab versus interferon beta-1b (Betaferon)						
SUNBEAM 2019	654	898	343	448	100.0%	0.95 [0.89 , 1.02]
Subtotal (95% CI)		**898**		**448**	**100.0%**	**0.95 [0.89 , 1.02]**
Total events:	654		343			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						

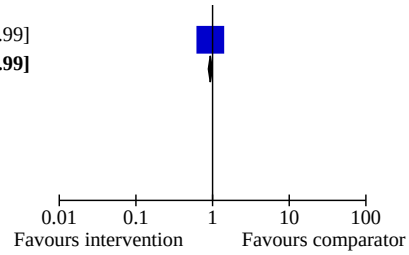


Analysis 3.4. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 4: Comparisons for new or enlarging T2-weighted MRI lesions (24 months)

Study or Subgroup	Intervention Events	Intervention Total	Comparator Events	Comparator Total	Weight	Risk Ratio IV, Random, 95% CI
3.4.1 Fingolimod versus placebo/ no treatment						
FREEDOMS 2010	345	707	267	339	100.0%	0.62 [0.56 , 0.68]
Subtotal (95% CI)		**707**		**339**	**100.0%**	**0.62 [0.56 , 0.68]**
Total events:	345		267			
Heterogeneity: Not applicable						
Test for overall effect: Z = 10.03 (P < 0.00001)						
3.4.2 Interferon beta 1a and 1b versus azathioprine						
MAIN 2014	26	73	23	77	100.0%	1.19 [0.75 , 1.89]
Subtotal (95% CI)		**73**		**77**	**100.0%**	**1.19 [0.75 , 1.89]**
Total events:	26		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
3.4.3 Interferon beta 1a (Avonex, Rebif) versus alemtuzumab						
CARE-MS I 2012	99	178	176	363	48.4%	1.15 [0.97 , 1.36]
CARE-MS II 2012	127	187	186	403	51.6%	1.47 [1.27 , 1.70]
Subtotal (95% CI)		**365**		**766**	**100.0%**	**1.30 [1.02 , 1.66]**
Total events:	226		362			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.83$, df = 1 (P = 0.03); $I^2 = 79\%$						
Test for overall effect: Z = 2.14 (P = 0.03)						
3.4.4 Interferon beta 1a (Avonex, Rebif) versus glatiramer acetate						
REGARD 2008	137	230	144	230	100.0%	0.95 [0.82 , 1.10]
Subtotal (95% CI)		**230**		**230**	**100.0%**	**0.95 [0.82 , 1.10]**
Total events:	137		144			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
3.4.5 Interferon beta 1a (Avonex, Rebif) versus interferon beta 1b (Betaferon)						
INCOMIN 2002	54	92	34	96	100.0%	1.66 [1.20 , 2.28]
Subtotal (95% CI)		**92**		**96**	**100.0%**	**1.66 [1.20 , 2.28]**
Total events:	54		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.09 (P = 0.002)						
3.4.6 Natalizumab versus placebo/ no treatment						
AFFIRM 2006	267	627	269	315	100.0%	0.50 [0.45 , 0.55]
Subtotal (95% CI)		**627**		**315**	**100.0%**	**0.50 [0.45 , 0.55]**
Total events:	267		269			
Heterogeneity: Not applicable						
Test for overall effect: Z = 13.41 (P < 0.00001)						
3.4.7 Ocrelizumab versus interferon beta 1a (Avonex, Rebif)						
OPERA I 2017	157	410	252	411	48.8%	0.62 [0.54 , 0.72]
OPERA II 2017	163	417	259	418	51.2%	0.63 [0.55 , 0.73]
Subtotal (95% CI)		**827**		**829**	**100.0%**	**0.63 [0.57 , 0.69]**
Total events:	320		511			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0\%$						
Test for overall effect: Z = 9.02 (P < 0.00001)						
3.4.8 Ozanimod versus interferon beta 1a (Avonex, Rebif)						
RADIANCE 2019	666	877	360	443	100.0%	0.93 [0.88 , 0.99]

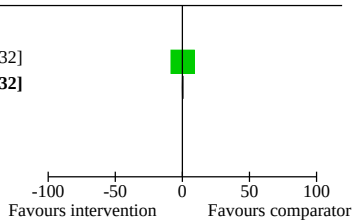
Analysis 3.4. (Continued)

3.4.8 Ozanimod versus interferon beta 1a (Avonex, Rebif)						
RADIANCE 2019	666	877	360	443	100.0%	0.93 [0.88 , 0.99]
Subtotal (95% CI)		**877**		**443**	**100.0%**	**0.93 [0.88 , 0.99]**
Total events:	666		360			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.28 (P = 0.02)						



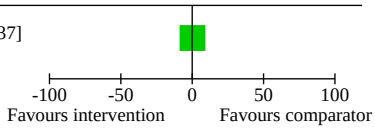
Analysis 3.5. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 5: Comparisons for quality of life total (non-MS related: EQ-5D VAS)

	Experimental			Control				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
3.5.1 Cladribine versus Placebo/no treatment									
CLARITY 2010	70.26	20	704	66.3	22.6	338	100.0%	0.19 [0.06 , 0.32]	
Subtotal (95% CI)			**704**			**338**	**100.0%**	**0.19 [0.06 , 0.32]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.86 (P = 0.004)									
Test for subgroup differences: Not applicable									



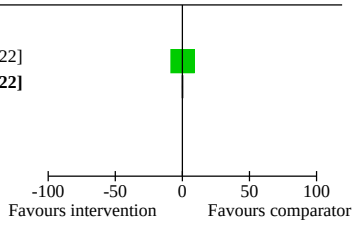
Analysis 3.6. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 6: Comparisons for quality of life total (non-MS related) (INDEX)

	Experimental			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
CLARITY 2010	0.715	0.22	704	0.66	0.26	338	0.24 [0.11 , 0.37]	
Test for subgroup differences: Not applicable								



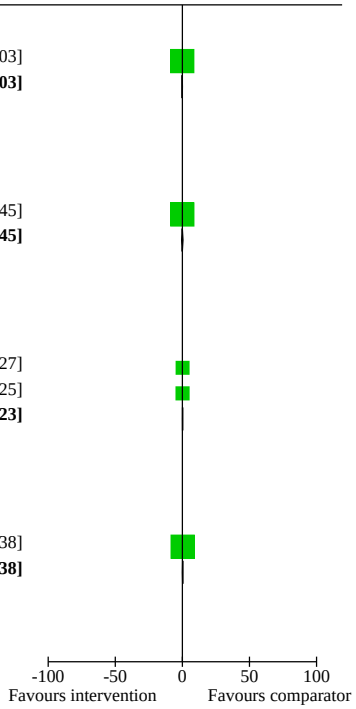
Analysis 3.7. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 7: Comparisons for quality of life - physical (non-MS related: SF-36)

	Experimental			Control				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
3.7.1 Teriflunomide versus Placebo/ no treatment									
TOWER 2014	-0.26	8.07	780	-1.08	8.07	389	100.0%	0.10 [-0.02 , 0.22]	
Subtotal (95% CI)			**780**			**389**	**100.0%**	**0.10 [-0.02 , 0.22]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.64 (P = 0.10)									
Test for subgroup differences: Not applicable									



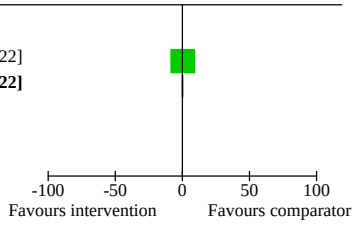
Analysis 3.8. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 8: Comparisons for quality of life - physical (MS related: MSQOL-54 PH; MSQoL-54; MSIS29 Psychological)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.8.1 Interferon beta 1a Avonex/Rebif versus Daclizumab								
DECIDE 2015	0.8	17.1	342	2.47	15.76	722	100.0%	-0.10 [-0.23 , 0.03]
Subtotal (95% CI)			**342**			**722**	**100.0%**	**-0.10 [-0.23 , 0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.57 (P = 0.12)								
3.8.2 Interferon beta 1b Betaferon versus Interferon beta 1a Avonex Rebif								
Mokhber 2014	63.98	24.32	46	65.37	28.65	23	100.0%	-0.05 [-0.55 , 0.45]
Subtotal (95% CI)			**46**			**23**	**100.0%**	**-0.05 [-0.55 , 0.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.83)								
3.8.3 Interferon beta 1a Avonex Rebif versus Ozanimod								
RADIANCE 2019	0.41	12.31	877	-1.53	12.32	443	49.6%	0.16 [0.04 , 0.27]
SUNBEAM 2019	1.67	12.11	898	0.05	12.58	448	50.4%	0.13 [0.02 , 0.25]
Subtotal (95% CI)			**1775**			**891**	**100.0%**	**0.14 [0.06 , 0.23]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.10$, df = 1 (P = 0.76); $I^2 = 0\%$								
Test for overall effect: Z = 3.52 (P = 0.0004)								
3.8.4 Daclizumab versus Placebo/No treatment								
SELECT 2013	-0.2	12.72	417	-3	13.5	204	100.0%	0.22 [0.05 , 0.38]
Subtotal (95% CI)			**417**			**204**	**100.0%**	**0.22 [0.05 , 0.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.52 (P = 0.01)								



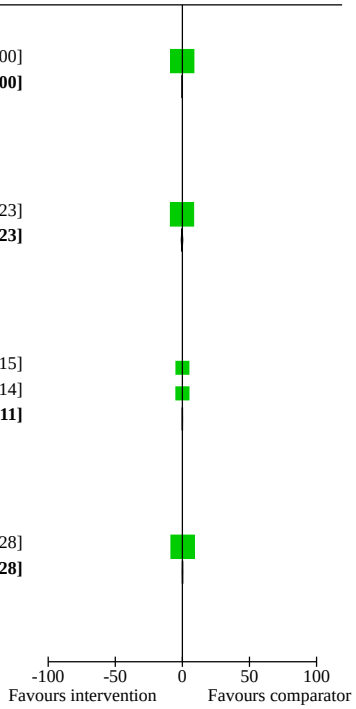
Analysis 3.9. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 9: Comparisons for quality of life - mental (Non-MS related: SF-36)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.9.1 Teriflunomide versus Placebo/ no treatment								
TOWER 2014	-1.74	11.6	780	-2.91	11.62	389	100.0%	0.10 [-0.02 , 0.22]
Subtotal (95% CI)			**780**			**389**	**100.0%**	**0.10 [-0.02 , 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.62 (P = 0.10)								
Test for subgroup differences: Not applicable								



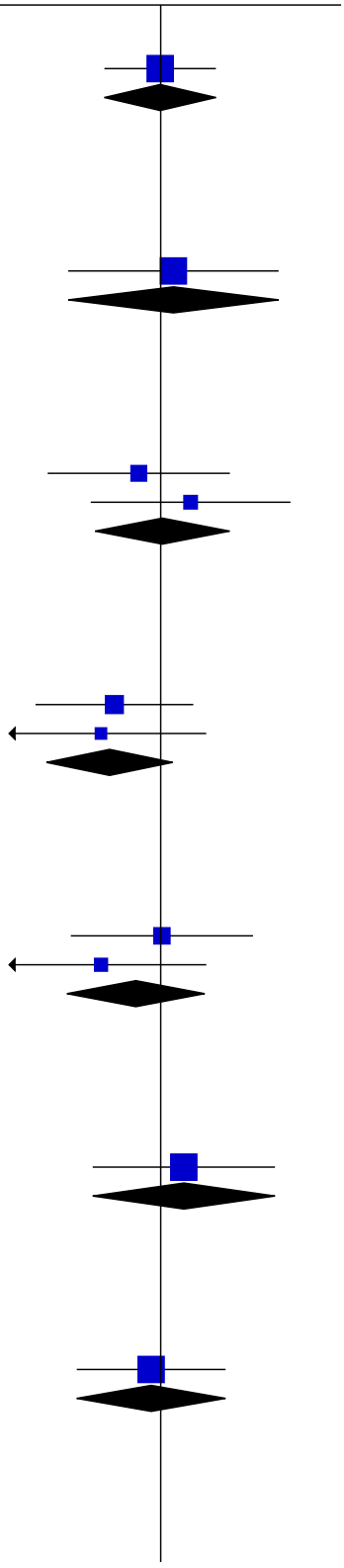
Analysis 3.10. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 10: Comparisons for quality of life - mental (MS related: MSQOL-54 PH; MSQoL-54; MSIS29 Psychological)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.10.1 Interferon beta 1a Avonex/Rebif versus Daclizumab								
DECIDE 2015	2.57	18.14	922	4.2	18.27	919	100.0%	-0.09 [-0.18 , 0.00]
Subtotal (95% CI)			**922**			**919**	**100.0%**	**-0.09 [-0.18 , 0.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.92 (P = 0.05)								
3.10.2 Interferon beta 1b Betaferon versus Interferon beta 1a Avonex Rebif								
Mokhber 2014	66.21	22.07	46	72.93	28.12	23	100.0%	-0.27 [-0.78 , 0.23]
Subtotal (95% CI)			**46**			**23**	**100.0%**	**-0.27 [-0.78 , 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.28)								
3.10.3 Interferon beta 1a Avonex Rebif versus Ozanimod								
RADIANCE 2019	-1.35	14.96	877	-1.83	16.42	443	49.6%	0.03 [-0.08 , 0.15]
SUNBEAM 2019	0.28	15.73	898	-0.12	15.24	448	50.4%	0.03 [-0.09 , 0.14]
Subtotal (95% CI)			**1775**			**891**	**100.0%**	**0.03 [-0.05 , 0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 0.69 (P = 0.49)								
3.10.4 Daclizumab versus Placebo/No treatment								
SELECT 2013	1.15	15.55	417	-0.6	14.4	204	100.0%	0.12 [-0.05 , 0.28]
Subtotal (95% CI)			**417**			**204**	**100.0%**	**0.12 [-0.05 , 0.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.35 (P = 0.18)								
Test for subgroup differences: Chi² = 0.00, df = 3 (P < 0.00001), I² = 0%								

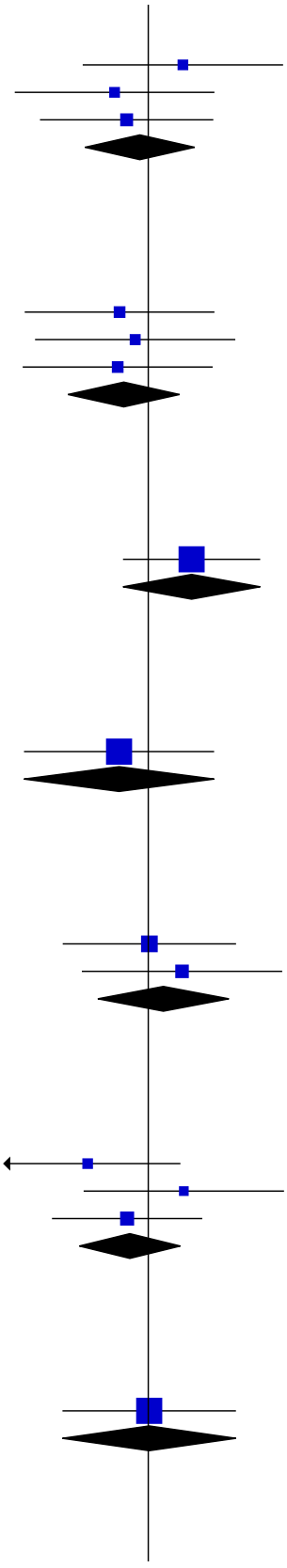


Analysis 3.11. Comparison 3: Treatment efficacy and safety (secondary outcomes): pairwise comparisons, Outcome 11: Mortality

Study or Subgroup	Intervention Events	Intervention Total	Comparator Events	Comparator Total	Weight	Risk Ratio IV, Random, 95% CI
3.11.1 Cladribine versus placebo/ no treatment						
CLARITY 2010	4	889	2	437	100.0%	0.98 [0.18 , 5.35]
Subtotal (95% CI)		**889**		**437**	**100.0%**	**0.98 [0.18 , 5.35]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
3.11.2 Daclizumab versus placebo/ no treatment						
SELECT 2013	1	417	0	204	100.0%	1.47 [0.06 , 35.96]
Subtotal (95% CI)		**417**		**204**	**100.0%**	**1.47 [0.06 , 35.96]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
3.11.3 Dimethyl fumarate versus placebo/ no treatment						
CONFIRM 2012	1	707	1	363	54.6%	0.51 [0.03 , 8.18]
DEFINE 2012	2	827	0	410	45.4%	2.48 [0.12 , 51.58]
Subtotal (95% CI)		**1534**		**773**	**100.0%**	**1.05 [0.14 , 8.12]**
Total events:	3		1			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.57$, df = 1 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 0.05 (P = 0.96)						
3.11.4 Fingolimod versus placebo/ no treatment						
FREEDOMS 2010	1	854	2	418	64.0%	0.24 [0.02 , 2.69]
FREEDOMS II 2014	0	728	1	355	36.0%	0.16 [0.01 , 3.99]
Subtotal (95% CI)		**1582**		**773**	**100.0%**	**0.21 [0.03 , 1.44]**
Total events:	1		3			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0\%$						
Test for overall effect: Z = 1.59 (P = 0.11)						
3.11.5 Glatiramer acetate versus placebo/ no treatment						
CONFIRM 2012	1	350	1	363	57.2%	1.04 [0.07 , 16.52]
GALA 2013	0	943	1	461	42.8%	0.16 [0.01 , 4.00]
Subtotal (95% CI)		**1293**		**824**	**100.0%**	**0.47 [0.06 , 3.81]**
Total events:	1		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.73$, df = 1 (P = 0.39); $I^2 = 0\%$						
Test for overall effect: Z = 0.71 (P = 0.48)						
3.11.6 Glatiramer acetate versus dimethyl fumarate						
CONFIRM 2012	1	350	1	707	100.0%	2.02 [0.13 , 32.20]
Subtotal (95% CI)		**350**		**707**	**100.0%**	**2.02 [0.13 , 32.20]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
3.11.7 Interferon beta 1b (Betaferon) versus glatiramer acetate						
BEYOND 2009	3	1796	1	448	100.0%	0.75 [0.08 , 7.18]
Subtotal (95% CI)		**1796**		**448**	**100.0%**	**0.75 [0.08 , 7.18]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
3.11.8 Interferon beta 1a (Avonex, Rebif) versus placebo/ no treatment						



Analysis 3.11. (Continued)



3.11.8 Interferon beta 1a (Avonex, Rebif) versus placebo/ no treatment

BRAVO 2014	1	447	0	450	29.9%	3.02 [0.12 , 73.94]
MSCRG 1996	0	85	1	87	30.1%	0.34 [0.01 , 8.26]
PRISMS 1998	1	373	1	187	40.0%	0.50 [0.03 , 7.97]
Subtotal (95% CI)		**905**		**724**	**100.0%**	**0.76 [0.13 , 4.39]**
Total events:	2		2			

Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 2 (P = 0.59); I² = 0%

Test for overall effect: Z = 0.30 (P = 0.76)

3.11.9 Interferon beta 1a (Avonex, Rebif) versus alemtuzumab

CAMMS223 2008	0	111	2	223	34.5%	0.40 [0.02 , 8.26]
CARE-MS I 2012	0	195	1	386	31.0%	0.66 [0.03 , 16.08]
CARE-MS II 2012	0	231	2	436	34.4%	0.38 [0.02 , 7.81]
Subtotal (95% CI)		**537**		**1045**	**100.0%**	**0.46 [0.08 , 2.71]**
Total events:	0		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 2 (P = 0.96); I² = 0%

Test for overall effect: Z = 0.86 (P = 0.39)

3.11.10 Interferon beta 1a (Avonex, Rebif) versus daclizumab

DECIDE 2015	4	922	1	919	100.0%	3.99 [0.45 , 35.60]
Subtotal (95% CI)		**922**		**919**	**100.0%**	**3.99 [0.45 , 35.60]**
Total events:	4		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.24 (P = 0.22)

3.11.11 Interferon beta 1a (Avonex, Rebif) versus fingolimod

TRANSFORMS 2010	0	435	2	857	100.0%	0.39 [0.02 , 8.18]
Subtotal (95% CI)		**435**		**857**	**100.0%**	**0.39 [0.02 , 8.18]**
Total events:	0		2			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.60 (P = 0.55)

3.11.12 Interferon beta 1a (Avonex, Rebif) versus glatiramer acetate

CombiRx 2013	1	250	1	259	57.2%	1.04 [0.07 , 16.47]
REGARD 2008	1	386	0	378	42.8%	2.94 [0.12 , 71.89]
Subtotal (95% CI)		**636**		**637**	**100.0%**	**1.62 [0.20 , 13.11]**
Total events:	2		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%

Test for overall effect: Z = 0.45 (P = 0.65)

3.11.13 Laquinimod versus placebo/ no treatment

ALLEGRO 2012	0	550	3	556	29.6%	0.14 [0.01 , 2.79]
BRAVO 2014	1	434	0	450	25.4%	3.11 [0.13 , 76.14]
CONCERTO 2021	1	727	2	740	45.1%	0.51 [0.05 , 5.60]
Subtotal (95% CI)		**1711**		**1746**	**100.0%**	**0.55 [0.11 , 2.78]**
Total events:	2		5			

Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 2 (P = 0.38); I² = 0%

Test for overall effect: Z = 0.72 (P = 0.47)

3.11.14 Laquinimod versus interferon beta 1a (Avonex, Rebif)

BRAVO 2014	1	434	1	447	100.0%	1.03 [0.06 , 16.41]
Subtotal (95% CI)		**434**		**447**	**100.0%**	**1.03 [0.06 , 16.41]**
Total events:	1		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.02 (P = 0.98)

Analysis 3.11. (Continued)

Test for overall effect: Z = 0.02 (P = 0.98)

3.11.15 Laquinimod versus placebo/ no treatment

ADVANCE 2014	2	1012	2	500	100.0%	0.49 [0.07 , 3.50]
Subtotal (95% CI)		**1012**		**500**	**100.0%**	**0.49 [0.07 , 3.50]**
Total events:	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

3.11.16 Natalizumab versus placebo/ no treatment

AFFIRM 2006	2	627	0	315	100.0%	2.52 [0.12 , 52.25]
Subtotal (95% CI)		**627**		**315**	**100.0%**	**2.52 [0.12 , 52.25]**
Total events:	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

3.11.17 Ocrelizumab versus interferon beta 1a (Avonex, Rebif)

OPERA I 2017	0	410	1	411	42.8%	0.33 [0.01 , 8.18]
OPERA II 2017	1	417	1	418	57.2%	1.00 [0.06 , 15.97]
Subtotal (95% CI)		**827**		**829**	**100.0%**	**0.63 [0.08 , 5.08]**
Total events:	1		2			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.26$, df = 1 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 0.44 (P = 0.66)

3.11.18 Ozanimod versus interferon beta 1a (Avonex, Rebif)

RADIANCE 2019	1	877	0	443	100.0%	1.52 [0.06 , 37.16]
Subtotal (95% CI)		**877**		**443**	**100.0%**	**1.52 [0.06 , 37.16]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)

3.11.19 Teriflunomide versus placebo/ no treatment

TOWER 2014	3	780	1	389	100.0%	1.50 [0.16 , 14.34]
Subtotal (95% CI)		**780**		**389**	**100.0%**	**1.50 [0.16 , 14.34]**
Total events:	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)

3.11.20 Teriflunomide versus ofatumumab

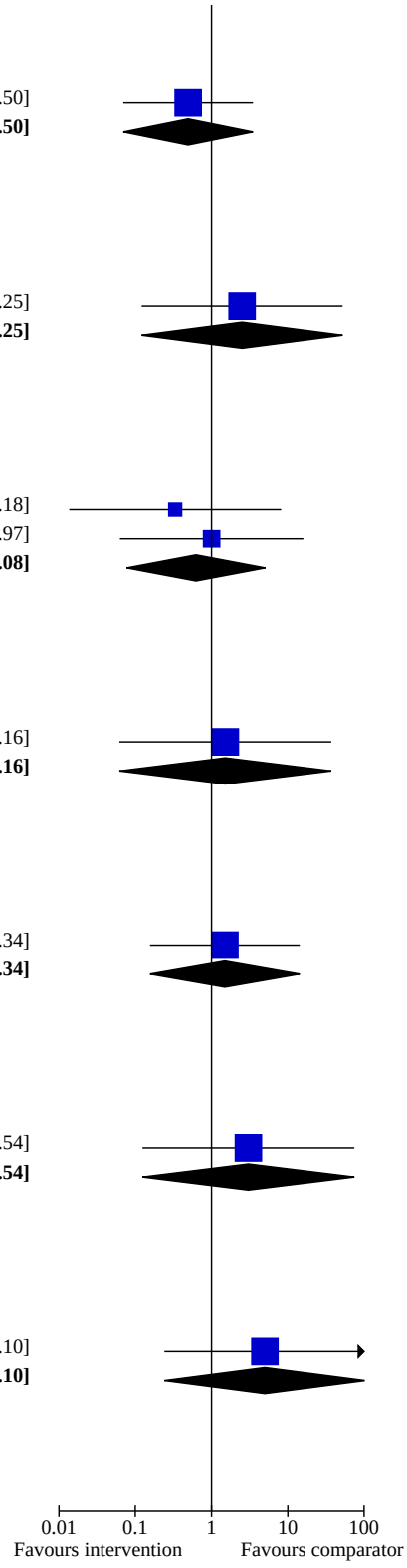
ASCLEPIOS II 2020	1	474	0	481	100.0%	3.04 [0.12 , 74.54]
Subtotal (95% CI)		**474**		**481**	**100.0%**	**3.04 [0.12 , 74.54]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

3.11.21 Teriflunomide versus ponesimod

OPTIMUM 2021	2	566	0	567	100.0%	5.01 [0.24 , 104.10]
Subtotal (95% CI)		**566**		**567**	**100.0%**	**5.01 [0.24 , 104.10]**
Total events:	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)



ADDITIONAL TABLES

Table 1. Assessment of adverse events/serious adverse events in included studies

Study	Did the researchers actively monitor for adverse events (AEs) or did they simply provide spontaneous reporting of AEs that arose?	Did the authors define serious AEs (SAEs) according to an accepted international classification and report the number of SAEs?
Achiron 1998	Not reported	SAEs not reported
ADVANCE 2014	Not reported	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
AFFIRM 2006	"*Treating neurologists were responsible for all aspects of patient care, including the management of adverse events".* Participants *"visited the clinic every 12 weeks for ... blood chemical and hematologic analyses, evaluation of adverse events...*" (page 901).	Insufficient information on SAEs definition
ALLEGRO 2012	"*Safety assessments were performed at screening, at baseline, and every 3 months until month 24*" (page 1002).	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ASCLEPIOS I 2020	"*Adverse events were recorded at all visits and graded according to the Common Terminology Criteria for Adverse Events (CTCAE).*" (page 548). *"Additional safety assessments included laboratory tests, physical examination (including examination of skin), vital sign measures, ECG evaluations and assessment of suicidality"* (page 21, Appendix).	*A serious adverse event (SAE) was defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)which met any one of the following criteria:* *• was fatal or life-threatening* *• resulted in persistent or significant disability/incapacity* *• constituted a congenital anomaly/birth defect* *• required in-patient hospitalisation or prolongation of existing hospitalisation, unless hospitalisation was for:* *- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (e.g. hospitalisation for multiple sclerosis relapse treatment)* *- elective or pre-planned treatment for a pre-existing condition that was unrelated to the indication under trial and had not worsened since signing the informed consent to treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission* *- social reasons and respite care in the absence of any deterioration in the patient's general condition* *• was medically significant, e.g. defined as an event that jeopardised the patient or may require medical or surgical intervention."* (Appendix, page 22).
ASCLEPIOS II 2020	*"Adverse events were recorded at all visits and graded according to the Common Terminology Criteria for Adverse Events (CTCAE)"* (page 548). *"Additional safety assessments included laboratory tests, physical examination (including examination of skin), vital sign measures, ECG evaluations and assessment of suicidality"* (page 21, Appendix).	*"A serious adverse event (SAE) was defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which met any one of the following criteria:* *• was fatal or life-threatening*

Table 1. Assessment of adverse events/serious adverse events in included studies *(Continued)*

		• resulted in persistent or significant disability/incapacity • constituted a congenital anomaly/birth defect • required in-patient hospitalisation or prolongation of existing hospitalisation, unless hospitalisation was for: - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (e.g. hospitalisation for multiple sclerosis relapse treatment) - elective or pre-planned treatment for a pre-existing condition that was unrelated to the indication under trial and had not worsened since signing the informed consent - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission - social reasons and respite care in the absence of any deterioration in the patient's general condition • was medically significant, e.g. defined as an event that jeopardised the patient or may require medical or surgical intervention." (Appendix, page 22).
ASSESS 2020	Not reported	Insufficient information on SAEs definition
BECOME 2009	"*After the initial interim analysis failed to raise any safety concerns with the use of monthly triple dose gadolinium, all patients still in the study were offered the option of obtaining additional monthly MRI scans for a second year of treatment*" (page 1977).	SAEs not reported
BEYOND 2009	"*Clinic visits were scheduled every 3 months to assess ... safety, and tolerability. The occurrence of new neurological symptoms and adverse events was assessed by telephone, 6 weeks after each visit*" (page 891).	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
Bornstein 1987	"*Self-evaluation reported to a clinical assistant*" (page 409)	SAEs not reported
BRAVO 2014	"*Patients were evaluated at 12 scheduled visits: months -1 (screening), 0 (baseline), 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24. Safety assessments (laboratory measures, vital signs) were performed at all visits, and electrocardiograms (ECGs) were performed at months -1, 0, 1, 2, 3, 6, 12, 18, and 24/early termination*" (page 775).	Insufficient information on SAEs definition
CAMMS223 2008	"*Safety was assessed quarterly by the treating neurologist, who was aware of study-group assignment*" (page 1787); "*Thyroid function and levels of antithyrotropin receptor antibodies and lymphocyte subpopulations were measured quarterly at a central laboratory*"; and "*All adverse events with an onset up to 36 months are reported. In addition, all serious adverse events and autoimmune-associated disor-*	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

Table 1. Assessment of adverse events/serious adverse events in included studies *(Continued)*

	ders occurring before March 1, 2008, are listed" (page 1788).	
CARE-MS I 2012	"*To assess safety, we undertook monthly questionnaire follow-up of patients, and did complete blood counts, serum creatinine, urinalysis, and microscopy monthly (every three months in patients in the interferon beta 1a group), and thyroid function tests every 3 months*"; "*Circulating lymphocyte subsets were assessed every 3 months in all patients and 1 month after alemtuzumab administration. We screened for anti-alemtuzumab antibodies with a bridging ELISA before and at 1 month, 3 months, and 12 months after each dosing*"; and "*We measured interferon beta 1a-neutralising antibodies at baseline and at 24 months with a cytopathic effect inhibition assay*" (page 1821).	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
CARE-MS II 2012	"*To assess safety, we undertook monthly questionnaire follow-up of patients, and did complete blood counts, serum creatinine, and urinalysis with microscopy monthly (every 3 months in patients in the interferon beta 1a group), and thyroid function tests every 3 months*"; "*We assessed circulating lymphocyte subsets every 3 months in all patients and 1 month after every course of alemtuzumab. We screened for anti-alemtuzumab antibodies with ELISA before and at 1 month, 3 months and 12 months after each dosing*"; and "*We measured interferon beta 1a-neutralising antibodies at baseline and at 24 months with a cytopathic effect inhibition assay*" (page 1832).	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
CLARITY 2010	Not reported	Insufficient information on SAEs definition
CombiRx 2013	"*Safety was assessed by recording all adverse events, serious and nonserious*" (page 329).	No information on SAE definition
CONCERTO 2021	"Safety endpoints included assessment of adverse events (AEs) throughout the study, and vital signs, electrocardiograms (ECGs), and clinical laboratory parameters at specific scheduled site visits. ECG findings assessed as “abnormal, clinically significant” were evaluated by the data monitoring committee (DMC) cardiologist. Assessment of tolerability included evaluation of the proportion of patients who prematurely discontinued treatment, including those with ETD due to AEs" (page 2).	Insufficient information on SAEs definition
CONFIRM 2012	"*Throughout the course of the study, every effort was made to remain alert to possible adverse events (AEs)*" and "*Any AE or SAE experienced by the subject was recorded on the CRF, regardless of the severity of the event or its relationship to study treatment*" (pages 66-7 of Protocol)	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
DECIDE 2015	Not reported	"A serious adverse event (SAE) is any untoward medical occurrence that at any dose: • results in death • in the view of the Investigator, places the subject at immediate risk of death (a life-threatening

Table 1. Assessment of adverse events/serious adverse events in included studies *(Continued)*

		event); however, this does not include an event that, had it occurred in a more severe form, might have caused death • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity, or • results in a congenital anomaly/birth defect. An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above" (Protocol).
DEFINE 2012	"*Study visits were scheduled every 4 weeks for safety assessments, including the monitoring of laboratory values*" (page 1100).	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
Etemadifar 2006	Not reported	SAEs not reported
Etemadifar 2007	"*Adverse events, vital signs and blood tests were monitored monthly*" (page 1724).	SAEs not reported
Fazekas 1997	Participants "*asked about safety monthly...*" (page 590).	SAEs not reported
FREEDOMS 2010	"*An independent data and safety monitoring board evaluated the safety*" and "*Study visits, including safety assessments, were scheduled at 2 weeks and 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24 months after randomization*" (page 389).	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
FREEDOMS II 2014	"*...safety assessments, were scheduled at 2 weeks and 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24 months after randomization*" (Appendix, page 2).	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
GALA 2013	"*Safety assessments included adverse events (AEs), standard clinical laboratory tests, vital signs, and electrocardiographic (ECG) measurements*" (page 707).	No information on SAE definition
Gobbi 2013	Not reported	SAEs not reported
GOLDEN 2017	*"AEs, SAEs and vital signs were assessed at each study visit"* (page 18).	No information on SAE definition
Goodkin 1991	"*Side effects were reported to the treating neurologist every 6 months*" (page 21).	SAEs not reported
IFNB MS Group 1993	"*Treating neurologist reviewed side effects, laboratory findings for toxicity ...*" (page 656).	SAEs not reported
INCOMIN 2002	"*Safety assessments included adverse events, vital signs, physical examination, and concomitant medications. Patients underwent haematology and biochemical tests, including liver-function tests, every 2*	SAEs not reported

Table 1. Assessment of adverse events/serious adverse events in included studies *(Continued)*

	weeks for the first 8 weeks, and then every 3 months" (page 1455).	
Johnson 1995	"*The evaluating physician monitored safety every 3 months...*" (page 1270).	Insufficient information on SAEs definition
Knobler 1993	*"At each patient visit, a nurse coordinator collected patient diaries of daily events and documented adverse events noted in these records."* (page 335).	SAEs not reported
Koch-Henriksen 2006	"*Patients were interviewed about side effects and had routine blood tests including hematology and liver function tests every 3 months and thyroid tests and neutralizing antibodies every 6 months*" (page 1057).	SAEs not reported
Lewanska 2002	"*Laboratory safety examinations were made at the beginning and at the end of the study period*" (page 566).	Insufficient information on SAEs definition
MAIN 2014	"*At scheduled (quarterly) and unscheduled (i.e. at the onset of new symptoms or complications) follow-up visits the treating neurologist recorded symptoms, blood test results, clinical AEs and their management*".	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
Millefiorini 1997	"*The safety of the treatment was assessed on the basis of adverse events volunteered by the patient either spontaneously or on questioning and monitoring of the main laboratory parameters*" (page 155).	Insufficient information on SAEs definition
Mokhber 2014	AEs not reported	SAEs not reported
MSCRG 1996	"*Study visits were scheduled at baseline and every 6 months. Treating physicians reviewed toxicity test results, examined patients, and made all medical decisions*" (page 286).	Insufficient information on SAEs definition
OPERA I 2017	Not reported	A serious adverse event is defined as any adverse event that, at any dose, fulfils at least one of the following criteria: # Is fatal; (results in death*; please note: death is an outcome, not an event) # Is life-threatening (please note: the term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe) # Requires in-patient hospitalisation or prolongation of existing hospitalisation # Results in persistent or significant disability/incapacity # Is a congenital anomaly/birth defect # Is medically significant or requires intervention to prevent one or other of the outcomes listed above (Appendix)
OPERA II 2017	Not reported	A serious adverse event is defined as any adverse event that, at any dose, fulfils at least one of the

Table 1. Assessment of adverse events/serious adverse events in included studies *(Continued)*

		following criteria: # Is fatal; (results in death*; please note: death is an outcome, not an event) # Is life-threatening (please note: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe) # Requires in-patient hospitalisation or prolongation of existing hospitalisation # Results in persistent or significant disability/incapacity # Is a congenital anomaly/birth defect # Is medically significant or requires intervention to prevent one or other of the outcomes listed above (Appendix)
OPTIMUM 2021	*"Safety assessments included adverse events recorded verbatim and later coded in accordance with MedDRA version 21 (International Council for Harmonisation) and predefined adverse events of special interest (AESIs)"* (page 560).	An SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria: • Fatal; • Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe; • Requiring inpatient hospitalisation or prolongation of existing hospitalisation; • Resulting in persistent or significant disability or incapacity; • Congenital anomaly or birth defect; • Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalisation but may be considered to be SAEs when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above (Protocol).
PRISMS 1998	"*A "treating" neurologist was responsible for overall medical management of the patient, including treatment of any side-effects*" (page 1499).	Insufficient information on SAEs definition
RADIANCE 2019	*"Adverse events were assessed at each visit"* (page 123).	Insufficient information on SAEs definition
REGARD 2008	"*Adverse events (including pregnancy), withdrawals owing to adverse events, serious adverse events, and laboratory results were obtained for safety comparisons*" (page 905).	Insufficient information on SAEs definition
SELECT 2013	"*Safety parameters were assessed at all visits*" (page 2168).	No information on SAE definition
SUNBEAM 2019	*"Adverse events were assessed at each visit"* (page 1012).	No information on SAE definition

Table 1. Assessment of adverse events/serious adverse events in included studies *(Continued)*

TEMSO 2011	"*A treating neurologist at each site was responsible for recording and managing adverse events and monitoring safety assessments*" and "*Safety was evaluated on the basis of adverse events reported by study participants or investigators. Laboratory tests were performed at the time of screening, at baseline, every 2 weeks for the first 24 weeks, and then every 6 weeks until study completion. Physical and neurologic examinations were performed at week 12 and then every 24 weeks. An abdominal ultrasonographic examination to assess for pancreatic abnormalities was performed before the study and then every 24 weeks, because of previous infrequent reports of pancreatitis associated with leflunomide use*" (pages 1294-5).	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
TOWER 2014	"*Safety was assessed through adverse event reporting (upon occurrence), clinical laboratory tests (every 2 weeks until week 24, then every 6 weeks while still on treatment), vital signs (at weeks 2 and 6, then every 6 weeks until week 24, then every 12 weeks while still on treatment), abdominal ultrasonography (at week 24, then every 24 weeks), and electrocardiography (at baseline and end of treatment)*" (page 248).	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).
TRANSFORMS 2010	"*An independent data and safety monitoring board evaluated overall safety in the fingolimod phase 3 program*" and "*Safety assessments were conducted during screening, at baseline, and at months 1, 2, 3, 6, 9, and 12*" (page 404).	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

AE: adverse events
CRF:
CTCAE:
DMC:
ECG:
ELISA:
ETD:
ICH:
SAE: serious adverse events

Table 2. Netleague: Relapse (12 months)

Terifluno-mide	**1.52 (1.28,1.80)**	1.03 (0.80,1.33)	0.79 (0.61,1.01)	0.60 (0.31,1.15)	2.16 (1.16,4.05)	1.24 (0.74,2.08)	1.15 (0.94,1.41)	0.92 (0.67,1.26)	0.98 (0.78,1.23)	**0.72 (0.56,0.93)**	0.84 (0.61,1.16)	1.38 (0.85,2.24)
0.66 (0.55,0.78)	**Place-bo/no treat-ment**	**0.68 (0.56,0.82)**	**0.52 (0.43,0.63)**	**0.40 (0.21,0.74)**	1.42 (0.78,2.60)	0.82 (0.50,1.33)	**0.76 (0.68,0.85)**	**0.60 (0.47,0.79)**	**0.64 (0.55,0.75)**	**0.48 (0.39,0.57)**	**0.55 (0.42,0.73)**	0.91 (0.58,1.43)
0.97 (0.75,1.25)	**1.47 (1.22,1.78)**	**Pegylat-ed inter-feron be-ta-1a**	0.76 (0.58,1.00)	0.58 (0.30,1.12)	2.10 (1.12,3.95)	1.20 (0.71,2.03)	1.12 (0.90,1.39)	0.89 (0.65,1.23)	0.95 (0.75,1.21)	**0.70 (0.54,0.91)**	0.82 (0.58,1.14)	1.34 (0.82,2.19)
1.27 (0.99,1.64)	**1.93 (1.60,2.33)**	**1.31 (1.00,1.71)**	**Natal-izumab**	0.76 (0.40,1.47)	2.75 (1.46,5.18)	1.58 (0.94,2.65)	**1.47 (1.18,1.82)**	1.17 (0.85,1.61)	1.25 (0.98,1.59)	0.92 (0.70,1.20)	1.07 (0.76,1.49)	1.76 (1.08,2.87)
1.67 (0.87,3.19)	**2.53 (1.35,4.73)**	1.72 (0.89,3.30)	1.31 (0.68,2.52)	**Mitox-antrone**	3.61 (1.51,8.59)	2.07 (0.94,4.56)	1.92 (1.02,3.62)	1.53 (0.78,3.02)	1.63 (0.86,3.11)	**1.20 (0.63,2.31)**	1.40 (0.71,2.77)	**2.30 (1.06,4.99)**
0.46 (0.25,0.87)	0.70 (0.38,1.28)	**0.48 (0.25,0.90)**	**0.36 (0.19,0.68)**	**0.28 (0.12,0.66)**	**Interfer-on be-ta-1a and -1b**	0.57 (0.26,1.24)	**0.53 (0.29,0.98)**	0.42 (0.22,0.82)	**0.45 (0.24,0.84)**	**0.33 (0.18,0.63)**	**0.39 (0.20,0.75)**	**0.64 (0.43,0.95)**
0.81 (0.48,1.35)	1.22 (0.75,1.99)	0.83 (0.49,1.40)	0.63 (0.38,1.07)	0.48 (0.22,1.07)	1.74 (0.80,3.78)	**Interfer-on be-ta-1b Betaferon**	0.93 (0.57,1.51)	0.74 (0.43,1.29)	0.79 (0.49,1.28)	**0.58 (0.36,0.93)**	0.68 (0.39,1.19)	1.11 (0.57,2.17)
0.87 (0.71,1.06)	**1.32 (1.18,1.47)**	0.89 (0.72,1.11)	**0.68 (0.55,0.85)**	**0.52 (0.28,0.98)**	**1.88 (1.02,3.46)**	1.08 (0.66,1.75)	**Interfer-on be-ta-1a**	0.80 (0.60,1.06)	0.85 (0.71,1.01)	**0.63 (0.53,0.75)**	**0.73 (0.54,0.98)**	1.20 (0.75,1.91)
1.09 (0.80,1.49)	**1.65 (1.27,2.15)**	1.12 (0.81,1.55)	0.86 (0.62,1.18)	0.65 (0.33,1.29)	**2.36 (1.22,4.54)**	1.35 (0.78,2.34)	1.25 (0.94,1.67)	**Im-munoglob-ulins**	1.07 (0.79,1.44)	0.79 (0.57,1.08)	0.91 (0.62,1.34)	1.50 (0.89,2.54)
1.02 (0.81,1.28)	**1.55 (1.33,1.80)**	1.05 (0.83,1.34)	0.80 (0.63,1.02)	0.61 (0.32,1.17)	**2.21 (1.19,4.11)**	1.27 (0.78,2.04)	1.18 (0.99,1.40)	0.94 (0.69,1.27)	**Glati-ramer ac-etate**	**0.74 (0.61,0.90)**	0.86 (0.63,1.18)	1.41 (0.87,2.27)
1.39 (1.07,1.79)	**2.10 (1.74,2.54)**	**1.43 (1.09,1.86)**	1.09 (0.83,1.42)	0.83 (0.43,1.60)	**3.00 (1.59,5.63)**	**1.72 (1.07,2.76)**	**1.60 (1.34,1.90)**	1.27 (0.92,1.76)	**1.36 (1.11,1.65)**	**Fin-golimod**	1.16 (0.83,1.63)	**1.91 (1.17,3.13)**

Table 2. Netleague: Relapse (12 months) *(Continued)*

1.19 (0.86,1.65)	**1.81 (1.37,2.39)**	1.23 (0.88,1.71)	0.94 (0.67,1.31)	0.71 (0.36,1.42)	**2.58 (1.33,5.00)**	1.48 (0.84,2.58)	**1.37 (1.02,1.85)**	1.09 (0.75,1.60)	1.17 (0.85,1.60)	0.86 (0.61,1.20)	**Daclizumab**	1.65 (0.97,2.80)
0.72 (0.45,1.18)	1.10 (0.70,1.73)	0.75 (0.46,1.22)	**0.57 (0.35,0.93)**	**0.43 (0.20,0.94)**	**1.57 (1.05,2.33)**	0.90 (0.46,1.74)	0.83 (0.52,1.33)	0.66 (0.39,1.12)	0.71 (0.44,1.14)	**0.52 (0.32,0.85)**	0.61 (0.36,1.03)	**Azathioprine**

Significant results are bolded and underlined

Table 3. Netleague: Relapse (24 months)

Teriflunomide	**0.70 (0.62,0.80)**	**1.22 (1.06,1.40)**	**0.68 (0.55,0.84)**	**0.57 (0.33,0.99)**	1.01 (0.86,1.19)	1.47 (0.79,2.71)	1.03 (0.86,1.23)	1.03 (0.87,1.20)	0.88 (0.68,1.14)	1.02 (0.86,1.21)	**0.65 (0.55,0.78)**	**0.75 (0.63,0.91)**	**0.64 (0.51,0.81)**	0.94 (0.60,1.46)	0.69 (0.55,0.86)
1.42 (1.25,1.63)	**Ponesimod**	**1.73 (1.43,2.10)**	0.97 (0.76,1.24)	0.81 (0.46,1.43)	**1.44 (1.16,1.78)**	**2.09 (1.11,3.92)**	**1.47 (1.18,1.83)**	**1.46 (1.19,1.80)**	1.26 (0.94,1.68)	**1.45 (1.17,1.80)**	0.93 (0.74,1.17)	1.07 (0.86,1.35)	0.92 (0.70,1.20)	1.34 (0.84,2.13)	0.98 (0.75,1.28)
0.82 (0.71,0.94)	**0.58 (0.48,0.70)**	**Placebo/no treatment**	**0.56 (0.48,0.65)**	**0.47 (0.27,0.80)**	**0.83 (0.76,0.91)**	1.21 (0.66,2.19)	**0.85 (0.76,0.94)**	**0.84 (0.78,0.91)**	0.73 (0.59,0.90)	**0.84 (0.76,0.93)**	**0.54 (0.48,0.60)**	**0.62 (0.55,0.70)**	**0.53 (0.44,0.64)**	0.77 (0.51,1.18)	0.57 (0.47,0.68)
1.47 (1.19,1.81)	1.03 (0.80,1.32)	**1.79 (1.53,2.09)**	**Natalizumab**	0.84 (0.48,1.46)	**1.48 (1.24,1.78)**	**2.16 (1.16,4.00)**	**1.51 (1.25,1.83)**	**1.51 (1.26,1.80)**	1.30 (0.99,1.69)	**1.50 (1.24,1.81)**	0.96 (0.79,1.17)	1.11 (0.91,1.35)	0.95 (0.74,1.21)	1.38 (0.88,2.17)	1.01 (0.79,1.29)
1.76 (1.01,3.06)	1.23 (0.70,2.18)	**2.14 (1.25,3.66)**	1.20 (0.68,2.09)	**Mitoxantrone**	**1.77 (1.03,3.05)**	**2.58 (1.15,5.76)**	**1.81 (1.05,3.13)**	**1.80 (1.05,3.10)**	1.55 (0.87,2.76)	**1.79 (1.04,3.09)**	1.15 (0.66,1.99)	1.32 (0.76,2.29)	1.13 (0.64,1.99)	1.65 (0.84,3.27)	1.21 (0.69,2.13)
0.99 (0.84,1.17)	**0.70 (0.56,0.86)**	**1.21 (1.10,1.32)**	**0.67 (0.56,0.81)**	**0.56 (0.33,0.97)**	**Laquinimod**	1.45 (0.79,2.66)	1.02 (0.89,1.18)	1.02 (0.91,1.14)	0.87 (0.69,1.10)	1.01 (0.88,1.16)	**0.65 (0.56,0.75)**	**0.75 (0.64,0.87)**	**0.64 (0.52,0.78)**	0.93 (0.61,1.43)	0.68 (0.56,0.83)
0.68 (0.37,1.26)	**0.48 (0.26,0.90)**	0.83 (0.46,1.51)	**0.46 (0.25,0.86)**	**0.39 (0.17,0.87)**	0.69 (0.38,1.26)	**Interferon beta 1a and 1b**	0.70 (0.38,1.29)	0.70 (0.38,1.28)	0.60 (0.32,1.14)	0.69 (0.38,1.27)	**0.45 (0.24,0.82)**	**0.51 (0.28,0.95)**	**0.44 (0.23,0.82)**	**0.64 (0.42,0.98)**	**0.47 (0.25,0.88)**
0.97 (0.82,1.16)	**0.68 (0.55,0.85)**	**1.18 (1.06,1.31)**	**0.66 (0.55,0.80)**	**0.55 (0.32,0.96)**	0.98 (0.85,1.13)	1.42 (0.78,2.61)	**Interferon beta-1b**	1.00 (0.88,1.12)	0.86 (0.68,1.09)	0.99 (0.89,1.10)	**0.64 (0.54,0.75)**	**0.73 (0.63,0.86)**	**0.62 (0.50,0.77)**	**0.91 (0.59,1.41)**	**0.67 (0.55,0.81)**

Table 3. Netleague: Relapse (24 months) *(Continued)*

0.97 (0.83,1.14)	**0.68 (0.56,0.84)**	**1.19 (1.10,1.28)**	**0.66 (0.56,0.79)**	**0.55 (0.32,0.95)**	0.98 (0.88,1.10)	1.43 (0.78,2.61)	1.00 (0.89,1.13)	**Interferon beta-1a**	0.86 (0.69,1.08)	0.99 (0.88,1.11)	**0.64 (0.56,0.73)**	**0.73 (0.64,0.84)**	**0.63 (0.51,0.77)**	0.92 (0.60,1.40)	**0.67 (0.57,0.79)**
1.13 (0.88,1.46)	0.80 (0.60,1.06)	**1.38 (1.11,1.71)**	0.77 (0.59,1.01)	0.64 (0.36,1.15)	1.14 (0.91,1.44)	1.66 (0.88,3.14)	1.17 (0.92,1.48)	1.16 (0.93,1.46)	**Immunoglobulins**	1.15 (0.91,1.46)	**0.74 (0.58,0.95)**	0.85 (0.67,1.09)	**0.73 (0.55,0.97)**	1.07 (0.67,1.71)	0.78 (0.59,1.03)
0.98 (0.83,1.17)	**0.69 (0.55,0.86)**	**1.19 (1.08,1.32)**	**0.67 (0.55,0.81)**	**0.56 (0.32,0.96)**	0.99 (0.86,1.14)	1.44 (0.79,2.64)	1.01 (0.91,1.12)	1.01 (0.90,1.13)	0.87 (0.68,1.10)	**Glatiramer acetate**	**0.64 (0.55,0.75)**	**0.74 (0.64,0.86)**	**0.63 (0.51,0.78)**	0.92 (0.60,1.42)	**0.67 (0.55,0.82)**
1.53 (1.28,1.83)	1.07 (0.86,1.34)	**1.86 (1.66,2.09)**	1.04 (0.85,1.26)	0.87 (0.50,1.51)	**1.54 (1.33,1.78)**	**2.24 (1.22,4.12)**	**1.57 (1.34,1.85)**	**1.57 (1.36,1.80)**	**1.35 (1.06,1.72)**	**1.56 (1.33,1.82)**	**Fingolimod**	1.15 (0.98,1.36)	0.98 (0.79,1.22)	1.44 (0.93,2.22)	1.05 (0.85,1.30)
1.33 (1.10,1.59)	0.93 (0.74,1.17)	**1.61 (1.43,1.82)**	0.90 (0.74,1.10)	0.76 (0.44,1.31)	**1.34 (1.15,1.55)**	**1.95 (1.06,3.58)**	**1.37 (1.17,1.60)**	**1.36 (1.18,1.57)**	1.17 (0.92,1.50)	**1.35 (1.17,1.56)**	0.87 (0.74,1.02)	**Dimethyl fumarate**	0.85 (0.68,1.06)	1.25 (0.81,1.93)	0.91 (0.74,1.13)
1.55 (1.23,1.96)	1.09 (0.84,1.43)	**1.89 (1.57,2.28)**	1.06 (0.83,1.35)	0.88 (0.50,1.56)	**1.57 (1.28,1.93)**	**2.28 (1.22,4.26)**	**1.60 (1.29,1.98)**	**1.59 (1.30,1.95)**	**1.37 (1.03,1.82)**	**1.58 (1.28,1.96)**	1.02 (0.82,1.26)	1.17 (0.94,1.46)	**Cladribine**	1.46 (0.92,2.31)	1.07 (0.82,1.38)
1.06 (0.68,1.65)	0.75 (0.47,1.18)	1.29 (0.85,1.97)	0.72 (0.46,1.13)	0.60 (0.31,1.20)	1.07 (0.70,1.65)	**1.56 (1.02,2.39)**	1.09 (0.71,1.69)	1.09 (0.71,1.67)	0.94 (0.59,1.50)	1.08 (0.70,1.67)	0.70 (0.45,1.07)	0.80 (0.52,1.24)	0.68 (0.43,1.08)	**Azathioprine**	0.73 (0.46,1.15)
1.45 (1.16,1.83)	1.02 (0.78,1.33)	**1.77 (1.48,2.12)**	0.99 (0.78,1.26)	0.83 (0.47,1.46)	**1.47 (1.20,1.79)**	**2.13 (1.14,3.99)**	**1.50 (1.23,1.82)**	**1.49 (1.27,1.76)**	1.28 (0.97,1.70)	**1.48 (1.22,1.80)**	0.95 (0.77,1.18)	1.10 (0.88,1.36)	0.94 (0.72,1.21)	1.37 (0.87,2.16)	**Alemtuzumab**

Significant results are bolded and underlined

Table 4. Netleague: Relapse (36 months)

Interferon beta-1a	0.79 (0.57,1.08)	**0.67 (0.60,0.75)**	**0.45 (0.32,0.65)**
1.27 (0.92,1.75)	**Glatiramer acetate**	0.85 (0.61,1.20)	**0.58 (0.36,0.93)**
1.49 (1.33,1.67)	1.17 (0.83,1.64)	**Daclizumab**	**0.67 (0.46,0.98)**
2.20 (1.54,3.16)	**1.74 (1.07,2.81)**	**1.48 (1.02,2.16)**	**Alemtuzumab**

Significant results are bolded and underlined

Table 5. Netleague: Disability (24 months)

Teri-flunomide	0.82 (0.57,1.19)	**1.31 (1.05,1.63)**	1.56 (0.92,2.62)	**0.71 (0.54,0.93)**	0.79 (0.51,1.24)	0.77 (0.56,1.07)	0.26 (0.06,1.10)	1.02 (0.76,1.38)	4.17 (0.40,43.94)		1.00 (0.74,1.36)	1.21 (0.88,1.66)	0.98 (0.51,1.87)	0.97 (0.72,1.29)	0.90 (0.67,1.20)	0.85 (0.65,1.13)	0.94 (0.68,1.30)	0.79 (0.29,2.19)	0.88 (0.57,1.37)
1.22 (0.84,1.77)	**Pones-timod**	1.60 (1.04,2.46)	**1.90 (1.00,3.60)**	0.86 (0.54,1.37)	0.97 (0.54,1.73)	0.94 (0.57,1.55)	0.32 (0.07,1.41)	1.25 (0.77,2.01)	5.09 (0.47,55.18)		1.22 (0.76,1.98)	1.47 (0.90,2.40)	1.20 (0.57,2.52)	1.18 (0.74,1.89)	1.09 (0.68,1.76)	1.04 (0.65,1.66)	1.14 (0.70,1.88)	0.96 (0.33,2.85)	1.07 (0.60,1.91)
0.76 (0.61,0.95)	**0.63 (0.41,0.96)**	**Place-bo/no treat-ment**	1.19 (0.74,1.91)	0.54 (0.38,0.77)	**0.61 (0.41,0.90)**	**0.59 (0.46,0.76)**	**0.20 (0.05,0.83)**	**0.78 (0.63,0.96)**	3.19 (0.31,33.21)		0.77 (0.62,0.94)	0.92 (0.73,1.16)	0.75 (0.41,1.37)	**0.74 (0.61,0.89)**	**0.68 (0.56,0.83)**	**0.65 (0.55,0.77)**	**0.72 (0.56,0.91)**	0.60 (0.22,1.63)	**0.67 (0.46,0.99)**
0.64 (0.38,1.08)	0.53 (0.28,1.00)	0.84 (0.52,1.35)	**Ozan-imod**	**0.45 (0.25,0.82)**	**0.51 (0.30,0.86)**	**0.50 (0.29,0.85)**	**0.17 (0.04,0.75)**	0.66 (0.40,1.09)	2.68 (0.25,29.32)		0.64 (0.40,1.04)	0.78 (0.51,1.17)	0.63 (0.29,1.36)	0.62 (0.39,1.00)	**0.58 (0.35,0.96)**	**0.55 (0.33,0.90)**	0.60 (0.35,1.02)	0.51 (0.17,1.53)	**0.57 (0.34,0.95)**
1.41 (1.08,1.86)	1.16 (0.73,1.84)	**1.85 (1.30,2.63)**	**2.20 (1.22,3.96)**	**Ofa-tu-mum-ab**	1.12 (0.66,1.90)	1.09 (0.71,1.68)	0.37 (0.08,1.59)	1.44 (0.96,2.17)	5.90 (0.55,63.10)		1.42 (0.94,2.13)	**1.71 (1.12,2.59)**	1.39 (0.69,2.79)	1.37 (0.92,2.04)	1.27 (0.85,1.89)	1.21 (0.82,1.78)	1.32 (0.86,2.03)	1.12 (0.39,3.21)	1.24 (0.74,2.09)
1.26 (0.80,1.98)	1.03 (0.58,1.85)	**1.65 (1.11,2.45)**	**1.96 (1.16,3.31)**	0.89 (0.53,1.51)	**Ocre-li-zum-ab**	0.98 (0.61,1.55)	0.33 (0.07,1.44)	1.29 (0.84,1.98)	5.26 (0.49,56.66)		1.26 (0.85,1.88)	**1.52 (1.10,2.09)**	1.24 (0.60,2.55)	1.22 (0.82,1.81)	1.13 (0.73,1.75)	1.08 (0.71,1.64)	1.18 (0.74,1.87)	1.00 (0.34,2.90)	1.11 (0.71,1.73)
1.29 (0.93,1.80)	1.06 (0.65,1.74)	**1.69 (1.33,2.16)**	**2.01 (1.18,3.42)**	0.91 (0.60,1.40)	1.03 (0.65,1.63)	**Na-tal-izum-ab**	0.33 (0.08,1.43)	1.32 (0.96,1.82)	5.39 (0.51,56.95)		1.30 (0.94,1.79)	**1.56 (1.12,2.18)**	1.27 (0.66,2.44)	1.25 (0.92,1.71)	1.16 (0.85,1.59)	1.10 (0.82,1.49)	1.21 (0.86,1.71)	1.02 (0.37,2.85)	1.14 (0.72,1.79)
3.87 (0.91,16.43)	3.17 (0.71,14.12)	**5.06 (1.21,21.16)**	**6.01 (1.33,27.11)**	2.74 (0.63,11.93)	3.07 (0.70,13.50)	2.99 (0.70,12.76)	**Mi-to-x-antrone**	3.95 (0.93,16.71)	**16.13 (1.04,251.30)**		3.87 (0.91,16.44)	**4.66 (1.10,19.85)**	3.79 (0.88,17.92)	3.74 (0.88,15.84)	3.46 (0.82,14.68)	3.30 (0.78,13.94)	3.62 (0.85,15.46)	3.06 (0.54,17.46)	3.40 (0.77,14.95)
0.98 (0.72,1.32)	0.80 (0.50,1.30)	1.28 (1.04,1.58)	1.52 (0.92,2.52)	0.69 (0.46,1.04)	0.78 (0.50,1.20)	0.76 (0.55,1.04)	0.25 (0.06,1.07)	**Laquin-imod**	4.08 (0.39,42.95)		0.98 (0.73,1.31)	1.18 (0.88,1.58)	0.96 (0.50,1.82)	0.95 (0.72,1.25)	0.88 (0.66,1.17)	0.84 (0.64,1.09)	0.92 (0.67,1.26)	0.77 (0.28,2.14)	0.86 (0.56,1.31)
0.24 (0.02,2.52)	0.20 (0.02,2.13)	0.31 (0.03,3.27)	0.37 (0.03,4.07)	0.17 (0.02,1.81)	0.19 (0.02,2.05)	0.19 (0.02,1.96)	**0.06 (0.00,0.97)**	0.24 (0.02,2.58)	**Interferon beta 1a and 1b**		0.24 (0.02,2.53)	0.29 (0.03,3.05)	0.23 (0.02,2.65)	0.23 (0.02,2.44)	0.21 (0.02,2.26)	0.20 (0.02,2.15)	0.22 (0.02,2.37)	0.19 (0.02,1.58)	0.21 (0.02,2.27)
1.00 (0.74,1.35)	0.82 (0.51,1.32)	**1.31 (1.06,1.61)**	1.55 (0.97,2.49)	0.71 (0.47,1.06)	0.79 (0.53,1.17)	0.77 (0.56,1.07)	0.26 (0.06,1.10)	1.02 (0.76,1.36)	4.16 (0.40,43.81)		**In-ter-fer-on**	1.20 (0.95,1.52)	0.98 (0.51,1.86)	0.97 (0.81,1.15)	0.89 (0.67,1.19)	0.85 (0.66,1.10)	0.93 (0.68,1.29)	0.79 (0.29,2.18)	0.88 (0.60,1.29)

Table 5. Netleague: Disability (24 months) *(Continued)*

											beta-1b								
0.83 (0.60,1.14)	0.68 (0.42,1.11)	1.09 (0.86,1.36)	1.29 (0.85,1.95)	**0.59 (0.39,0.89)**	**0.66 (0.48,0.90)**	**0.64 (0.46,0.90)**	**0.21 (0.05,0.91)**	0.85 (0.63,1.13)	3.46 (0.33,36.45)	0.83 (0.66,1.05)	**Interferon beta-1a**	0.81 (0.42,1.55)	0.80 (0.64,1.01)	0.74 (0.55,1.00)	**0.71 (0.54,0.93)**	0.78 (0.56,1.08)	0.66 (0.24,1.82)	**0.73 (0.54,0.99)**
1.02 (0.53,1.95)	0.84 (0.40,1.76)	1.34 (0.73,2.45)	1.59 (0.73,3.47)	0.72 (0.36,1.45)	0.81 (0.39,1.67)	0.79 (0.41,1.52)	0.26 (0.06,1.25)	1.04 (0.55,1.98)	4.26 (0.38,47.93)	1.02 (0.54,1.94)	1.23 (0.64,2.35)	**Immunoglobulins**	0.99 (0.52,1.87)	0.91 (0.48,1.73)	0.87 (0.46,1.64)	0.96 (0.50,1.84)	0.81 (0.25,2.59)	0.90 (0.44,1.84)
1.03 (0.77,1.38)	0.85 (0.53,1.36)	**1.35 (1.12,1.64)**	1.61 (1.00,2.58)	0.73 (0.49,1.09)	0.82 (0.55,1.22)	0.80 (0.59,1.09)	0.27 (0.06,1.13)	1.06 (0.80,1.39)	4.31 (0.41,45.27)	1.04 (0.87,1.23)	1.25 (0.99,1.57)	1.01 (0.54,1.91)	**Glatiramer acetate**	0.93 (0.70,1.22)	0.88 (0.71,1.10)	0.97 (0.71,1.32)	0.82 (0.30,2.25)	0.91 (0.62,1.34)
1.12 (0.83,1.50)	0.92 (0.57,1.47)	**1.46 (1.20,1.78)**	**1.74 (1.04,2.90)**	0.79 (0.53,1.18)	0.89 (0.57,1.37)	0.86 (0.63,1.18)	0.29 (0.07,1.22)	1.14 (0.86,1.52)	4.66 (0.44,48.94)	1.12 (0.84,1.49)	1.35 (1.00,1.82)	1.09 (0.58,2.07)	1.08 (0.82,1.42)	**Fingolimod**	0.95 (0.73,1.24)	1.05 (0.76,1.43)	0.88 (0.32,2.43)	0.98 (0.64,1.51)
1.17 (0.89,1.55)	0.96 (0.60,1.53)	**1.53 (1.29,1.81)**	**1.82 (1.11,2.99)**	0.83 (0.56,1.22)	0.93 (0.61,1.41)	0.91 (0.67,1.22)	0.30 (0.07,1.28)	1.20 (0.92,1.56)	4.88 (0.47,51.23)	1.17 (0.91,1.51)	**1.41 (1.08,1.85)**	1.15 (0.61,2.16)	1.13 (0.91,1.42)	1.05 (0.81,1.36)	**Dimethyl fumarate**	1.10 (0.82,1.48)	0.93 (0.34,2.54)	1.03 (0.68,1.55)
1.07 (0.77,1.48)	0.88 (0.53,1.44)	**1.40 (1.10,1.78)**	1.66 (0.98,2.82)	0.76 (0.49,1.16)	0.85 (0.53,1.34)	0.83 (0.59,1.17)	0.28 (0.06,1.18)	1.09 (0.79,1.50)	4.45 (0.42,47.01)	1.07 (0.78,1.47)	1.29 (0.92,1.80)	1.05 (0.54,2.01)	1.03 (0.76,1.41)	0.96 (0.70,1.31)	0.91 (0.68,1.23)	**Cladribine**	0.84 (0.30,2.35)	0.94 (0.60,1.48)
1.26 (0.46,3.50)	1.04 (0.35,3.06)	1.66 (0.61,4.47)	1.97 (0.65,5.91)	0.89 (0.31,2.57)	1.00 (0.34,2.92)	0.98 (0.35,2.72)	0.33 (0.06,1.87)	1.29 (0.47,3.57)	5.27 (0.63,44.07)	1.27 (0.46,3.50)	1.53 (0.55,4.23)	1.24 (0.39,3.97)	1.22 (0.44,3.37)	1.13 (0.41,3.12)	1.08 (0.39,2.96)	1.18 (0.43,3.29)	**Azathioprine**	1.11 (0.38,3.23)
1.14 (0.73,1.77)	0.93 (0.52,1.66)	**1.49 (1.01,2.19)**	**1.77 (1.06,2.96)**	0.80 (0.48,1.35)	0.90 (0.58,1.41)	0.88 (0.56,1.39)	0.29 (0.07,1.29)	1.16 (0.76,1.78)	4.74 (0.44,51.02)	1.14 (0.77,1.68)	**1.37 (1.01,1.87)**	1.11 (0.54,2.29)	1.10 (0.75,1.62)	1.02 (0.66,1.57)	0.97 (0.64,1.47)	1.07 (0.68,1.68)	0.90 (0.31,2.61)	**Alemtuzumab**

Significant results are bolded and underlined

Table 6. Netleague: Disability (36 months)

Interferon beta-1a	1.13 (0.82,1.57)	**0.72 (0.58,0.90)**	**0.37 (0.20,0.68)**
0.88 (0.64,1.23)	**Glatiramer acetate**	**0.64 (0.43,0.94)**	**0.33 (0.17,0.66)**
1.39 (1.12,1.73)	**1.57 (1.06,2.33)**	**Daclizumab**	**0.52 (0.27,0.99)**
2.68 (1.47,4.88)	**3.03 (1.53,6.03)**	**1.93 (1.01,3.68)**	**Alemtuzumab**

Significant results are bolded and underlined

Table 7. Netleague: Discontinuation due to adverse events

Teriflunomide	**2.76 (1.32,5.79)**	**0.55 (0.36,0.84)**	1.96 (0.73,5.27)	0.55 (0.25,1.21)	1.10 (0.67,1.78)	**0.45 (0.20,0.99)**	0.86 (0.39,1.89)	0.80 (0.45,1.42)	1.66 (0.14,19.14)	1.24 (0.52,3.00)	0.81 (0.45,1.45)	1.36 (0.20,9.48)	0.81 (0.46,1.42)	1.01 (0.59,1.73)	0.74 (0.42,1.30)	1.40 (0.67,2.90)	0.76 (0.23,2.46)	3.43 (0.36,33.1)	**0.21 (0.09,0.49)**
0.36 (0.17,0.76)	**Ponesimod**	**0.20 (0.08,0.47)**	0.71 (0.21,2.44)	**0.20 (0.07,0.59)**	**0.40 (0.16,0.96)**	**0.16 (0.05,0.48)**	**0.31 (0.11,0.92)**	**0.29 (0.11,0.74)**	0.60 (0.05,7.72)	0.45 (0.14,1.47)	**0.29 (0.11,0.75)**	0.49 (0.06,3.93)	**0.29 (0.12,0.74)**	**0.36 (0.15,0.91)**	**0.27 (0.11,0.68)**	0.51 (0.18,1.43)	0.27 (0.07,1.10)	1.24 (0.11,13.4)	**0.08 (0.03,0.23)**
1.82 (1.19,2.79)	**5.04 (2.15,11.82)**	**Placebo/ no treatment**	**3.58 (1.47,8.73)**	1.01 (0.52,1.95)	**2.00 (1.05,3.81)**	0.82 (0.42,1.60)	1.57 (0.81,3.05)	**1.46 (1.00,2.15)**	3.02 (0.27,33.6)	**2.27 (1.05,4.91)**	1.48 (0.99,2.20)	2.49 (0.37,16.5)	**1.48 (1.02,2.14)**	**1.84 (1.31,2.57)**	1.35 (0.94,1.95)	**2.55 (1.40,4.63)**	1.38 (0.46,4.15)	6.26 (0.67,58.0)	**0.39 (0.19,0.79)**
0.51 (0.19,1.37)	1.41 (0.41,4.83)	**0.28 (0.11,0.68)**	**Peginterferon beta-1a**	**0.28 (0.09,0.85)**	0.56 (0.19,1.67)	**0.23 (0.07,0.70)**	0.44 (0.14,1.33)	0.41 (0.15,1.08)	0.84 (0.06,11.0)	0.63 (0.19,2.06)	0.41 (0.16,1.09)	0.69 (0.09,5.62)	0.41 (0.16,1.08)	0.51 (0.20,1.33)	**0.38 (0.14,0.99)**	0.71 (0.24,2.08)	0.39 (0.09,1.59)	1.75 (0.16,19.2)	**0.11 (0.03,0.34)**
1.81 (0.83,3.98)	**5.01 (1.70,14.7)**	0.99 (0.41,1.91)	**3.56 (1.17,10.8)**	**Ozanimod**	1.99 (0.79,5.00)	0.81 (0.38,1.74)	1.56 (0.61,3.98)	1.45 (0.71,3.00)	3.00 (0.25,36.5)	2.25 (0.88,5.79)	1.47 (0.87,2.49)	2.47 (0.33,18.3)	1.47 (0.76,2.85)	1.83 (0.93,3.59)	1.34 (0.65,2.79)	**2.53 (1.25,5.13)**	1.37 (0.38,4.96)	6.22 (0.61,63.5)	**0.38 (0.17,0.86)**
0.91 (0.56,1.48)	**2.52 (1.04,6.10)**	**0.50 (0.26,0.95)**	1.79 (0.60,5.38)	0.50 (0.20,1.27)	**Ofatumumab**	0.41 (0.16,1.04)	0.79 (0.31,1.98)	0.73 (0.35,1.55)	1.51 (0.12,18.8)	1.13 (0.42,3.10)	0.74 (0.35,1.58)	1.24 (0.17,9.18)	0.74 (0.35,1.55)	0.92 (0.44,1.90)	0.68 (0.32,1.42)	1.27 (0.53,3.06)	0.69 (0.19,2.47)	3.13 (0.31,31.8)	**0.19 (0.07,0.51)**
2.23 (1.01,4.92)	**6.16 (2.08,18.25)**	1.22 (0.52,2.40)	**4.38 (1.43,13.37)**	1.23 (0.38,2.62)	2.44 (0.96,6.20)	**Ocrelizumab**	1.92 (0.75,4.94)	1.79 (0.86,3.73)	3.69 (0.30,45.0)	**2.77 (1.07,7.18)**	**1.81 (1.05,3.11)**	3.04 (0.41,22.6)	1.81 (0.92,3.55)	**2.24 (1.13,4.46)**	1.65 (0.79,3.47)	**3.11 (1.52,6.39)**	1.69 (0.47,6.13)	7.65 (0.75,78.3)	0.47 (0.21,1.07)
1.16 (0.53,2.55)	**3.21 (1.09,9.43)**	0.64 (0.33,1.23)	2.28 (0.75,6.91)	0.64 (0.25,1.63)	1.27 (0.51,3.20)	0.52 (0.20,1.34)	**Natalizumab**	0.93 (0.43,2.00)	1.92 (0.16,23.4)	1.44 (0.53,3.92)	0.94 (0.43,2.03)	1.58 (0.21,11.7)	0.94 (0.44,2.00)	1.17 (0.56,2.45)	0.86 (0.40,1.83)	1.62 (0.66,3.95)	0.88 (0.24,3.17)	3.98 (0.39,40.6)	**0.25 (0.09,0.65)**
1.25 (0.70,2.21)	**3.45 (1.35,8.77)**	0.68 (0.47,1.00)	2.45 (0.93,6.46)	0.69 (0.33,1.42)	1.37 (0.65,2.89)	0.56 (0.27,1.17)	1.07 (0.50,2.31)	**Laquinimod**	2.06 (0.18,23.7)	1.55 (0.66,3.62)	1.01 (0.62,1.66)	1.70 (0.25,11.7)	1.01 (0.61,1.68)	1.26 (0.77,2.05)	0.92 (0.55,1.56)	1.74 (0.89,3.40)	0.94 (0.29,3.03)	4.28 (0.45,40.9)	**0.26 (0.12,0.58)**

Table 7. Netleague: Discontinuation due to adverse events *(Continued)*

0.60 (0.05,6.98)	1.67 (0.13,21.50)	0.33 (0.03,3.69)	1.19 (0.09,15.49)	0.33 (0.03,4.05)	0.66 (0.05,8.02)	0.27 (0.02,3.30)	0.52 (0.04,6.34)	0.48 (0.04,5.56)	**Interferon beta 1a and 1b**	0.75 (0.06,9.41)	0.49 (0.04,5.62)	0.82 (0.04,17.62)	0.49 (0.04,5.59)	0.61 (0.05,6.92)	0.45 (0.04,5.12)	0.84 (0.07,10.08)	0.46 (0.03,6.47)	2.07 (0.82,5.20)	0.13 (0.01,1.58)
0.80 (0.33,1.94)	2.22 (0.70,7.02)	**0.44 (0.20,0.95)**	1.58 (0.49,5.14)	0.44 (0.17,1.14)	0.88 (0.32,2.41)	**0.36 (0.14,0.93)**	0.69 (0.26,1.88)	0.64 (0.28,1.51)	1.33 (0.11,16.66)	**Interferon beta-1b**	0.65 (0.30,1.42)	1.10 (0.14,8.47)	0.65 (0.32,1.33)	0.81 (0.37,1.77)	0.60 (0.26,1.35)	1.12 (0.46,2.75)	0.61 (0.16,2.34)	2.76 (0.26,29.16)	**0.17 (0.06,0.46)**
1.23 (0.69,2.21)	**3.41 (1.33,8.73)**	0.68 (0.45,1.01)	2.42 (0.91,6.43)	0.68 (0.40,1.16)	1.35 (0.63,2.88)	**0.55 (0.32,0.95)**	1.06 (0.49,2.30)	0.99 (0.60,1.62)	2.04 (0.18,23.49)	1.54 (0.70,3.35)	**Interferon beta-1a**	1.68 (0.24,11.64)	1.00 (0.67,1.49)	1.24 (0.82,1.89)	0.91 (0.55,1.51)	**1.72 (1.08,2.75)**	0.94 (0.29,3.01)	4.23 (0.44,40.69)	0.26 (0.14,0.48)
0.73 (0.11,5.11)	2.03 (0.25,16.18)	0.40 (0.06,2.67)	1.44 (0.18,11.68)	0.40 (0.05,3.01)	0.80 (0.11,5.94)	0.33 (0.04,2.46)	0.63 (0.09,4.70)	0.59 (0.09,4.06)	1.22 (0.06,26.06)	0.91 (0.12,7.06)	0.59 (0.09,4.12)	**Immunoglobulins**	0.59 (0.09,4.09)	0.74 (0.11,5.06)	0.54 (0.08,3.74)	1.03 (0.14,7.47)	0.56 (0.06,4.97)	2.52 (0.14,46.85)	0.16 (0.02,1.18)
1.24 (0.70,2.17)	**3.41 (1.35,8.64)**	**0.68 (0.47,0.98)**	2.43 (0.92,6.37)	0.68 (0.35,1.32)	1.35 (0.64,2.85)	0.55 (0.28,1.09)	1.06 (0.50,2.27)	0.99 (0.59,1.65)	2.05 (0.18,23.40)	1.54 (0.75,3.14)	1.00 (0.67,1.49)	1.68 (0.24,11.58)	**Glatiramer acetate**	1.24 (0.83,1.86)	0.92 (0.59,1.42)	1.72 (0.95,3.15)	0.94 (0.29,2.99)	4.24 (0.44,40.50)	**0.26 (0.13,0.54)**
0.99 (0.58,1.71)	**2.74 (1.10,6.86)**	**0.54 (0.39,0.76)**	1.95 (0.75,5.05)	0.55 (0.28,1.08)	1.09 (0.53,2.25)	**0.45 (0.22,0.89)**	0.86 (0.41,1.80)	0.80 (0.49,1.30)	1.64 (0.14,18.73)	1.24 (0.56,2.70)	0.80 (0.53,1.22)	1.35 (0.20,9.25)	0.80 (0.54,1.20)	**Fingolimod**	0.74 (0.46,1.18)	1.39 (0.75,2.57)	0.75 (0.24,2.38)	3.41 (0.36,32.44)	**0.21 (0.10,0.44)**
1.35 (0.77,2.36)	**3.73 (1.48,9.42)**	0.74 (0.51,1.07)	**2.65 (1.01,6.94)**	0.74 (0.36,1.54)	1.48 (0.71,3.10)	0.61 (0.29,1.27)	1.16 (0.55,2.48)	1.08 (0.64,1.83)	2.24 (0.20,25.57)	1.68 (0.74,3.80)	1.09 (0.66,1.81)	1.84 (0.27,12.64)	1.09 (0.70,1.70)	1.36 (0.85,2.18)	**Dimethyl fumarate**	1.88 (0.96,3.69)	1.02 (0.32,3.26)	4.63 (0.48,44.24)	0.29 (0.13,0.63)
0.72 (0.34,1.49)	1.98 (0.70,5.60)	**0.39 (0.22,0.70)**	1.41 (0.48,4.11)	**0.39 (0.19,0.80)**	0.78 (0.33,1.89)	0.32 (0.16,0.66)	0.62 (0.25,1.51)	0.57 (0.29,1.12)	1.19 (0.10,14.18)	0.89 (0.36,2.18)	**0.58 (0.36,0.93)**	0.98 (0.13,7.10)	0.58 (0.32,1.06)	0.72 (0.39,1.33)	0.53 (0.27,1.04)	**Daclizumab**	0.54 (0.16,1.90)	2.46 (0.24,24.66)	**0.15 (0.07,0.33)**

Table 7. Netleague: Discontinuation due to adverse events *(Continued)*

1.32 (0.41,4.29)	3.65 (0.91,14.66)	0.72 (0.24,2.17)	2.59 (0.63,10.67)	0.73 (0.20,2.63)	1.45 (0.40,5.18)	**0.59 (0.16,2.15)**	1.14 (0.32,4.11)	1.06 (0.33,3.39)	2.19 (0.15,30.92)	1.64 (0.43,6.30)	1.07 (0.33,3.44)	1.80 (0.20,16.05)	1.07 (0.33,3.41)	1.33 (0.42,4.20)	0.98 (0.31,3.12)	1.84 (0.53,6.44)	**Cladribine**	4.53 (0.38,54.29)	0.28 (0.08,1.04)
0.29 (0.03,2.81)	0.81 (0.07,8.75)	0.16 (0.02,1.48)	0.57 (0.05,6.30)	0.16 (0.02,1.64)	0.32 (0.03,3.25)	0.13 (0.01,1.34)	0.25 (0.02,2.57)	0.23 (0.02,2.24)	0.48 (0.19,1.21)	0.36 (0.03,3.83)	0.24 (0.02,2.27)	0.40 (0.02,7.39)	0.24 (0.02,2.26)	0.29 (0.03,2.79)	0.22 (0.02,2.06)	0.41 (0.04,4.09)	0.22 (0.02,2.65)	**Azathioprine**	0.06 (0.01,0.64)
4.72 (2.05,10.89)	**13.04 (3.97,39.80)**	**2.59 (1.06,5.32)**	**9.27 (2.95,29.14)**	**2.60 (1.16,5.83)**	**5.17 (1.97,13.60)**	2.12 (0.64,4.79)	**4.07 (1.53,10.79)**	**3.79 (1.74,8.25)**	7.82 (0.63,96.72)	**5.87 (2.16,15.92)**	**3.82 (1.68,7.03)**	6.43 (0.85,48.71)	**3.82 (1.84,7.95)**	**4.75 (2.27,9.95)**	**3.50 (1.59,7.68)**	**6.59 (3.05,14.27)**	3.58 (0.76,13.31)	**16.19 (6.56,168.25)**	**Alemtuzumab**

Significant results are bolded and underlined

Table 8. Netleague: Serious adverse events

Teriflunomid	1.07 (0.63,1.83)	0.87 (0.61,1.23)	0.93 (0.47,1.87)	1.30 (0.67,2.52)	1.31 (0.88,1.95)	0.87 (0.45,1.65)	1.07 (0.57,2.01)	0.77 (0.01,41.49)	1.08 (0.68,1.72)	0.80 (0.43,1.48)	1.05 (0.65,1.68)	0.81 (0.51,1.30)	0.74 (0.47,1.16)	0.90 (0.53,1.51)	1.64 (0.93,2.92)	1.20 (0.62,2.30)	1.32 (0.72,2.40)
0.93 (0.55,1.58)	**Ponesimod**	0.80 (0.43,1.52)	0.87 (0.36,2.08)	1.21 (0.51,2.83)	1.22 (0.63,2.36)	0.81 (0.35,1.85)	1.00 (0.44,2.27)	0.72 (0.01,39.98)	1.01 (0.50,2.04)	0.74 (0.33,1.68)	0.97 (0.48,1.98)	0.75 (0.37,1.53)	0.69 (0.34,1.38)	0.83 (0.40,1.75)	1.53 (0.70,3.34)	1.11 (0.48,2.59)	1.23 (0.55,2.73)
1.16 (0.81,1.64)	1.24 (0.66,2.35)	**Placebo/ no treatment**	1.08 (0.59,1.96)	1.50 (0.85,2.64)	1.52 (0.89,2.57)	1.00 (0.58,1.72)	1.24 (0.73,2.09)	0.89 (0.02,47.22)	1.25 (0.92,1.70)	0.92 (0.55,1.54)	1.21 (0.88,1.67)	0.94 (0.68,1.28)	0.86 (0.64,1.13)	1.04 (0.71,1.52)	**1.90 (1.21,2.99)**	1.39 (0.80,2.40)	1.52 (0.94,2.48)
1.07 (0.54,2.15)	1.15 (0.48,2.76)	0.93 (0.51,1.69)	**Pegylated interferon beta-1a**	1.39 (0.61,3.17)	1.41 (0.63,3.12)	0.93 (0.41,2.08)	1.15 (0.52,2.55)	0.83 (0.01,45.82)	1.16 (0.59,2.27)	0.86 (0.39,1.88)	1.12 (0.57,2.21)	0.87 (0.44,1.71)	0.79 (0.41,1.54)	0.96 (0.47,1.96)	1.76 (0.83,3.74)	1.29 (0.57,2.90)	1.41 (0.65,3.06)
0.77 (0.40,1.50)	0.83 (0.35,1.94)	0.67 (0.38,1.17)	0.72 (0.32,1.64)	**Ozanimod**	1.01 (0.47,2.19)	0.67 (0.35,1.26)	0.83 (0.38,1.79)	0.59 (0.01,32.80)	0.83 (0.45,1.55)	0.62 (0.31,1.24)	0.81 (0.50,1.29)	0.62 (0.35,1.10)	0.57 (0.32,1.01)	0.69 (0.36,1.34)	1.27 (0.69,2.33)	0.92 (0.42,2.03)	1.02 (0.56,1.85)
0.76 (0.51,1.13)	0.82 (0.42,1.59)	0.66 (0.39,1.12)	0.71 (0.32,1.58)	0.99 (0.46,2.14)	**Ofatumumab**	0.66 (0.31,1.40)	0.82 (0.39,1.72)	0.59 (0.01,32.28)	0.83 (0.45,1.52)	0.61 (0.29,1.27)	0.80 (0.43,1.48)	0.62 (0.33,1.14)	0.56 (0.31,1.03)	0.68 (0.36,1.31)	1.26 (0.63,2.52)	0.91 (0.43,1.96)	1.01 (0.49,2.06)

Table 8. Netleague: Serious adverse events *(Continued)*

1.16 (0.61,2.20)	1.24 (0.54,2.86)	1.00 (0.58,1.71)	1.08 (0.48,2.41)	1.50 (0.79,2.84)	1.51 (0.71,3.22)	**Ocrelizumab**	1.24 (0.58,2.63)	0.89 (0.02,48.95)	1.25 (0.69,2.27)	0.92 (0.47,1.81)	1.21 (0.78,1.86)	0.94 (0.54,1.61)	0.85 (0.49,1.48)	1.04 (0.55,1.97)	**1.90 (1.07,3.39)**	1.38 (0.64,2.99)	1.52 (0.86,2.69)
0.93 (0.50,1.76)	1.00 (0.44,2.29)	0.81 (0.48,1.37)	0.87 (0.39,1.93)	1.21 (0.56,2.62)	1.22 (0.58,2.58)	0.81 (0.38,1.72)	**Natalizumab**	0.72 (0.01,39.49)	1.01 (0.55,1.86)	0.75 (0.36,1.54)	0.98 (0.53,1.81)	0.76 (0.41,1.39)	0.69 (0.38,1.25)	0.84 (0.44,1.60)	1.54 (0.77,3.08)	1.12 (0.52,2.40)	1.23 (0.60,2.52)
1.30 (0.02,69.85)	1.39 (0.03,77.78)	1.12 (0.02,59.50)	1.21 (0.02,67.07)	1.68 (0.03,92.82)	1.70 (0.03,93.36)	1.12 (0.02,61.73)	1.39 (0.03,76.26)	**Mitoxantrone**	1.40 (0.03,75.32)	1.04 (0.02,56.73)	1.36 (0.03,72.88)	1.05 (0.02,56.38)	0.96 (0.02,51.41)	1.16 (0.02,62.84)	2.13 (0.04,116.10)	1.55 (0.03,85.61)	1.71 (0.03,93.46)
0.92 (0.58,1.47)	0.99 (0.49,2.01)	0.80 (0.59,1.09)	0.86 (0.44,1.69)	1.20 (0.64,2.23)	1.21 (0.66,2.23)	0.80 (0.44,1.45)	0.99 (0.54,1.82)	0.71 (0.01,38.21)	**Laquinimod**	0.74 (0.41,1.32)	0.97 (0.64,1.46)	0.75 (0.49,1.14)	0.68 (0.46,1.03)	0.83 (0.51,1.35)	1.52 (0.90,2.57)	1.11 (0.59,2.08)	1.22 (0.70,2.11)
1.25 (0.67,2.33)	1.35 (0.59,3.05)	1.08 (0.65,1.81)	1.17 (0.53,2.57)	1.62 (0.81,3.26)	1.64 (0.79,3.43)	1.08 (0.55,2.13)	1.34 (0.65,2.78)	0.97 (0.02,52.91)	1.36 (0.75,2.44)	**Interferon beta-1b**	1.31 (0.78,2.19)	1.01 (0.67,1.53)	0.93 (0.55,1.58)	1.12 (0.62,2.04)	**2.06 (1.11,3.83)**	1.50 (0.71,3.19)	1.65 (0.88,3.12)
0.96 (0.59,1.54)	1.03 (0.50,2.10)	0.83 (0.60,1.14)	0.89 (0.45,1.76)	1.24 (0.78,1.98)	1.25 (0.68,2.32)	0.83 (0.54,1.28)	1.02 (0.55,1.90)	0.74 (0.01,39.57)	1.03 (0.69,1.56)	0.76 (0.46,1.28)	**Interferon beta-1a**	0.77 (0.56,1.07)	**0.71 (0.51,0.99)**	0.86 (0.53,1.38)	**1.57 (1.07,2.30)**	1.15 (0.61,2.17)	1.26 (0.87,1.82)
1.24 (0.77,1.98)	1.33 (0.65,2.70)	1.07 (0.78,1.46)	1.15 (0.59,2.26)	1.60 (0.91,2.83)	1.62 (0.88,2.99)	1.07 (0.62,1.84)	1.32 (0.72,2.43)	0.95 (0.02,51.09)	1.34 (0.87,2.04)	0.99 (0.65,1.49)	1.29 (0.93,1.79)	**Glatiramer acetate**	0.91 (0.65,1.29)	1.11 (0.71,1.72)	**2.03 (1.26,3.28)**	1.48 (0.78,2.79)	**1.63 (1.00,2.66)**
1.35 (0.86,2.12)	1.45 (0.72,2.91)	1.17 (0.88,1.55)	1.26 (0.65,2.44)	1.75 (0.99,3.10)	1.77 (0.97,3.22)	1.17 (0.68,2.02)	1.45 (0.80,2.63)	1.04 (0.02,55.77)	1.46 (0.97,2.19)	1.08 (0.63,1.83)	**1.41 (1.01,1.97)**	1.09 (0.78,1.54)	**Fingolimod**	1.21 (0.77,1.92)	**2.22 (1.37,3.60)**	1.62 (0.87,3.01)	**1.78 (1.09,2.92)**
1.11 (0.66,1.87)	1.20 (0.57,2.52)	0.96 (0.66,1.41)	1.04 (0.51,2.11)	1.45 (0.74,2.81)	1.46 (0.76,2.80)	0.96 (0.51,1.83)	1.19 (0.62,2.29)	0.86 (0.02,46.39)	1.21 (0.74,1.96)	0.89 (0.49,1.62)	1.17 (0.73,1.87)	0.90 (0.58,1.40)	0.82 (0.52,1.30)	**Dimethyl fumarate**	**1.83 (1.03,3.26)**	1.34 (0.68,2.61)	1.47 (0.81,2.67)
0.61 (0.34,1.08)	0.65 (0.30,1.43)	**0.53 (0.33,0.83)**	0.57 (0.27,1.20)	0.79 (0.43,1.45)	0.80 (0.40,1.60)	**0.53 (0.30,0.94)**	0.65 (0.32,1.30)	0.47 (0.01,25.48)	0.66 (0.39,1.11)	0.49 (0.26,0.90)	**0.64 (0.43,0.93)**	**0.49 (0.31,0.79)**	**0.45 (0.28,0.73)**	**0.55 (0.31,0.97)**	**Daclizumab**	0.73 (0.36,1.49)	0.80 (0.47,1.36)
0.83 (0.43,1.60)	0.90 (0.39,2.08)	0.72 (0.42,1.25)	0.78 (0.35,1.75)	1.08 (0.49,2.38)	1.09 (0.51,2.35)	0.72 (0.33,1.56)	0.89 (0.42,1.91)	0.64 (0.01,35.41)	0.90 (0.48,1.70)	0.67 (0.31,1.41)	0.87 (0.46,1.65)	0.68 (0.36,1.27)	0.62 (0.33,1.15)	0.75 (0.38,1.46)	1.37 (0.67,2.80)	**Cladribine**	1.10 (0.53,2.30)

Table 8. Netleague: Serious adverse events *(Continued)*

0.76 (0.42,1.38)	0.81 (0.37,1.82)	0.66 (0.40,1.07)	0.71 (0.33,1.53)	0.98 (0.54,1.78)	0.99 (0.48,2.04)	0.66 (0.37,1.16)	0.81 (0.40,1.66)	0.58 (0.01,31.91)	0.82 (0.47,1.42)	0.61 (0.32,1.14)	0.79 (0.55,1.15)	0.61 (0.38,1.00)	**0.56 (0.34,0.92)**	0.68 (0.37,1.24)	1.25 (0.73,2.12)	0.91 (0.44,1.89)	**Alemtuzumab**

Significant results are bolded and underlined

APPENDICES

Appendix 1. Search strategy - CENTRAL

#	Query
#1	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only
#2	MeSH descriptor: [Demyelinating Diseases] this term only
#3	MeSH descriptor: [Multiple Sclerosis] explode all trees
#4	MeSH descriptor: [Myelitis, Transverse] explode all trees
#5	MeSH descriptor: [Optic Neuritis] explode all trees
#6	("clinically isolated" NEXT syndrome*):ti,ab
#7	(devic OR "devic s" OR devics):ti,ab
#8	(disseminated NEXT sclerosis*):ti,ab
#9	(demyelinating NEXT (disease* OR disorder*)):ti,ab
#10	((demyelinating OR necrotising OR necrotizing OR transverse) NEXT myelitis*):ti,ab
#11	multiple sclerosis:ti,ab OR MS:ti
#12	(neuropapilliti* OR ((optic OR retrobulbar) NEXT neuriti*)):ti,ab
#13	((neuromyelitis NEXT optica*) OR ("nmo spectrum" NEXT disorder*)):ti,ab
#14	{OR #1-#13}
#15	MeSH descriptor: [Adrenal Cortex Hormones] this term only and with qualifier(s): [therapeutic use - TU, adverse effects - AE]
#16	MeSH descriptor: [Alemtuzumab] explode all trees
#17	MeSH descriptor: [Azathioprine] explode all trees
#18	MeSH descriptor: [Cladribine] explode all trees
#19	MeSH descriptor: [Cyclophosphamide] explode all trees
#20	MeSH descriptor: [Daclizumab] explode all trees
#21	MeSH descriptor: [Dimethyl Fumarate] explode all trees
#22	MeSH descriptor: [Fingolimod Hydrochloride] explode all trees
#23	MeSH descriptor: [Glatiramer Acetate] explode all trees
#24	MeSH descriptor: [Immunoglobulins] this term only and with qualifier(s): [therapeutic use - TU, adverse effects - AE, drug effects - DE]

(Continued)

#25	MeSH descriptor: [Immunoglobulins, Intravenous] explode all trees
#26	MeSH descriptor: [Interferon-beta] explode all trees
#27	MeSH descriptor: [Interferon Type I] this term only
#28	MeSH descriptor: [Methotrexate] explode all trees
#29	MeSH descriptor: [Methylprednisolone] this term only
#30	MeSH descriptor: [Mitoxantrone] explode all trees
#31	MeSH descriptor: [Natalizumab] explode all trees
#32	MeSH descriptor: [Prednisolone] this term only
#33	MeSH descriptor: [Rituximab] explode all trees
#34	(("adrenal cortex" NEXT hormone*) OR corticoid*):ti,ab
#35	(corticosteroid* OR (cortico NEXT steroid*)):ti
#36	(alemtuzumab* OR campath* OR lemtrada*):ti,ab
#37	(avonex* OR rebif*):ti,ab
#38	(aubagio* OR teriflunomide*):ti,ab
#39	(azathioprine* OR azothioprine* OR imurel* OR imuran* OR immuran*):ti,ab
#40	(bafiertam* OR (monomethyl NEXT fumarate*) OR ("methyl hydrogen" NEXT fumarate*) OR methylhydrogenfumarate*):ti,ab
#41	((beta* NEAR/2 interferon*) OR fiblaferon* OR (fibroblast NEXT interferon*) OR IFNbeta* OR (IFN NEXT beta*)):ti,ab OR interferon*:ti
#42	(betaferon* OR betaseron* OR (beta NEXT seron*) OR extavia*):ti,ab
#43	(copaxone* OR "Cop 1" OR "copolymer 1" OR glatiramer* OR glatopa* OR "TV 5010" OR "TV5010"):ti,ab
#44	(cladribine* OR leustatin* OR mavenclad* OR movectro*):ti,ab
#45	(cyclophosphamide* OR cyclophosphane* OR cytophosphan* OR cytoxan* OR endoxan* OR neosar* OR procytox* OR sendoxan*):ti,ab
#46	(daclizumab* OR zinbryta* OR zenapax*):ti,ab
#47	(dimethylfumarate* OR (dimethyl NEXT fumarate*) OR "BG 00012" OR "BG00012" OR "BG12" OR (diroximel NEXT fumarate*) OR tecfidera* OR vumerity*):ti,ab
#48	(fingolimod* OR gilenya* OR gilenia* OR "FTY 720" OR "FTY720"):ti,ab
#49	(kesimpta* OR ofatumumab* OR "HUMAX CD20 2F2" OR "GSK 1841157" OR "GSK1841157"):ti,ab

(Continued)

#50	(immunoglobulin*):ti OR ((intravenous NEXT immunoglobulin*) OR (IV NEXT immunoglobulin*) OR IVIG):ti,ab
#51	(laquinimod* OR "ABR 215062" OR "ABR215062"):ti,ab
#52	(mayzent* OR siponimod* OR "BAF 312" OR "BAF312"):ti,ab
#53	(methotrexate* OR amethopterin* OR mexate*):ti,ab
#54	(methylprednisolone* OR metipred*):ti,ab
#55	(mitoxantrone* OR mitozantrone* OR ralenova* OR novantron* OR onkotrone*):ti,ab
#56	(natalizumab* OR tysabri* OR antegren*):ti,ab
#57	(ocrelizumab* OR ocrevus* OR "R 1594" OR "PR070769"):ti,ab
#58	(ozanimod* OR zeposia* OR "RPC1063"):ti,ab
#59	(peginterferon* OR (pegylated NEXT interferon*) OR plegridy* OR ("peg ifn" NEXT beta*)):ti,ab
#60	(prednisolone* OR predonine*):ti,ab
#61	(rituximab* OR rituxan* OR mabthera* OR "IDEC C2B8"):ti,ab
#62	{OR #15-#61}
#63	#14 AND #62
#64	#14 AND #62 in Trials

Appendix 2. Search strategy - MEDLINE (PubMed)

#	Query
1	("adverse effects" [Subheading]) AND "Multiple Sclerosis/drug therapy"[Majr]
2	"demyelinating autoimmune diseases, cns"[MeSH Terms:noexp]
3	"Demyelinating Diseases"[MeSH Terms:noexp]
4	"Multiple Sclerosis"[MeSH Terms]
5	"myelitis, transverse"[MeSH Terms]
6	"Optic Neuritis"[MeSH Terms]
7	"clinically isolated syndrome*"[Title/Abstract]
8	"devic"[Title/Abstract] OR "devic s"[Title/Abstract] OR "devics"[Title/Abstract]
9	"disseminated sclerosis*"[Title/Abstract]

(Continued)

10	"demyelinating disease*"[Title/Abstract] OR "demyelinating disorder*"[Title/Abstract]
11	"demyelinating myelitis*"[Title/Abstract] OR "necrotising myelitis*"[Title/Abstract] OR "necrotizing myelitis*"[Title/Abstract] OR "transverse myel*"[Title/Abstract]
12	"multiple sclerosis*"[Title/Abstract] OR "MS"[Title]
13	"neuropapilliti*"[Title/Abstract] OR "optic neuriti*"[Title/Abstract] OR "retrobulbar neuriti*"[Title/Abstract]
14	"neuromyelitis optica*"[Title/Abstract] OR "nmo spectrum disorder*"[Title/Abstract]
15	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16	("Adrenal Cortex Hormones/adverse effects"[Mesh:NoExp] OR "Adrenal Cortex Hormones/drug effects"[Mesh:NoExp] OR "Adrenal Cortex Hormones/drug therapy"[Mesh:NoExp] OR "Adrenal Cortex Hormones/therapeutic use"[Mesh:NoExp])
17	"Alemtuzumab"[MeSH Terms]
18	"Azathioprine"[MeSH Terms]
19	"Cladribine"[MeSH Terms]
20	"Cyclophosphamide"[MeSH Terms:noexp]
21	"Daclizumab"[MeSH Terms]
22	"Dimethyl Fumarate"[MeSH Terms]
23	"Fingolimod Hydrochloride"[MeSH Terms]
24	"Glatiramer Acetate"[MeSH Terms]
25	("Immunoglobulins/adverse effects"[Mesh:NoExp] OR "Immunoglobulins/drug effects"[Mesh:NoExp] OR "Immunoglobulins/therapeutic use"[Mesh:NoExp] OR "Immunoglobulins, Intravenous"[MeSH Terms])
26	"Interferon-beta"[MeSH Terms]
27	"Interferon Type I"[MeSH Terms:noexp]
28	"Methotrexate"[MeSH Terms]
29	"Methylprednisolone"[MeSH Terms:noexp]
30	"Mitoxantrone"[MeSH Terms]
31	"Natalizumab"[MeSH Terms]
32	"Prednisolone"[MeSH Terms:noexp]
33	"Rituximab"[MeSH Terms]
34	"adrenal cortex hormone*"[Title/Abstract] OR "corticosteroid*"[Title] OR "cortico steroid*"[Title] OR "corticoid*"[Title/Abstract]

(Continued)

35	"alemtuzumab*"[Title/Abstract] OR "campath*"[Title/Abstract] OR "lemtrada*"[Title/Abstract]
36	avonex*[Title/Abstract] OR rebif*[Title/Abstract]
37	"aubagio*"[Title/Abstract] OR "teriflunomide*"[Title/Abstract]
38	"azathioprine*"[Title/Abstract] OR "azothioprine*"[Title/Abstract] OR "imurel*"[Title/Abstract] OR "imuran*"[Title/Abstract] OR "immuran*"[Title/Abstract]
39	"bafiertam*"[Title/Abstract] OR "monomethyl fumarate*"[Title/Abstract] OR "methyl hydrogen fumarate*"[Title/Abstract] OR "methylhydrogenfumarate*"[Title/Abstract]
40	"beta interferon*"[Title/Abstract] OR "beta 1 interferon*"[Title/Abstract] OR "interferon beta*"[Title/Abstract] OR "fiblaferon*"[Title/Abstract] OR "fibroblast interferon*"[Title/Abstract] OR "IFNbeta*"[Title/Abstract] OR "IFN beta*"[Title/Abstract] OR "interferon*"[Title]
41	"betaferon*"[Title/Abstract] OR "betaseron*"[Title/Abstract] OR "beta seron*"[Title/Abstract] OR "extavia*"[Title/Abstract]
42	"copaxone*"[Title/Abstract] OR "Cop 1"[Title/Abstract] OR "copolymer 1"[Title/Abstract] OR "glatiramer*"[Title/Abstract] OR "glatopa*"[Title/Abstract] OR "TV 5010"[Title/Abstract] OR "TV5010"[Title/Abstract]
43	"cladribine*"[Title/Abstract] OR "leustatin*"[Title/Abstract] OR "mavenclad*"[Title/Abstract] OR "movectro*"[Title/Abstract]
44	"cyclophosphamide*"[Title/Abstract] OR "cyclophosphane*"[Title/Abstract] OR "cytophosphan*"[Title/Abstract] OR "cytoxan*"[Title/Abstract] OR "endoxan*"[Title/Abstract] OR "neosar*"[Title/Abstract] OR "procytox*"[Title/Abstract] OR "sendoxan*"[Title/Abstract]
45	"daclizumab*"[Title/Abstract] OR "zinbryta*"[Title/Abstract] OR "zenapax*"[Title/Abstract]
46	"dimethylfumarate"[Title/Abstract] OR "dimethyl fumarate*"[Title/Abstract] OR "BG 00012"[Title/Abstract] OR "BG00012"[Title/Abstract] OR "BG 12"[Title/Abstract] OR "diroximel fumarate*"[Title/Abstract] OR "tecfidera*"[Title/Abstract] OR "vumerity*"[Title/Abstract]
47	"fingolimod*"[Title/Abstract] OR "gilenya*"[Title/Abstract] OR "gilenia*"[Title/Abstract] OR "FTY 720"[Title/Abstract] OR "FTY720"[Title/Abstract]
48	"immunoglobulin*"[Title] OR "intravenous immunoglobulin*"[Title/Abstract] OR "IV immunoglobulin*"[Title/Abstract] OR "IVIG"[Title/Abstract]
49	"kesimpta*"[Title/Abstract] OR "ofatumumab*"[Title/Abstract] OR "HUMAX CD20 2F2"[Title/Abstract] OR "GSK 1841157"[Title/Abstract] OR "GSK1841157"[Title/Abstract]
50	"laquinimod*"[Title/Abstract] OR "ABR 215062"[Title/Abstract] OR "ABR215062"[Title/Abstract]
51	"mayzent*"[Title/Abstract] OR "siponimod*"[Title/Abstract] OR "BAF 312"[Title/Abstract] OR "BAF312"[Title/Abstract]
52	"methotrexate*"[Title/Abstract] OR "amethopterin*"[Title/Abstract] OR "mexate*"[Title/Abstract]
53	"methylprednisolone*"[Title/Abstract] OR "metipred*"[Title/Abstract]
54	"mitoxantrone*"[Title/Abstract] OR "mitozantrone*"[Title/Abstract] OR "ralenova*"[Title/Abstract] OR "novantron*"[Title/Abstract] OR "onkotrone*"[Title/Abstract]

(Continued)

55	"natalizumab*"[Title/Abstract] OR "tysabri*"[Title/Abstract] OR "antegren*"[Title/Abstract]
56	"ocrelizumab*"[Title/Abstract] OR "ocrevus*"[Title/Abstract] OR "R 1594"[Title/Abstract] OR "PR070769"[Title/Abstract]
57	"ozanimod*"[Title/Abstract] OR "zeposia*"[Title/Abstract] OR "RPC1063"[Title/Abstract]
58	"peginterferon*"[Title/Abstract] OR "pegylated interferon*"[Title/Abstract] OR "plegridy*"[Title/Abstract] OR "peg ifn beta*"[Title/Abstract]
59	"prednisolone*"[Title/Abstract] OR "predonine*"[Title/Abstract]
60	"rituximab*"[Title/Abstract] OR "rituxan*"[Title/Abstract] OR "mabthera*"[Title/Abstract] OR "IDEC C2B8"[Title/Abstract]
61	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60
62	#15 AND #61
63	#1 OR #62
64	randomized controlled trial [pt]
65	controlled clinical trial [pt]
66	randomized [tiab]
67	placebo [tiab]
68	"Clinical Trials as Topic"[Mesh:NoExp]
69	randomly [tiab]
70	trial [ti]
71	#64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70
72	animals [mh] NOT humans [mh]
73	#71 NOT #72
74	#63 AND #73

Appendix 3. Search strategy - Embase

1	'demyelinating disease'/de
2	'multiple sclerosis'/de
3	'optic neuritis'/de

(Continued)

4	'transverse myelitis'/exp
5	'clinically isolated syndrome*':ab,ti
6	devic:ab,ti OR 'devic s':ab.ti OR devics:ab,it
7	'disseminated sclerosis*':ab,ti
8	(demyelinating NEAR/1 (disease* OR disorder*)):ab,ti
9	((demyelinating OR necrotising OR necrotizing OR transverse) NEAR/1 myelitis*):ab,ti
10	'multiple sclerosis*':ab,ti OR 'MS':ti
11	neuropapilliti*:ab,ti OR ((optic OR retrobulbar) NEAR/1 neuriti*"):ab,ti
12	'neuromyelitis optica*':ab,ti OR 'nmo spectrum disorder*':ab,ti
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	'alemtuzumab'/de
15	'azathioprine'/de
16	'beta interferon'/exp
17	'cladribine'/de
18	'corticosteroid'/de/ae OR 'corticosteroid'/de/dt
19	'cyclophosphamide'/de/ae OR 'cyclophosphamide'/de/dt
20	'daclizumab'/de
21	'dimethyl fumarate'/de
22	'fingolimod'/de
23	'glatiramer'/de
24	'immunoglobulin'/de/ae or 'immunoglobulin'/de/dt or 'immunoglobulin'/de/iv
25	'methotrexate'/de/ae or 'methotrexate'/de/dt
26	'methylprednisolone'/de
27	'mitoxantrone'/de
28	'natalizumab'/de
29	'prednisolone'/de
30	'rituximab'/de
31	'adrenal cortex hormone*':ab,ti OR 'corticosteroid*':ti OR 'cortico steroid*':ti OR 'corticoid*':ab,ti

(Continued)

32	'alemtuzumab*':ab,ti OR 'campath*':ab,ti OR 'lemtrada*':ab,ti
33	avonex*:ab,ti OR rebif*:ab,ti
34	'aubagio*':ab,ti OR 'teriflunomide*':ab,ti
35	'azathioprine*':ab,ti OR 'azothioprine*':ab,ti OR 'imurel*':ab,ti OR 'imuran*':ab,ti OR 'immuran*':ab,ti
36	'bafiertam*':ab,ti OR 'monomethyl fumarate*':ab,ti OR 'methyl hydrogen fumarate*':ab,ti OR 'methylhydrogenfumarate*':ab,ti
37	'beta interferon*':ab,ti OR 'beta 1 interferon*':ab,ti OR 'interferon beta*':ab,ti OR 'fiblaferon*':ab,ti OR 'fibroblast interferon*':ab,ti OR 'IFNbeta*':ab,ti OR 'IFN beta*':ab,ti OR 'interferon':ti
38	'betaferon*':ab,ti OR 'betaseron*':ab,ti OR 'beta seron*':ab,ti OR 'extavia*':ab,ti
39	'copaxone*':ab,ti OR 'Cop 1':ab,ti OR 'copolymer 1':ab,ti OR 'glatiramer*':ab,ti OR 'glatopa*':ab,ti OR 'TV 5010':ab,ti OR 'TV5010':ab,ti
40	'cladribine*':ab,ti OR 'leustatin*':ab,ti OR 'mavenclad*':ab,ti OR 'movectro*':ab,ti
41	'cyclophosphamide*':ab,ti OR 'cyclophosphane*':ab,ti OR 'cytophosphan*':ab,ti OR 'cytoxan*':ab,ti OR 'endoxan*':ab,ti OR 'neosar*':ab,ti OR 'procytox*':ab,ti OR 'sendoxan*':ab,ti
42	'daclizumab*':ab,ti OR 'zinbryta*':ab,ti OR 'zenapax*':ab,ti
43	'dimethylfumarate*':ab,ti OR 'dimethyl fumarate*':ab,ti OR 'BG 00012':ab,ti OR 'BG00012':ab,ti OR 'BG 12':ab,ti OR 'diroximel fumarate*':ab,ti OR 'tecfidera*':ab,ti OR 'vumerity*':ab,ti
44	'fingolimod*':ab,ti OR 'gilenya*':ab,ti OR 'gilenia*':ab,ti OR 'FTY 720':ab,ti OR 'FTY720':ab,ti
45	'immunoglobulin*':ti OR 'intravenous immunoglobulin*':ab,ti OR "IV immunoglobulin*":ab,ti OR "IVIG":ab,ti
46	'kesimpta*':ab,ti OR 'ofatumumab*':ab,ti OR 'HUMAX CD20 2F2':ab,ti OR 'GSK 1841157':ab,ti OR 'GSK1841157':ab,ti
47	'laquinimod*':ab,ti OR 'ABR 215062':ab,ti OR 'ABR215062':ab,ti
48	'mayzent*':ab,ti OR 'siponimod*':ab,ti OR 'BAF 312':ab,ti OR 'BAF312':ab,ti
49	'methotrexate*':ab,ti OR 'amethopterin*':ab,ti OR 'mexate*':ab,ti
50	'methylprednisolone*':ab,ti OR 'metipred*':ab,ti
51	'mitoxantrone*':ab,ti OR 'mitozantrone*':ab,ti OR 'ralenova*':ab,ti OR 'novantron*':ab,ti OR 'onkotrone*':ab,ti
52	'natalizumab*':ab,ti OR 'tysabri*':ab,ti OR 'antegren*':ab,ti
53	'ocrelizumab*':ab,ti OR 'ocrevus*':ab,ti OR 'R 1594':ab,ti OR 'PR070769':ab,ti
54	'ozanimod*':ab,ti OR 'zeposia*':ab,ti OR 'RPC1063':ab,ti
55	'peginterferon*':ab,ti OR 'pegylated interferon*':ab,ti OR 'plegridy*':ab,ti OR 'peg ifn beta*':ab,ti

(Continued)

56	'prednisolone*':ab,ti OR 'predonine*':ab,ti
57	'rituximab*':ab,ti OR 'rituxan*':ab,ti OR 'mabthera*':ab,ti OR 'IDEC C2B8':ab,ti
58	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57
59	#13 AND #58
60	'randomized controlled trial'/de
61	'controlled clinical trial'/de
62	random*:ti,ab,tt
63	'randomization'/de
64	'intermethod comparison'/de
65	placebo:ti,ab,tt
66	(compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)
67	((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
68	(open NEXT/1 label):ti,ab,tt
69	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
70	'double blind procedure'/de
71	(parallel NEXT/1 group*):ti,ab,tt
72	(crossover:ti,ab,tt OR 'cross over':ti,ab,tt)
73	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt
74	(assigned:ti,ab,tt OR allocated:ti,ab,tt)
75	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt
76	(volunteer:ti,ab,tt OR volunteers:ti,ab,tt)
77	'human experiment'/de
78	trial:ti,tt
79	#60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78

(Continued)

80	(((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))
81	('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))
82	('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))
83	('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt))
84	(nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)
85	'random field*':ti,ab,tt
86	('random cluster' NEAR/4 sampl*):ti,ab,tt
87	(review:ab AND review:it) NOT trial:ti,tt
88	('we searched':ab AND (review:ti,tt OR review:it))
89	'update review':ab
90	(databases NEAR/5 searched):ab
91	((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)
92	('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
93	#80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92
94	#77 NOT #93
95	#59 AND #94
95	([medline]/lim OR [pubmed-not-medline]/lim)
96	#95 NOT #96

Appendix 4. Search strategy - Clinical trial registers

World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch)

Search terms: relapsing multiple sclerosis, filtered for "Phase 2" "Phase 3" trials.

US National Institutes of Health clinical trial register (www.clinicaltrials.gov)

Search term: "relapsing multiple sclerosis".

Appendix 5. State utility values and effect thresholds for the primary outcomes in relapsing-remitting multiple sclerosis

Primary outcomes	Reference or utility description	Utility	1-Utility	T1 Absolute risk per 1000	95% CI Lower Absolute	95% CI Upper Absolute	T2 Absolute risk per 1000	95% CI Lower Absolute	95% CI Upper Absolute	T3 Absolute risk per 1000	95% CI Lower Absolute	95% CI Upper Absolute	T1 Absolute Complete	T2 Absolute Complete	T3 Absolute Complete
Relapse of Multiple Sclerosis 12 and 24 months	Hawton 2016	0,534	0,466	33	19	48	66	47	84	128	99	156	33 (19 to 48)	66 (47 to 84)	128 (99 to 156)
Relapse of Multiple Sclerosis 36 months	None, assumed	0,62	0.38	41	23	59	81	58	103	157	122	191	41 (23 to 59)	81 (58 to 103)	157 (122 to 191)
Disability or dependency (EDSS = 6) 24 and 36 months	Chataway 2021	0,481	0,519	30	17	43	59	43	76	115	89	140	30 (17 to 43)	59 (43 to 76)	115 (89 to 140)
Serious adverse events	None, assumed	0,600	0,400	39	22	56	77	55	98	149	116	182	39 (22 to 56)	77 (55 to 98)	149 (116 to 182)
Discontinuation of treatment due to adverse events	None, assumed	0,850	0,150	104	59	149	205	147	262	397	309	485	104 (59 to 149)	205 (147 to 262)	397 (309 to 485)

Appendix 6. Netleague table: T1 lesions (12 months)

Ozanimod	0.86 (0.37,2.01)	2.05 (1.80,2.33)	1.48 (1.00,2.19)	1.00 (0.71,1.41)
1.16 (0.50,2.72)	**Interferon beta-1b**	2.39 (1.03,5.53)	1.72 (0.69,4.31)	1.16 (0.47,2.86)
0.49 (0.43,0.55)	**0.42 (0.18,0.97)**	**Interferon beta-1a**	0.72 (0.50,1.04)	0.49 (0.35,0.67)
0.68 (0.46,1.00)	0.58 (0.23,1.46)	1.39 (0.96,2.01)	**Glatiramer acetate**	0.68 (0.56,0.82)
1.00 (0.71,1.41)	0.86 (0.35,2.11)	**2.05 (1.49,2.82)**	**1.48 (1.22,1.79)**	**Fingolimod**

Significant results are bolded and underlined

Appendix 7. Netleague table: T1 lesions (24 months)

Placebo/no treatment	0.30 (0.18,0.49)	0.09 (0.05,0.16)	0.11 (0.07,0.17)	0.16 (0.08,0.31)	0.34 (0.21,0.55)	0.59 (0.42,0.84)	0.29 (0.23,0.38)	0.50 (0.37,0.69)	0.13 (0.08,0.23)
3.33 (2.03,5.47)	**Ozanimod**	0.31 (0.24,0.41)	0.36 (0.18,0.72)	0.53 (0.32,0.88)	1.14 (1.00,1.31)	1.97 (1.39,2.80)	0.98 (0.56,1.71)	1.68 (1.01,2.79)	0.44 (0.32,0.62)
10.69 (6.29,18.18)	**3.21 (2.44,4.21)**	**Ocrelizumab**	1.16 (0.57,2.37)	1.71 (0.99,2.93)	3.66 (2.89,4.63)	6.32 (4.23,9.43)	3.14 (1.73,5.67)	5.38 (3.13,9.26)	1.42 (0.97,2.09)
9.22 (5.72,14.85)	**2.77 (1.39,5.50)**	0.86 (0.42,1.76)	**Natalizumab**	1.47 (0.64,3.37)	3.15 (1.61,6.19)	5.45 (3.02,9.84)	2.71 (1.57,4.66)	4.64 (2.63,8.20)	1.23 (0.58,2.57)
6.27 (3.18,12.37)	**1.88 (1.14,3.11)**	0.59 (0.34,1.01)	0.68 (0.30,1.56)	**Interferon beta-1b**	2.14 (1.32,3.48)	3.70 (2.07,6.64)	1.84 (0.89,3.81)	3.16 (1.59,6.29)	0.83 (0.47,1.48)
2.92 (1.82,4.70)	0.88 (0.77,1.00)	**0.27 (0.22,0.35)**	**0.32 (0.16,0.62)**	**0.47 (0.29,0.76)**	**Interferon beta-1a**	1.73 (1.25,2.39)	0.86 (0.50,1.48)	1.47 (0.90,2.40)	0.39 (0.29,0.53)
1.69 (1.19,2.40)	**0.51 (0.36,0.72)**	**0.16 (0.11,0.24)**	**0.18 (0.10,0.33)**	**0.27 (0.15,0.48)**	**0.58 (0.42,0.80)**	**Glatiramer acetate**	0.50 (0.32,0.77)	0.85 (0.59,1.23)	0.22 (0.14,0.35)
3.41 (2.62,4.43)	1.02 (0.58,1.79)	**0.32 (0.18,0.58)**	**0.37 (0.21,0.64)**	0.54 (0.26,1.13)	1.17 (0.68,2.01)	**2.01 (1.30,3.12)**	**Fingolimod**	1.72 (1.14,2.58)	0.45 (0.24,0.84)
1.99 (1.46,2.71)	**0.60 (0.36,0.99)**	**0.19 (0.11,0.32)**	**0.22 (0.12,0.38)**	**0.32 (0.16,0.63)**	0.68 (0.42,1.11)	1.17 (0.81,1.69)	**0.58 (0.39,0.87)**	**Dimethyl fumarate**	0.26 (0.15,0.47)
7.52 (4.27,13.25)	**2.26 (1.62,3.16)**	0.70 (0.48,1.04)	0.82 (0.39,1.71)	1.20 (0.68,2.13)	**2.57 (1.90,3.50)**	**4.45 (2.85,6.94)**	**2.21 (1.18,4.12)**	**3.79 (2.13,6.75)**	**Alemtuzumab**

Significant results are bolded and underlined

Appendix 8. Netleague table: T2 lesions (12 months)

Placebo/ no treatment	2.01 (0.43,9.51)	2.12 (0.45,9.97)	0.51 (0.45,0.57)	0.98 (0.30,3.28)	2.37 (0.50,11.30)	1.89 (0.40,8.99)	1.00 (0.97,1.04)
0.50 (0.11,2.34)	**Natalizumab**	1.05 (0.99,1.12)	0.25 (0.05,1.17)	0.49 (0.26,0.91)	1.17 (0.99,1.39)	0.94 (0.82,1.08)	0.50 (0.11,2.34)
0.47 (0.10,2.22)	0.95 (0.89,1.02)	**Interferon beta-1b**	0.24 (0.05,1.11)	0.46 (0.25,0.86)	1.12 (0.96,1.30)	0.89 (0.79,1.01)	0.47 (0.10,2.22)
1.97 (1.76,2.22)	3.98 (0.86,18.45)	4.18 (0.90,19.35)	**Interferon beta-1a**	1.94 (0.59,6.36)	4.67 (0.99,21.93)	3.73 (0.80,17.45)	1.98 (1.75,2.23)
1.02 (0.30,3.38)	**2.05 (1.10,3.82)**	**2.15 (1.16,4.00)**	0.51 (0.16,1.68)	**Immunoglobulins**	2.40 (1.26,4.57)	1.92 (1.02,3.63)	1.02 (0.31,3.38)
0.42 (0.09,2.02)	0.85 (0.72,1.01)	0.90 (0.77,1.05)	0.21 (0.05,1.01)	0.42 (0.22,0.79)	**Glatiramer acetate**	0.80 (0.73,0.88)	0.42 (0.09,2.02)
0.53 (0.11,2.51)	1.07 (0.93,1.22)	1.12 (0.99,1.26)	0.27 (0.06,1.25)	0.52 (0.28,0.98)	**1.25 (1.14,1.38)**	**Fingolimod**	0.53 (0.11,2.51)
1.00 (0.96,1.04)	2.01 (0.43,9.48)	2.12 (0.45,9.94)	0.51 (0.45,0.57)	0.98 (0.30,3.27)	2.36 (0.50,11.26)	1.89 (0.40,8.96)	**Daclizumab**

Significant results are bolded and underlined

Appendix 9. Netleague table: T2 lesions (24 months)

Ozanimod	0.67 (0.52,0.86)	0.65 (0.43,0.98)	1.07 (0.88,1.29)	1.12 (0.83,1.52)	0.82 (0.63,1.05)
1.49 (1.16,1.91)	**Ocrelizumab**	0.96 (0.64,1.44)	1.59 (1.35,1.88)	1.67 (1.26,2.22)	1.22 (0.96,1.54)
1.55 (1.02,2.34)	1.04 (0.70,1.56)	**Interferon beta-1b**	1.66 (1.15,2.39)	1.74 (1.13,2.69)	1.27 (0.84,1.90)
0.93 (0.77,1.13)	**0.63 (0.53,0.74)**	**0.60 (0.42,0.87)**	**Interferon beta-1a**	1.05 (0.83,1.33)	0.76 (0.64,0.90)
0.89 (0.66,1.20)	**0.60 (0.45,0.79)**	**0.57 (0.37,0.89)**	0.95 (0.75,1.20)	**Glatiramer acetate**	0.73 (0.54,0.97)
1.22 (0.95,1.58)	0.82 (0.65,1.04)	0.79 (0.53,1.19)	**1.31 (1.11,1.55)**	**1.38 (1.03,1.84)**	**Alemtuzumab**

Significant results are bolded and underlined

Appendix 10. Netleague table: Cognitive decline

Ozanimod	-1.29 (-2.34,-0.24)	-1.10 (-1.64,-0.57)	-0.20 (-0.31,-0.09)	-0.10 (-0.31,0.11)	0.00 (-0.25,0.26)	-0.11 (-0.26,0.05)
1.29 (0.24,2.34)	**Natalizumab**	0.18 (-0.72,1.09)	1.09 (0.04,2.13)	1.19 (0.13,2.25)	1.29 (0.22,2.36)	1.18 (0.13,2.23)
1.10 (0.57,1.64)	-0.18 (-1.09,0.72)	**Interferon beta-1b**	0.90 (0.38,1.43)	1.01 (0.45,1.56)	1.11 (0.54,1.68)	1.00 (0.46,1.53)
0.20 (0.09,0.31)	**-1.09 (-2.13,-0.04)**	**-0.90 (-1.43,-0.38)**	**Interferon beta-1a**	0.10 (-0.07,0.28)	0.21 (-0.02,0.43)	0.10 (-0.01,0.20)
0.10 (-0.11,0.31)	**-1.19 (-2.25,-0.13)**	**-1.01 (-1.56,-0.45)**	-0.10 (-0.28,0.07)	**Glatiramer acetate**	0.10 (-0.04,0.24)	-0.01 (-0.21,0.20)
-0.00 (-0.26,0.25)	**-1.29 (-2.36,-0.22)**	**-1.11 (-1.68,-0.54)**	-0.21 (-0.43,0.02)	-0.10 (-0.24,0.04)	**Fingolimod**	-0.11 (-0.36,0.14)
0.11 (-0.05,0.26)	**-1.18 (-2.23,-0.13)**	**-1.00 (-1.53,-0.46)**	-0.10 (-0.20,0.01)	0.01 (-0.20,0.21)	0.11 (-0.14,0.36)	**Daclizumab**

Significant results are bolded and underlined

Appendix 11. Netleague Table: MS-related - QoL Physical

Placebo/no treatment	0.50 (0.29,0.71)	0.41 (-0.13,0.95)	0.36 (0.16,0.55)	0.22 (0.05,0.38)
-0.50 (-0.71,-0.29)	**Ozanimod**	-0.09 (-0.60,0.42)	-0.14 (-0.23,-0.06)	-0.29 (-0.41,-0.16)
-0.41 (-0.95,0.13)	0.09 (-0.42,0.60)	**Interferon-beta 1b**	-0.05 (-0.55,0.45)	-0.19 (-0.70,0.31)

(Continued)

-0.36 (-0.55,-0.16)	**0.14 (0.06,0.23)**	0.05 (-0.45,0.55)	**Interferon beta-1a**	-0.14 (-0.23,-0.05)
-0.22 (-0.38,-0.05)	**0.29 (0.16,0.41)**	0.19 (-0.31,0.70)	**0.14 (0.05,0.23)**	**Daclizumab**

Significant results are bolded and underlined

Appendix 12. Netleague table: MS-related - QoL mental

Placebo/no treatment	0.05 (-0.15,0.26)	0.30 (-0.24,0.84)	0.03 (-0.17,0.22)	0.12 (-0.05,0.28)
-0.05 (-0.26,0.15)	**Ozanimod**	0.25 (-0.26,0.75)	-0.03 (-0.11,0.05)	0.06 (-0.06,0.18)
-0.30 (-0.84,0.24)	-0.25 (-0.75,0.26)	**Interferon beta-1b**	-0.27 (-0.78,0.23)	-0.18 (-0.70,0.33)
-0.03 (-0.22,0.17)	0.03 (-0.05,0.11)	0.27 (-0.23,0.78)	**Interferon beta-1a**	0.09 (-0.00,0.18)
-0.12 (-0.28,0.05)	-0.06 (-0.18,0.06)	0.18 (-0.33,0.70)	-0.09 (-0.18,0.00)	**Daclizumab**

Significant results are bolded and underlined

Appendix 13. Netleague table: Mortality

Teriflunomide	0.20 (0.01,4.15)	0.67 (0.07,6.43)	0.33 (0.02,6.60)	0.64 (0.01,39.06)	0.33 (0.01,8.06)	0.26 (0.01,7.32)	1.68 (0.04,74.58)	0.34 (0.02,5.00)	0.25 (0.01,8.73)	0.42 (0.03,5.56)	0.33 (0.02,5.19)	0.25 (0.02,4.17)	0.50 (0.03,9.90)	0.21 (0.01,4.40)	0.66 (0.04,11.16)	0.92 (0.04,21.31)
5.03 (0.24,104.87)	**Ponesimod**	3.35 (0.08,148.41)	1.65 (0.02,118.04)	3.21 (0.02,533.64)	1.65 (0.02,136.16)	1.32 (0.01,119.55)	8.46 (0.07,1089.21)	1.70 (0.03,98.56)	1.24 (0.01,134.15)	2.11 (0.04,113.88)	1.65 (0.03,100.04)	1.26 (0.02,79.14)	2.51 (0.04,177.79)	1.08 (0.01,78.17)	3.30 (0.05,210.02)	4.64 (0.06,366.18)
1.50 (0.16,14.45)	0.30 (0.01,13.20)	**Placebo/no treatment**	0.49 (0.07,3.51)	0.96 (0.03,29.63)	0.49 (0.01,24.84)	0.39 (0.03,4.50)	2.52 (0.12,52.69)	0.51 (0.12,2.18)	0.37 (0.02,5.81)	0.63 (0.18,2.17)	0.49 (0.10,2.38)	0.38 (0.07,1.98)	0.75 (0.11,5.24)	0.32 (0.04,2.37)	0.98 (0.18,5.39)	1.38 (0.16,12.14)
3.04 (0.15,60.92)	0.60 (0.01,43.17)	2.03 (0.28,14.44)	**Pegylated interferon beta-1a**	1.94 (0.04,101.26)	1.00 (0.01,80.08)	0.80 (0.04,18.24)	5.11 (0.14,190.62)	1.03 (0.09,11.85)	0.75 (0.03,22.07)	1.28 (0.13,13.00)	1.00 (0.08,12.37)	0.76 (0.06,9.99)	1.52 (0.10,24.08)	0.65 (0.04,10.72)	1.99 (0.15,26.78)	2.81 (0.15,52.43)
1.57 (0.03,95.69)	0.31 (0.00,51.77)	1.04 (0.03,32.33)	0.52 (0.01,26.86)	**Ozanimod**	0.51 (0.00,94.21)	0.41 (0.01,18.94)	2.63 (0.03,258.10)	0.53 (0.01,19.23)	0.38 (0.01,26.53)	0.66 (0.03,16.20)	0.51 (0.01,18.39)	0.39 (0.01,15.86)	0.78 (0.02,38.16)	0.34 (0.01,13.58)	1.03 (0.02,47.34)	1.45 (0.04,56.59)
3.05 (0.12,75.03)	0.61 (0.01,50.16)	2.04 (0.04,102.90)	1.00 (0.01,80.67)	1.95 (0.01,357.76)	**Ofatumumab**	0.80 (0.01,81.20)	5.13 (0.04,733.94)	1.03 (0.02,67.75)	0.75 (0.01,90.73)	1.28 (0.02,78.46)	1.00 (0.01,68.68)	0.77 (0.01,54.28)	1.52 (0.02,121.58)	0.65 (0.01,53.40)	2.00 (0.03,143.98)	2.82 (0.03,249.58)
3.80 (0.14,105.70)	0.76 (0.01,68.36)	2.54 (0.22,28.92)	1.25 (0.05,28.51)	2.43 (0.05,111.65)	1.25 (0.01,126.01)	**Ocrelizumab**	6.40 (0.13,314.04)	1.28 (0.09,18.29)	0.93 (0.03,30.12)	1.60 (0.20,13.03)	1.25 (0.09,17.38)	0.95 (0.06,15.63)	1.90 (0.09,39.79)	0.82 (0.05,13.39)	2.49 (0.13,48.58)	3.51 (0.22,55.19)
0.59 (0.01,26.33)	0.12 (0.00,15.23)	0.40 (0.02,8.28)	0.20 (0.01,7.29)	0.38 (0.00,37.19)	0.19 (0.00,27.85)	0.16 (0.00,7.68)	**Natalizumab**	0.20 (0.01,5.85)	0.15 (0.00,8.85)	0.25 (0.01,6.65)	0.20 (0.01,5.99)	0.15 (0.00,4.77)	0.30 (0.01,10.96)	0.13 (0.00,4.84)	0.39 (0.01,12.69)	0.55 (0.01,23.00)
2.96 (0.20,43.79)	0.59 (0.01,34.16)	1.97 (0.46,8.49)	0.97 (0.08,11.23)	1.89 (0.05,68.70)	0.97 (0.01,63.74)	0.78 (0.05,11.08)	4.98 (0.17,144.15)	**Laquinimod**	0.73 (0.03,15.24)	1.25 (0.24,6.35)	0.97 (0.13,7.41)	0.74 (0.09,6.35)	1.48 (0.13,16.31)	0.63 (0.06,6.53)	1.94 (0.21,18.24)	2.73 (0.24,30.65)
4.07 (0.11,144.47)	0.81 (0.01,87.90)	2.71 (0.17,42.83)	1.34 (0.05,39.53)	2.60 (0.04,179.19)	1.33 (0.01,161.37)	1.07 (0.03,34.52)	6.85 (0.11,414.99)	1.37 (0.07,28.81)	**Interferon beta-1b**	1.71 (0.11,27.28)	1.34 (0.14,12.88)	1.02 (0.04,23.95)	2.03 (0.09,47.04)	0.87 (0.03,22.62)	2.67 (0.10,68.21)	3.76 (0.14,101.34)

(Continued)

2.38 (0.18,31.38)	0.47 (0.01,25.46)	1.59 (0.46,5.45)	0.78 (0.08,7.95)	1.52 (0.06,37.34)	0.78 (0.01,47.61)	0.63 (0.08,5.09)	4.00 (0.15,106.34)	0.80 (0.16,4.09)	0.58 (0.04,9.31)	**Interferon beta-1a**	0.78 (0.16,3.83)	0.60 (0.09,3.79)	1.19 (0.13,10.76)	0.51 (0.08,3.25)	1.56 (0.19,12.76)	2.20 (0.37,13.10)	
3.04 (0.19,48.02)	0.61 (0.01,36.67)	2.03 (0.42,9.80)	1.00 (0.08,12.39)	1.94 (0.05,69.46)	1.00 (0.01,68.33)	0.80 (0.06,11.14)	5.12 (0.17,156.95)	1.03 (0.14,7.83)	0.75 (0.08,7.21)	1.28 (0.26,6.29)	**Glatiramer acetate**	0.76 (0.09,6.86)	1.52 (0.17,13.40)	0.65 (0.06,6.75)	2.00 (0.20,20.26)	2.81 (0.26,30.74)	
3.98 (0.24,66.17)	0.79 (0.01,49.69)	2.66 (0.50,14.01)	1.31 (0.10,17.16)	2.54 (0.06,102.67)	1.31 (0.02,92.51)	1.05 (0.06,17.16)	6.70 (0.21,214.15)	1.35 (0.16,11.51)	0.98 (0.04,22.96)	1.68 (0.26,10.64)	1.31 (0.15,11.76)	**Fingolimod**	1.99 (0.16,25.07)	0.85 (0.07,10.21)	2.61 (0.24,28.19)	3.68 (0.28,48.08)	
2.00 (0.10,39.69)	0.40 (0.01,28.22)	1.34 (0.19,9.35)	0.66 (0.04,10.45)	1.28 (0.03,62.43)	0.66 (0.01,52.36)	0.53 (0.03,11.05)	3.37 (0.09,124.42)	0.68 (0.06,7.47)	0.49 (0.02,11.39)	0.84 (0.09,7.64)	0.66 (0.07,5.80)	0.50 (0.04,6.34)	**Dimethyl fumarate**	0.43 (0.03,6.60)	1.31 (0.10,17.42)	1.85 (0.11,31.56)	
4.66 (0.23,95.45)	0.93 (0.01,67.21)	3.11 (0.42,22.88)	1.53 (0.09,25.20)	2.98 (0.07,120.38)	1.53 (0.02,124.61)	1.23 (0.07,20.13)	7.84 (0.21,297.55)	1.58 (0.15,16.19)	1.15 (0.04,29.68)	1.96 (0.31,12.50)	1.53 (0.15,15.84)	1.17 (0.10,13.98)	2.33 (0.15,35.74)	**Daclizumab**	3.06 (0.22,42.09)	4.30 (0.33,56.42)	
1.52 (0.09,25.92)	0.30 (0.00,19.32)	1.02 (0.19,5.58)	0.50 (0.04,6.74)	0.97 (0.02,44.90)	0.50 (0.01,35.96)	0.40 (0.02,7.82)	2.57 (0.08,83.53)	0.52 (0.05,4.84)	0.37 (0.01,9.58)	0.64 (0.08,5.25)	0.50 (0.05,5.09)	0.38 (0.04,4.13)	0.76 (0.06,10.10)	0.33 (0.02,4.50)	**Cladribine**	1.41 (0.09,22.21)	
1.08 (0.05,24.97)	0.22 (0.00,16.99)	0.72 (0.08,6.34)	0.36 (0.02,6.65)	0.69 (0.02,27.06)	0.35 (0.00,31.43)	0.28 (0.02,4.48)	1.82 (0.04,76.33)	0.37 (0.03,4.10)	0.27 (0.01,7.18)	0.46 (0.08,2.72)	0.36 (0.03,3.89)	0.27 (0.02,3.55)	0.54 (0.03,9.23)	0.23 (0.02,3.04)	0.71 (0.05,11.20)	**Alemtuzumab**	

Significant results are bolded and underlined

Appendix 14. Relative treatment ranking (SUCRA and Mean Rank)

Relapses at 12 months			
Treatment	SUCRA	PrBest	MeanRank
placebo_no treatment	11.9	0.0	11.6
azathioprine	22.3	0.1	10.3
daclizumab	73.5	4.8	4.2
fingolimod	89.4	19.8	2.3
glatiramer_acetate	54.7	0.0	6.4
immunoglobulins	62.7	1.0	5.5
interferon_beta_1a_1b	2.4	0.0	12.7
interferon_beta1b_Betaferon	30.0	0.3	9.4
interferon_beta1a_Avonex_Rebif	31.2	0.0	9.3
pegylated_interferon_beta1a	47.3	0.0	7.3
mitoxantrone	91.4	67.4	2.0
natalizumab	81.7	6.5	3.2
teriflunomide	51.5	0.0	6.8

Relapses at 24 months			
Treatment	SUCRA	PrBest	MeanRank
placebo_no treatment	5.6	0.0	15.2
alemtuzumab	77.0	5.5	4.4
azathioprine	40.2	1.0	10.0
cladribine	85.6	16.4	3.2
dimethylfumarate	64.1	0.1	6.4
fingolimod	84.6	8.5	3.3
glatiramer_acetate	28.9	0.0	11.7

(Continued)

immunoglobulins	48.5	0.1	8.7
interferon_beta_1a_1b	6.8	0.1	15.0
interferon_beta1b_Betaferon	26.5	0.0	12.0
interferon_beta1a_Avonex_Rebif	27.2	0.0	11.9
laquinimod	31.1	0.0	11.3
mitoxantrone	88.2	58.9	2.8
natalizumab	78.8	5.4	4.2
ponesimod	74.4	4.2	4.8
teriflunomide	32.5	0.0	11.1

Relapses at 36 months

Treatment	SUCRA	PrBest	MeanRank
alemtuzumab	98.9	97.2	1.0
daclizumab	61.4	1.9	2.2
glatiramer_acetate	37.3	0.9	2.9
interferon_beta1a_Avonex_Rebif	2.4	0.0	3.9

Disability at 24 months

Treatment	SUCRA	PrBest	MeanRank
placebo_no treatment	12.5	0.0	16.7
alemtuzumab	59.4	0.5	8.3
azathioprine	62.2	6.9	7.8
cladribine	51.2	0.1	9.8
dimethylfumarate	65.1	0.0	7.3
fingolimod	57.7	0.0	8.6
glatiramer_acetate	46.2	0.0	10.7

(Continued)

immunoglobulins	46.2	0.9	10.7
interferon_beta_1a_1b	10.9	1.4	17.0
interferon_beta1b_Betaferon	40.9	0.0	11.6
interferon_beta1a_Avonex_Rebif	19.7	0.0	15.5
laquinimod	38.5	0.0	12.1
mitoxantrone	95.4	83.8	1.8
natalizumab	75.9	0.8	5.3
ocrelizumab	70.8	1.2	6.3
ofatumumab	81.6	3.2	4.3
ozanimod	9.3	0.0	17.3
ponesimod	65.6	1.1	7.2
teriflunomide	40.9	0.0	11.6

Disability at 36 months

Treatment	SUCRA	PrBest	MeanRank
alemtuzumab	99.2	97.7	1.0
daclizumab	66.9	2.3	2.0
glatiramer_acetate	7.9	0.0	3.8
interferon_beta1a_Avonex_Rebif	26.0	0.0	3.2

Number of patients with any serious adverse events

Treatment	SUCRA	PrBest	MeanRank
placebo_no treatment	69.5	0.4	6.2
alemtuzumab	24.7	0.1	13.8
cladribine	34.5	1.1	12.1
daclizumab	10.2	0.0	16.3

(Continued)

dimethylfumarate	63.1	3.1	7.3
fingolimod	84.6	12.2	3.6
glatiramer_acetate	75.5	3.0	5.2
interferon_beta1b_Betaferon	73.6	12.0	5.5
interferon_beta1a_Avonex_Rebif	45.9	0.0	10.2
laquinimod	41.8	0.2	10.9
pegylated_interferon_beta1a	58.1	7.3	8.1
mitoxantrone	56.3	46.3	8.4
natalizumab	44.6	2.3	10.4
ocrelizumab	66.5	7.3	6.7
ofatumumab	26.1	0.3	13.6
ozanimod	27.7	0.3	13.3
ponesimod	45.1	3.6	10.3
Teriflunomide	52.2	0.6	9.1

Number of patients who discontinued treatment due to adverse events

Treatment	SUCRA	PrBest	MeanRank
placebo_no treatment	83.4	0.2	4.2
alemtuzumab	99.0	85.5	1.2
azathioprine	14.7	0.1	17.2
cladribine	59.8	2.5	8.6
daclizumab	25.9	0.0	15.1
dimethylfumarate	64.5	0.0	7.7
fingolimod	42.0	0.0	12.0
glatiramer_acetate	58.1	0.0	9.0
immunoglobulins	37.9	3.4	12.8
interferon_beta_1a_1b	35.8	5.0	13.2

(Continued)

interferon_beta1b_Betaferon	33.3	0.0	13.7
interferon_beta1a_Avonex_Rebif	58.0	0.0	9.0
laquinimod	58.8	0.0	8.8
pegylated_interferon_beta1a	17.5	0.0	16.7
natalizumab	53.4	0.2	9.8
ocrelizumab	87.0	2.7	3.5
ofatumumab	38.8	0.0	12.6
ozanimod	79.2	0.5	4.9
ponesimod	9.2	0.0	18.2
teriflunomide	43.7	0.0	11.7

T2 at 12 months

Treatment	SUCRA	PrBest	MeanRank
placebo_no treatment	60.9	0.0	3.3
fingolimod	52.4	1.8	3.9
glatiramer_acetate	5.6	0.0	6.7
immunoglobulins	76.7	14.9	2.4
interferon_beta1b_Betaferon	21.5	0.0	5.7
interferon_beta1a_Avonex_Rebif	93.0	83.1	1.4
natalizumab	39.9	0.3	4.6

Cognitive decline

Treatment	SUCRA	PrBest	MeanRank
daclizumab	38.0	0.0	4.7
fingolimod	13.4	0.0	6.2
glatiramer_acetate	39.4	0.0	4.6

(Continued)

interferon_beta1b_Betaferon	89.1	34.7	1.7
interferon_beta1a_Avonex_Rebif	63.8	0.0	3.2
natalizumab	93.1	65.3	1.4
ozanimod	13.2	0.0	6.2

Mortality

Treatment	SUCRA	PrBest	MeanRank
placebo_no treatment	34.6	0.0	11.5
alemtuzumab	29.7	0.5	12.3
cladribine	38.4	0.7	10.9
daclizumab	69.0	9.8	6.0
dimethylfumarate	46.4	2.2	9.6
fingolimod	65.6	5.8	6.5
glatiramer_acetate	58.3	1.0	7.7
interferon_beta1b_Betaferon	62.8	13.3	6.9
interferon_beta1a_Avonex_Rebif	50.9	0.1	8.8
laquinimod	57.8	2.2	7.8
pegylated_interferon_beta1a	57.8	6.0	7.8
natalizumab	23.2	1.5	13.3
ocrelizumab	63.4	9.8	6.9
ofatumumab	55.8	15.7	8.1
ozanimod	42.0	7.1	10.3
ponesimod	65.2	24.3	6.6
teriflunomide	29.0	0.1	12.4

Appendix 15. Heterogeneity results within the network analyses

Outcomes	Tau² heterogeneity
Disability worsening at 24 months	7,08E-13
Relapses at 12 months	8,81E-13
Relapse at 24 months	0,001071
Number of patients with any serious adverse events	0,026563
New gadolinium-enhancing positive T1-weighted MRI lesions at 24 months	3,97E-09
New or enlarging T2-weighted MRI lesions at 24 months	0,008532
Mortality	2,47E-14

Appendix 16. Incoherence results within the network analyses

Relapses at 12 months

Loop-specific heterogeneity approach

Loop	IF	seIF	z_value	P value	CI_95	Loop_Heterog_tau2
placebo_no treatment-glatiramer_acetate-interferon_beta1b_Betaferon-natalizumab	1.500	1.537	0.976	0.329	(0.00,4.51)	0.000
fingolimod-glatiramer_acetate-interferon_beta1b_Betaferon	0.430	0.508	0.846	0.397	(0.00,1.43)	0.000
placebo_no treatment-fingolimod-glatiramer_acetate-interferon_beta1a_Avonex_Rebif	0.077	0.205	0.374	0.709	(0.00,0.48)	0.000

Node splitting approach

Legend: 01 placebo_no treatment; 02 azathioprine; 03 daclizumab; 04 fingolimod; 05 glatiramer_acetate; 06 immunoglobulins; 07 interferon_beta_1a_1b; 08 interferon_beta1b_Betaferon; 09 interferon_beta1a_Avonex_Rebif; 10 pegylated_interferon_beta1a; 11 mitoxantrone; 12 natalizumab; 13 teriflunomide

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>	|z|
01 02	* -.0945262	.2313167	3.64e-06	70.73365	-.0945298	70.73403	0.999	2.63e-07
01 03	.	.	.	.	.	.	.	.
01 05	-.4332853	.0849317	-.4626259	.1815716	.0293406	.2004536	0.884	3.17e-06
01 06	.	.	.	.	.	.	.	.
01 09	-.2804489	.0580191	-.2282869	.1920469	-.0521619	.2006196	0.795	1.62e-07
01 10	.	.	.	.	.	.	.	.
01 11	.	.	.	.	.	.	.	.
01 12	-.6530345	.0967946	-1.943467	1.507434	1.290432	1.510538	0.393	2.15e-10
01 13	.	.	.	.	.	.	.	.
02 07	*.4482822	.202676	.6373341	141.1615	-.1890519	141.1614	0.999	2.38e-11
04 05	.2521364	.1443599	.3551627	.1395838	-.1030263	.2008069	0.608	1.15e-09
04 08	.6670705	.3164247	.3652477	.3736056	.3018228	.4895969	0.538	1.04e-09
04 09	.4816581	.1032262	.4294976	.1720251	.0521605	.2006197	0.795	2.23e-09
05 08	-.015269	.3707962	.4285262	.3251413	-.4437952	.4931592	0.368	4.85e-09
08 12	-1.704703	1.48626	-.4143131	.2695219	-1.29039	1.510502	0.393	1.47e-08

* Warning: all the evidence about these contrasts comes from the trials which directly compare them.

Global test: 'design-by-treatment' approach

chi2 (3) = 1.49

Prob > chi2 = 0.6847

Relapses at 24 months

Loop-specific heterogeneity approach

Loop	IF	seIF	z_value	P value	CI_95	Loop_Heterog_tau2
glatiramer_acetate-interferon_beta_1a_1b-interferon_beta1b_Betaferon	0.356	0.292	1.219	0.223	(0.00,0.93)	0.023
placebo_no treatment-interferon_beta_1a_1b-interferon_beta1b_Betaferon	0.279	0.125	2.233	0.026	(0.03,0.52)	0.000
placebo_no treatment-dimethylfumarate-glatiramer_acetate	0.184	0.141	1.308	0.191	(0.00,0.46)	0.000
placebo_no treatment-interferon_beta1b_Betaferon-interferon_beta1a_Avonex_Rebif	0.138	0.114	1.208	0.227	(0.00,0.36)	0.000
placebo_no treatment-glatiramer_acetate-interferon_beta1b_Betaferon	0.060	0.125	0.481	0.631	(0.00,0.31)	0.000
placebo_no treatment-glatiramer_acetate-interferon_beta_1a_1b	0.016	0.214	0.075	0.940	(0.00,0.44)	0.013

Node splitting approach

Legend: 01 placebo_no treatment: 02 alemtuzumab; 03 azathioprine: 04 cladribine; 05 dimethylfumarate; 06 fingolimod; 07 glatiramer_acetate; 08 immunoglobulins; 09 interferon_beta_1a_1b; 10 interferon_beta1b_Betaferon; 11 interferon_beta1a_Avonex_Rebif; 12 laquinimod, 13 mitoxantrone; 14 natalizumab; 15 ponesimod; 16 teriflunomide

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P >	|z|
01 03	* -.2570451	.2139034	1.09e-06	100.3446	-.2570462	100.3449	0.998	.0327223
01 04	.	.	.	.	.	.	.	.
01 05	* -.5006495	.0590203	-.2244922	.2051982	-.2761573	.2135659	0.196	1.79e-08
01 06	.	.	.	.	.	.	.	.
01 07	-.1767334	.0716521	-.1904449	.0794975	.0137115	.1031108	0.894	.048782
01 08	.	.	.	.	.	.	.	.
01 10	-.1122048	.0581842	-.2427882	.0742592	.1305834	.0943389	0.166	.027287
01 11	-.1808806	.0495952	-.1386792	.084888	-.0422014	.0977358	0.666	.0453869
01 12	* -.1964215	.0476116	.0095158	.2022038	-.2059373	.2063344	0.318	.0381523
01 13	.	.	.	.	.	.	.	.
01 14	.	.	.	.	.	.	.	.
01 16	* -.1962107	.0711622	.3534283	100.2727	-.549639	100.2727	0.996	.0327224
02 11	*.4003873	.0838057	-.7411533	140.8694	1.141541	140.8695	0.994	.0327225
03 09	*.4442123	.2174285	.9583024	198.4799	-.5140901	198.4798	0.998	.0327224
05 07	.1903543	.0993593	.4072015	.0911696	-.2168472	.1365608	0.112	1.24e-08
07 10	.0340972	.0850304	-.0212557	.0929274	.0553529	.1310159	0.673	.0568357
07 11	-.0674633	.1120635	.043583	.0764704	-.1110462	.1356685	0.413	.0477717

(Continued)

10 11	.2104597	.1072561	-.069814	.054668	.2802737	.1203847	0.020	2.52e-09
11 12	.0996389	.1004172	-.0676833	.0673619	.1673222	.120989	0.167	.0270014
15 16	*.3534692	.0676721	-.7458861	198.049	1.099355	198.0491	0.996	.0327224

Global test: 'design-by-treatment' approach

chi2 (7) = 9.66

Prob > chi2 = 0.2086

Disability at 24 months

Loop-specific heterogeneity approach

Loop	IF	seIF	z_value	P value	CI_95	Loop_Heterog_tau2
placebo_no treatment-interferon_be-ta_1a_1b interferon_beta1b_Betaferon	0.641	0.412	1.557	0.120	(0.00,1.45)	0.036
placebo_no treatment-glatiramer_acetate-interferon_beta1b_Betaferon	0.426	0.302	1.410	0.159	(0.00,1.02)	0.000
placebo_no treatment-interferon_beta1b_Betaferon-interferon_beta1a_Avonex_Rebif	0.333	0.319	1.044	0.296	(0.00,0.96)	0.000
placebo_no treatment-dimethylfumarate-glatiramer_ acetate	0.221	0.271	0.818	0.413	(0.00,0.75)	0.000
glatiramer_acetate-interferon_beta_1a_1b-interferon_beta1b_Betaferon	0.170	0.297	0.572	0.567	(0.00,0.75)	0.000
placebo_no treatment-glatiramer_acetate-interferon_beta_1a_1b	0.028	0.328	0.087	0.931	(0.00,0.67)	0.017

Node splitting approach

Legend: 02 alemtuzumab; 03 azathioprine; 05 dimethyl fumarate; 07 glatiramer acetate; 9 interferon_beta_1a_1b; 10 interferon_beta1b_Betaferon; 11 interferon_beta1a_Avonex_Rebif; 12 laquinimod; 15 ocrelizumab; 16 ofatumumab; 17 ozanimod; 18 ponesimod; 19 teriflunomide

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P >	|z|
01 03	* -.5039052	.507133	4.70e-07	100.0435	-.5039057	100.0448	0.996	5.56e-07
01 04	.	.	.	.	.	.	.	.
01 05	* -.3934932	.090072	-.9469336	.3809025	.5534404	.3949495	0.161	8.94e-08
01 06	.	.	.	.	.	.	.	.
01 07	-.206089	.1292208	-.4225181	.144688	.2164292	.1931026	0.262	4.50e-09
01 08	.	.	.	.	.	.	.	.
01 10	-.1372845	.1863635	-.3385388	.1544499	.2012543	.242046	0.406	.0282679
01 11	-.3438557	.164695	.171058	.161874	-.5149137	.2289957	0.025	4.23e-08
01 12	* -.259541	.1076144	.0743749	.4869733	-.3339159	.492589	0.498	1.35e-08
01 13	.	.	.	.	.	.	.	.
01 14	.	.	.	.	.	.	.	.
01 19	* -.2696088	.1122025	.2968303	57.62789	-.5664391	57.628	0.992	3.25e-07
02 11	*.3161827	.1574691	-.4792639	141.0927	.7954466	141.093	0.996	3.39e-08
03 09	* 1.662784	1.083196	2.670594	199.9222	-1.00781	199.9193	0.996	6.39e-09
05 07	.1810622	.163678	.0525936	.1893388	.1284686	.2536744	0.613	.0488181
07 10	.0675035	.1044646	-.0513098	.1685388	.1188133	.1982881	0.549	3.31e-07
07 11	.2892109	.2174604	.1907303	.1418737	.0984806	.2596481	0.704	9.98e-09
10 11	.3916469	.1733208	.0053712	.162104	.3862757	.2373136	0.104	2.26e-09

(Continued)

11 12	-.1732741	.2438342	-.1615571	.1872829	-.011717	.3082021	0.970	1.64e-06
11 15	* -.4194929	.1630964	-.2562527	143.0782	-.1632402	143.0781	0.999	9.21e-07
11 17	*.253832	.211184	.4160241	199.0372	-.162192	199.0371	0.999	4.05e-07
16 19	*.3460116	.1392108	-.8846486	140.9476	1.23066	140.9478	0.993	1.20e-07
18 19	*.1984755	.18991	-.7378082	200.335	.9362838	200.3353	0.996	1.14e-07

Global test: 'design-by-treatment' approach

chi2 (7) = 7.65

Prob > chi2 = 0.3648

Number of patients who discontinued treatment due to adverse

Loop-specific heterogeneity approach

Loop	IF	seIF	z_value	P value	CI_95	Loop_Heterog_tau2
glatiramer_acetate-interferon_beta1b_Betaferon-interferon_beta1a_Avonex_Rebif	1.883	1.201	1.568	0.117	(0.00,4.24)	0.000
placebo_no treatment-fingolimod-interferon_beta1b_Betaferon	1.813	1.570	1.155	0.248	(0.00,4.89)	0.000
placebo_no treatment-glatiramer_acetate-interferon_beta1b_Betaferon	1.519	1.367	1.111	0.267	(0.00,4.20)	0.240
fingolimod-glatiramer_acetate-interferon_beta1a_Avonex_Rebif	1.319	0.477	2.766	0.006	(0.38,2.25)	0.000
placebo_no treatment-dimethylfumarate-glatiramer_acetate	1.024	0.477	2.148	0.032	(0.09,1.96)	0.000
placebo_no treatment-fingolimod-interferon_beta1a_Avonex_Rebif	0.607	0.437	1.388	0.165	(0.00,1.46)	0.000
fingolimod-glatiramer_acetate-interferon_beta1b_Betaferon	0.575	1.268	0.454	0.650	(0.00,3.06)	0.000
placebo_no treatment-daclizumab-interferon_beta1a_Avonex_Rebif	0.433	0.828	0.523	0.601	(0.00,2.06)	0.000
placebo_no treatment-fingolimod-glatiramer_acetate	0.412	0.552	0.747	0.455	(0.00,1.49)	0.073
placebo_no treatment-interferon_beta1a_Avonex_Rebif-laquinimod	0.306	0.465	0.658	0.510	(0.00,1.22)	0.000
placebo_no treatment-interferon_beta1b_Betaferon-natalizumab	0.256	2.009	0.128	0.899	(0.00,4.19)	0.000
placebo_no treatment-glatiramer_acetate-interferon_beta1a_Avonex_Rebif	0.248	0.535	0.464	0.643	(0.00,1.30)	0.048
placebo_no treatment-interferon_beta1b_Betaferon-interferon_beta1a_Avonex_Rebif	0.067	1.546	0.043	0.966	(0.00,3.10)	0.000

Node-splitting approach

Legend: 01 placebo_no treatment; 02 alemtuzumab; 03 azathioprine; 04 cladribine; 05 daclizumab; 06 dimethylfumarate; 07 fingolimod; 08 glatiramer_acetate; 09 immunoglobulins; 10 interferon_beta_1a_1b; 11 interferon_beta1b_Betaferon; 12 interferon_beta1a_Avonex_Rebif; 13 laquinimod; 14 pegylated_interferon_beta1a; 15 natalizumab; 16 ocrelizumab; 17 ofatumumab; 18 ozanimod; 19 ponesimod; 20 teriflunomide

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P >	|z|
01 03	* 1.834319	1.1366	-4.92e-08	70.71251	1.834319	70.72164	0.979	.200121
01 04	.	.	.	.	.	.	.	.
01 05	1.319182	.7847679	.8715889	.3277569	.447593	.8504618	0.599	.2036387
01 06	*.1877989	.1753516	1.554317	.668328	-1.366518	.7014721	0.051	.1605433
01 07	.5486801	.218467	.7590425	.3275151	-.2103624	.3942692	0.594	.2303197
01 08	.3264118	.2751741	.4665002	.2632105	-.1400884	.3714918	0.706	.2138806
01 09	.	.	.	.	.	.	.	.
01 11	2.05675	1.055662	.6246882	.4135214	1.432062	1.133764	0.207	.187843
01 12	.4096479	.3588912	.3915939	.2575563	.018054	.4428049	0.967	.2187159
01 13	*.3953083	.2069711	.1694286	.8288467	.2258796	.8568408	0.792	.213742
01 14	.	.	.	.	.	.	.	.
01 15	.4906229	.3428084	-.5419259	1.755179	1.032549	1.788343	0.564	.1981475
01 20	*.6014311	.2164219	-.3998697	57.79476	1.001301	57.79517	0.986	.2001209
02 12	* 1.341204	.3110236	-.5594934	115.4463	1.900698	115.4474	0.987	.2001205
03 10	* -.7281069	.4696984	-4.396745	141.5112	3.668638	141.5106	0.979	.200121
05 12	-.5058994	.2519318	-.9534543	.8122868	.4475549	.8504588	0.599	.2036393
06 08	-.1827816	.2936224	.484674	.3637799	-.6674556	.4719476	0.157	.2041796

(Continued)

07 08	.2286105	.3195476	-.462412	.2275504	.6910225	.3922879	0.078	.1346849
07 11	-.3120719	1.186405	.2805945	.4288642	-.5926664	1.261536	0.638	.2064715
07 12	-.7822081	.3150972	.1104342	.2470597	-.8926423	.4004057	0.026	.1339707
08 11	.0342173	.4383159	1.216929	.62566	-1.182711	.7639166	0.122	.1842717
08 12	.3157022	.2875631	-.3220622	.2951343	.6377644	.4129254	0.122	.200185
11 12	-1.609355	1.122629	-.2608311	.4216551	-1.348524	1.199206	0.261	.1958431
11 15	-1.309736	1.708393	-.2773837	.528545	-1.032353	1.788288	0.564	.1981477
12 13	-.1883362	.3616584	.1523722	.3533185	-.3407084	.5056381	0.500	.2001823
12 16	* -.5911208	.2773232	-1.372353	141.2246	.7812318	141.2245	0.996	.200121
12 18	* -.3843554	.2696658	-1.165592	141.6234	.781237	141.6232	0.996	.200121
17 20	* -.0916438	.2473965	1.294498	141.322	-1.386142	141.3225	0.992	.2001208
19 20	* -1.016312	.3771066	2.219157	200.0552	-3.235469	200.056	0.987	.2001206

Global test: 'design-by-treatment' approach

chi2 (12) = 17.79

Prob > chi2 = 0.1223

Number of patients with any serious adverse events

Loop-specific heterogeneity approach

Loop	IF	seIF	z_value	P value	CI_95	Loop_Heterog_tau2
fingolimod-glatiramer_acetate-interferon_beta1b_Betaferon	1.436	1.115	1.288	0.198	(0.00,3.62)	0.000
placebo_no treatment-fingolimod-interferon_beta1a_Avonex_Rebif	1.072	0.351	3.059	0.002	(0.39,1.76)	0.000
placebo_no treatment-glatiramer_acetate-interferon_beta1b_Betaferon-mitoxantrone	0.922	1.728	0.533	0.594	(0.00,4.31)	0.000
fingolimod-glatiramer_acetate-interferon_beta1a_Avonex_Rebif	0.672	0.379	1.773	0.076	(0.00,1.42)	0.000
placebo_no treatment-fingolimod-interferon_beta1b_Betaferon-mitoxantrone	0.591	2.021	0.293	0.770	(0.00,4.55)	0.000
placebo_no treatment-glatiramer_acetate-interferon_beta1a_Avonex_Rebif	0.477	0.386	1.233	0.217	(0.00,1.23)	0.000
placebo_no treatment-interferon_beta1a_Avonex_Rebif-laquinimod	0.464	0.420	1.104	0.270	(0.00,1.29)	0.000
placebo_no treatment-daclizumab-interferon_beta1a_Avonex_Rebif	0.115	0.465	0.248	0.804	(0.00,1.03)	0.000
placebo_no treatment-fingolimod-glatiramer_acetate	0.081	0.412	0.197	0.844	(0.00,0.89)	0.016
placebo_no treatment-dimethylfumarate-glatiramer_acetate	0.066	0.413	0.161	0.872	(0.00,0.87)	0.000

Node-splitting approach

Legend: 01 placebo_no treatment; 02 alemtuzumab; 03 cladribine; 04 daclizumab; 05 dimethylfumarate; 06 fingolimod; 07 glatiramer_acetate; 08 interferon_beta1b_Betaferon; 09 interferon_beta1a_Avonex_Rebif; 10 laquinimod; 11 pegylated_interferon_beta1a, 12 mitoxantrone; 13 natalizumab; 14 ocrelizumab; 15 ofatumumab; 16 ozanimod; 17 ponesimod; 18 teriflunomid

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P >	|z|
01 03	.	.	.	.	.	.	.	.
01 04	.3428866	.3817169	.802092	.2761009	-.4592053	.4711046	0.330	.1575602
01 05	*.0556375	.2119341	-.1473965	.6903484	.203034	.7324158	0.782	.1742325
01 06	-.0228729	.1569174	-.4561463	.2390813	.4332733	.28545	0.129	.1186132
01 07	-.031225	.232689	-.1053027	.233563	.0740776	.3305784	0.823	.1777305
01 09	-.3283261	.2894794	.3864828	.16897	-.7148089	.3329177	0.032	.0994794
01 10	*.1768693	.1507448	1.209744	.6557727	-1.032875	.6693295	0.123	.1316775
01 11	.	.	.	.	.	.	.	.
01 12	.	.	.	.	.	.	.	.
01 13	.1930908	.2715744	1.036819	1.724306	-.8437285	1.745561	0.629	.1629926
01 18	*.1450165	.1787431	-.2041606	57.75152	.3491771	57.7518	0.995	.162982
02 09	* -.2318932	.1878924	.6117821	115.4494	-.8436752	115.4498	0.994	.1629816
04 09	-.5492827	.2138156	-.0900696	.4197882	-.4592131	.4711044	0.330	.1575601
05 07	.0716263	.3085539	-.3138284	.3397194	.3854547	.4640617	0.406	.1680184
06 07	-.0912678	.3223812	.1652162	.2108298	-.256484	.3851997	0.506	.1661498
06 08	-1.471952	1.08103	.1759312	.2722382	-1.647883	1.114781	0.139	.15900
06 09	.7751266	.1764042	-.0321093	.1905354	.8072359	.2596578	0.002	6.62e-09

(Continued)

07 08	.0580226	.210515	-1.399373	.929647	1.457396	.9531579	0.126	.1588889
07 09	.1920621	.2255781	.3323936	.2533859	-.1403315	.3390923	0.679	.1701762
08 13	1.098543	1.703981	.2548833	.3784494	.8436594	1.745502	0.629	.1629925
09 10	.1392244	.3317816	-.0336998	.2762681	.1729242	.4313749	0.689	.1719299
09 14	* -.1894782	.2210728	-.569363	141.0286	.3798848	141.0285	0.998	.1629818
09 16	*.2146838	.2392691	-.1652021	141.3956	.3798859	141.3955	0.998	.1629818
15 18	* -.2705523	.2015877	.5605836	141.3354	-.8311359	141.3358	0.995	.1629819
17 18	* -.0722457	.2710577	.3622811	199.9601	-.4345268	199.9605	0.998	.1629819

Global test: 'design-by-treatment' approach

chi2 (9) = 17.10

Prob > chi2 = 0.0472

T1 at 24 months

Not available because the loop is from a three-arm trial

Mortality

Loop-specific heterogeneity approach

Loop	IF	seIF	z_value	P value	CI_95	Loop_Heterog_tau2
placebo_no treatment-dimethylfumarate-glatiramer_acetate	2.570	2.401	1.070	0.284	(0.00,7.28)	0.000
placebo_no treatment-fingolimod-interferon_beta1b_Betaferon	2.223	2.042	1.089	0.276	(0.00,6.23)	0.000
placebo_no treatment-daclizumab-interferon_beta1b_Betaferon	2.043	2.175	0.939	0.348	(0.00,6.31)	0.000
placebo_no treatment-interferon_beta1b_Betaferon-interferon_beta1a_Avonex_Rebif	0.938	1.746	0.537	0.591	(0.00,4.36)	0.000
placebo_no treatment-glatiramer_acetate-interferon_beta1b_Betaferon	0.005	1.759	0.003	0.998	(0.00,3.45)	0.000

Node-splitting approach

Legend: 01 placebo_no treatment; 02 alemtuzumab; 03 cladribine; 04 daclizumab; 05 dimethylfumarate; 06 fingolimod; 07 glatiramer_acetate; 08 interferon_beta1b_Betaferon; 09 interferon_beta1a_Avonex_Rebif; 10 laquinimod; 11 pegylated_interferon_beta1a; 12 natalizumab; 13 ocrelizumab; 14 ofatumumab; 15 ozanimod; 16 ponesimod; 17 teriflunomide

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P >	|z|
01 03	.	.	.	.	.	.	.	.
01 04	.3872938	1.635224	-2.098304	1.301368	2.485598	2.08986	0.234	4.68e-10
01 05	*.0498859	1.045421	-3.414747	3.172237	3.464633	3.340278	0.300	7.79e-09
01 06	-1.558059	.9808201	.7447321	1.689007	-2.302791	1.953139	0.238	1.13e-09
01 07	-.7580824	1.070181	-.6438539	1.214709	-.1142285	1.618887	0.944	3.87e-09
01 09	-.3763916	.8870431	-.5561923	.944136	.1798007	1.32751	0.892	1.06e-09
01 10	* -.5907255	.8229333	-1.325653	2.642811	.7349276	2.887507	0.799	1.87e-09
01 11	.	.	.	.	.	.	.	.
01 12	.	.	.	.	.	.	.	.
01 17	*.4041773	1.156373	1.365061	70.71739	-.9608841	70.72684	0.989	3.42e-09
02 09	* -.7862706	.9114372	-.1355699	115.4759	-.6507007	115.4867	0.996	6.52e-08
04 09	1.386241	1.11899	-1.099755	1.765078	2.485995	2.089923	0.234	1.49e-10
05 07	.7045749	1.415727	-2.21705	1.791678	2.921625	2.283598	0.201	6.40e-09
06 09	-.9342955	1.550265	1.368746	1.188316	-2.303042	1.953325	0.238	4.13e-09
07 08	* -.2904746	1.15591	1.125949	200.0812	-1.416424	200.0779	0.994	5.40e-09
07 09	.4836877	1.070668	-.0726993	1.245284	.556387	1.642294	0.735	1.37e-09
09 10	.0295228	1.156668	-.4847674	1.194938	.5142903	1.663055	0.757	1.20e-09

(Continued)

09 13	* -.4696163	1.070196	.4523735	141.4509	-.9219897	141.4469	0.995	1.13e-09
09 15	*.4173734	1.634033	1.339329	200.005	-.9219556	199.9983	0.996	4.06e-09
14 17	* 1.115367	1.634275	-.3066883	200.0305	1.422055	200.0505	0.994	6.24e-10
16 17	* 1.614738	1.550333	-.8061935	200.0064	2.420932	200.0244	0.990	6.42e-10

Global test: 'design-by-treatment' approach

chi2 (7) = 5.94

Prob > chi2 = 0.5465

Appendix 17. Subgroup analyses

Relapse at 12 months

Mc Donald criteria

teriflunomide	**1.52 (1.28,1.80)**	1.03 (0.80,1.33)	0.79 (0.61,1.02)	1.30 (0.76,2.25)	1.24 (0.82,1.88)	1.02 (0.80,1.30)	0.77 (0.53,1.10)	0.84 (0.61,1.16)
0.66 (0.55,0.78)	placebo_no treatment	**0.68 (0.56,0.82)**	**0.52 (0.43,0.63)**	0.86 (0.51,1.44)	0.82 (0.56,1.20)	**0.67 (0.56,0.80)**	**0.51 (0.37,0.70)**	**0.55 (0.42,0.73)**
0.97 (0.75,1.25)	**1.47 (1.22,1.78)**	pegylated_interferon_beta1a	0.76 (0.58,1.00)	1.27 (0.73,2.20)	1.21 (0.79,1.84)	0.99 (0.77,1.27)	0.75 (0.51,1.08)	0.82 (0.58,1.14)
1.27 (0.99,1.64)	**1.93 (1.60,2.33)**	**1.31 (1.00,1.71)**	natalizumab	1.66 (0.96,2.87)	**1.58 (1.04,2.41)**	**1.29 (1.00,1.67)**	0.98 (0.67,1.42)	1.07 (0.76,1.49)
0.77 (0.44,1.32)	**1.16 (0.69,1.95)**	0.79 (0.46,1.37)	0.60 (0.35,1.04)	interferon_beta1b_Betaferon	0.95 (0.57,1.61)	0.78 (0.48,1.27)	**0.59 (0.36,0.95)**	0.64 (0.36,1.16)
0.80 (0.53,1.22)	**1.22 (0.84,1.78)**	0.83 (0.54,1.26)	**0.63 (0.41,0.96)**	1.05 (0.62,1.77)	interferon_beta1a_Avonex_Rebif	0.82 (0.58,1.15)	**0.62 (0.50,0.76)**	0.68 (0.42,1.08)
0.98 (0.77,1.25)	**1.49 (1.26,1.77)**	1.01 (0.79,1.31)	0.77 (0.60,1.00)	1.28 (0.79,2.09)	1.22 (0.87,1.71)	glatiramer_acetate	**0.76 (0.58,0.99)**	0.83 (0.60,1.14)
1.30 (0.91,1.87)	**1.98 (1.44,2.72)**	1.34 (0.93,1.94)	1.02 (0.71,1.48)	**1.70 (1.05,2.75)**	**1.62 (1.32,1.98)**	**1.32 (1.01,1.74)**	fingolimod	1.09 (0.72,1.67)
1.19 (0.86,1.65)	**1.81 (1.37,2.39)**	1.23 (0.88,1.71)	0.94 (0.67,1.31)	1.55 (0.86,2.79)	1.48 (0.93,2.37)	1.21 (0.87,1.68)	0.91 (0.60,1.40)	daclizumab

Poser criteria

placebo_no treatment	**0.40 (0.21,0.74)**	1.65 (0.77,3.55)	**0.76 (0.67,0.85)**	**0.60 (0.47,0.79)**	**0.41 (0.21,0.82)**	0.91 (0.58,1.43)
2.53 (1.35,4.73)	mitoxantrone	**4.19 (1.56,11.24)**	**1.91 (1.01,3.61)**	1.53 (0.78,3.02)	1.04 (0.41,2.63)	**2.30 (1.06,4.99)**
0.60 (0.28,1.30)	**0.24 (0.09,0.64)**	interferon_beta_1a_1b	**0.46 (0.21,0.99)**	**0.37 (0.16,0.82)**	**0.25 (0.09,0.69)**	0.55 (0.30,1.02)
1.32 (1.18,1.48)	**0.52 (0.28,0.99)**	**2.19 (1.01,4.74)**	interferon_beta1a_Avonex_Rebif	0.80 (0.60,1.07)	0.55 (0.27,1.09)	1.20 (0.75,1.92)
1.65 (1.27,2.15)	0.65 (0.33,1.29)	**2.73 (1.22,6.13)**	1.25 (0.94,1.66)	immunoglobulins	0.68 (0.33,1.42)	1.50 (0.89,2.54)
2.43 (1.23,4.81)	0.96 (0.38,2.42)	**4.02 (1.44,11.20)**	1.83 (0.92,3.67)	1.47 (0.71,3.05)	glatiramer_acetate	2.21 (0.97,5.02)
1.10 (0.70,1.73)	**0.43 (0.20,0.94)**	1.82 (0.98,3.36)	0.83 (0.52,1.33)	0.66 (0.39,1.12)	0.45 (0.20,1.03)	azathioprine

Relapse at 24 months

Mc Donald criteria

terifluno-mide	**0.70 (0.57,0.86)**	1.22 (0.99,1.50)	**0.68 (0.50,0.92)**	1.00 (0.77,1.31)	0.97 (0.66,1.43)	0.94 (0.69,1.29)	0.92 (0.67,1.27)	**0.66 (0.51,0.85)**	**0.74 (0.57,0.97)**	**0.64 (0.47,0.89)**	**0.63 (0.43,0.91)**
1.42 (1.16,1.75)	ponesi-mod	**1.73 (1.29,2.32)**	0.97 (0.67,1.40)	**1.43 (1.02,1.99)**	1.38 (0.89,2.13)	1.35 (0.93,1.95)	1.31 (0.90,1.92)	0.94 (0.67,1.30)	1.05 (0.75,1.47)	0.92 (0.63,1.34)	0.89 (0.58,1.36)
0.82 (0.67,1.01)	**0.58 (0.43,0.77)**	placebo_no treatment	**0.56 (0.45,0.70)**	**0.82 (0.70,0.97)**	0.80 (0.57,1.10)	**0.78 (0.62,0.98)**	**0.76 (0.59,0.97)**	**0.54 (0.46,0.63)**	**0.61 (0.52,0.72)**	**0.53 (0.42,0.67)**	**0.51 (0.38,0.70)**
1.47 (1.08,1.99)	1.03 (0.72,1.49)	**1.79 (1.43,2.23)**	natalizum-ab	**1.47 (1.12,1.94)**	1.42 (0.96,2.11)	**1.39 (1.01,1.91)**	1.35 (0.98,1.88)	0.97 (0.74,1.27)	1.09 (0.83,1.43)	0.95 (0.68,1.31)	0.92 (0.63,1.34)
1.00 (0.77,1.30)	**0.70 (0.50,0.98)**	**1.21 (1.03,1.43)**	**0.68 (0.52,0.89)**	laquini-mod	0.97 (0.67,1.39)	0.94 (0.75,1.19)	0.92 (0.69,1.23)	**0.66 (0.52,0.82)**	**0.74 (0.59,0.93)**	**0.64 (0.48,0.86)**	**0.62 (0.46,0.85)**
1.03 (0.70,1.52)	0.73 (0.47,1.12)	1.26 (0.91,1.74)	0.70 (0.47,1.04)	1.03 (0.72,1.48)	interfer-on_be-ta1b_Betafer-on	0.98 (0.65,1.45)	0.95 (0.77,1.18)	**0.68 (0.47,0.97)**	0.76 (0.55,1.06)	0.66 (0.44,1.00)	0.65 (0.41,1.02)
1.06 (0.78,1.44)	0.74 (0.51,1.08)	**1.29 (1.02,1.62)**	**0.72 (0.52,0.99)**	1.06 (0.84,1.34)	1.03 (0.69,1.53)	interfer-on_be-ta1a_Avonex_Rebif	0.98 (0.70,1.36)	**0.70 (0.53,0.92)**	0.78 (0.59,1.04)	**0.68 (0.49,0.95)**	**0.66 (0.54,0.81)**
1.09 (0.79,1.49)	0.76 (0.52,1.11)	**1.32 (1.04,1.68)**	0.74 (0.53,1.02)	1.09 (0.81,1.46)	1.05 (0.85,1.30)	1.03 (0.73,1.43)	glati-ramer_ac-etate	**0.71 (0.53,0.95)**	0.80 (0.63,1.02)	**0.70 (0.50,0.98)**	0.68 (0.46,1.00)
1.52 (1.17,1.98)	1.07 (0.77,1.49)	**1.85 (1.58,2.17)**	1.04 (0.79,1.36)	**1.53 (1.22,1.91)**	**1.47 (1.03,2.11)**	**1.44 (1.09,1.90)**	**1.40 (1.05,1.87)**	fingolimod	1.13 (0.90,1.42)	0.98 (0.73,1.31)	0.95 (0.67,1.34)
1.35 (1.04,1.76)	0.95 (0.68,1.33)	**1.64 (1.39,1.94)**	0.92 (0.70,1.21)	**1.35 (1.07,1.71)**	1.31 (0.95,1.81)	1.28 (0.96,1.70)	1.25 (0.98,1.59)	0.89 (0.71,1.12)	dimethyl-fumarate	0.87 (0.65,1.17)	0.85 (0.60,1.20)
1.55 (1.13,2.14)	1.09 (0.75,1.59)	**1.89 (1.49,2.41)**	1.06 (0.76,1.47)	**1.56 (1.16,2.08)**	**1.50 (1.00,2.26)**	**1.47 (1.05,2.05)**	**1.43 (1.02,2.02)**	1.02 (0.76,1.36)	1.15 (0.86,1.54)	cladribine	0.97 (0.66,1.43)
1.60 (1.10,2.31)	1.12 (0.74,1.71)	**1.95 (1.43,2.64)**	1.09 (0.75,1.59)	**1.60 (1.18,2.18)**	1.55 (0.99,2.44)	**1.51 (1.24,1.85)**	**1.47 (1.00,2.18)**	1.05 (0.74,1.48)	1.18 (0.84,1.68)	1.03 (0.70,1.52)	alem-tuzumab

Poser criteria

placebo_no treatment	**0.47 (0.27,0.80)**	**0.84 (0.72,0.97)**	**0.87 (0.79,0.97)**	**0.73 (0.58,0.91)**	0.90 (0.77,1.04)	0.77 (0.50,1.18)
2.14 (1.24,3.68)	mitoxantrone	**1.79 (1.02,3.14)**	**1.86 (1.07,3.23)**	1.55 (0.86,2.79)	**1.92 (1.09,3.36)**	1.65 (0.83,3.29)
1.20 (1.03,1.39)	**0.56 (0.32,0.98)**	interferon_beta1b_Betaferon	1.04 (0.87,1.25)	0.87 (0.66,1.13)	1.07 (0.88,1.31)	0.93 (0.59,1.45)
1.15 (1.03,1.27)	**0.54 (0.31,0.93)**	0.96 (0.80,1.15)	interferon_beta1a_Avonex_Rebif	0.83 (0.65,1.06)	1.03 (0.88,1.20)	0.89 (0.57,1.38)
1.38 (1.10,1.72)	0.64 (0.36,1.16)	1.15 (0.88,1.51)	1.20 (0.94,1.53)	immunoglobulins	1.24 (0.95,1.61)	1.07 (0.66,1.72)
1.12 (0.96,1.29)	**0.52 (0.30,0.92)**	0.93 (0.76,1.14)	0.97 (0.83,1.14)	0.81 (0.62,1.05)	glatiramer_acetate	0.86 (0.55,1.35)
1.29 (0.84,1.98)	0.60 (0.30,1.21)	1.08 (0.69,1.70)	1.13 (0.73,1.75)	0.94 (0.58,1.52)	1.16 (0.74,1.82)	azathioprine

Disability at 24 months

Mc Donald criteria

teri-fluno-mide	0.82 (0.57,1.19)	**1.31 (1.05,1.63)**	1.33 (0.72,2.46)	**0.71 (0.54,0.93)**	0.68 (0.39,1.18)	0.77 (0.56,1.07)	0.89 (0.64,1.25)	1.22 (0.80,1.87)	1.03 (0.66,1.63)	1.14 (0.79,1.66)	0.90 (0.67,1.20)	0.88 (0.67,1.17)	0.94 (0.68,1.30)	0.75 (0.44,1.30)
1.22 (0.84,1.77)	ponesi-mod	**1.60 (1.04,2.46)**	1.62 (0.79,3.33)	0.86 (0.54,1.37)	0.83 (0.42,1.62)	0.94 (0.57,1.55)	1.09 (0.66,1.80)	1.49 (0.85,2.62)	1.26 (0.70,2.26)	1.39 (0.82,2.36)	1.09 (0.68,1.76)	1.08 (0.68,1.72)	1.14 (0.70,1.88)	0.92 (0.47,1.78)
0.76 (0.61,0.95)	**0.63 (0.41,0.96)**	place-bo_no treat-ment	1.02 (0.57,1.80)	**0.54 (0.38,0.77)**	**0.52 (0.31,0.86)**	**0.59 (0.46,0.75)**	**0.68 (0.53,0.88)**	0.93 (0.65,1.34)	0.79 (0.53,1.17)	0.87 (0.65,1.18)	0.68 (0.56,0.83)	**0.67 (0.57,0.80)**	**0.72 (0.56,0.91)**	**0.57 (0.35,0.95)**
0.75 (0.41,1.39)	0.62 (0.30,1.26)	0.98 (0.55,1.74)	ozani-mod	0.53 (0.27,1.04)	**0.51 (0.30,0.86)**	0.58 (0.31,1.08)	0.67 (0.37,1.21)	0.92 (0.47,1.81)	0.78 (0.51,1.17)	0.86 (0.45,1.64)	0.67 (0.37,1.23)	0.66 (0.36,1.21)	0.70 (0.38,1.31)	**0.57 (0.34,0.95)**
1.41 (1.08,1.86)	1.16 (0.73,1.84)	**1.85 (1.30,2.63)**	1.88 (0.96,3.68)	ofatu-mumab	0.96 (0.52,1.78)	1.09 (0.71,1.68)	1.26 (0.82,1.95)	**1.73 (1.04,2.86)**	1.46 (0.86,2.48)	**1.61 (1.02,2.56)**	1.27 (0.85,1.89)	1.25 (0.84,1.85)	1.32 (0.86,2.03)	1.06 (0.58,1.96)
1.47 (0.85,2.56)	1.21 (0.62,2.36)	**1.93 (1.16,3.21)**	**1.96 (1.16,3.31)**	1.04 (0.56,1.93)	ocre-lizumab	1.14 (0.65,2.00)	1.32 (0.78,2.23)	1.80 (0.96,3.36)	**1.52 (1.10,2.09)**	1.68 (0.93,3.04)	1.32 (0.76,2.28)	1.30 (0.76,2.23)	1.38 (0.78,2.43)	1.11 (0.71,1.73)
1.29 (0.93,1.80)	1.06 (0.65,1.74)	**1.69 (1.33,2.16)**	1.72 (0.92,3.21)	0.91 (0.60,1.40)	0.88 (0.50,1.54)	natal-izumab	1.16 (0.81,1.64)	**1.58 (1.02,2.45)**	1.34 (0.84,2.13)	**1.48 (1.00,2.17)**	1.16 (0.85,1.59)	1.14 (0.84,1.54)	1.21 (0.86,1.71)	0.97 (0.56,1.70)
1.12 (0.80,1.56)	0.92 (0.56,1.51)	**1.46 (1.14,1.88)**	1.49 (0.83,2.68)	0.79 (0.51,1.22)	0.76 (0.45,1.28)	0.86 (0.61,1.23)	laquini-mod	1.37 (0.88,2.12)	1.15 (0.76,1.75)	1.28 (0.86,1.89)	1.00 (0.73,1.38)	0.99 (0.73,1.34)	1.05 (0.74,1.49)	0.84 (0.50,1.41)
0.82 (0.54,1.25)	0.67 (0.38,1.18)	1.07 (0.75,1.54)	1.09 (0.55,2.15)	**0.58 (0.35,0.96)**	0.56 (0.30,1.04)	**0.63 (0.41,0.98)**	0.73 (0.47,1.14)	interfer-on_be-ta1b_Betafer-on	0.85 (0.49,1.45)	0.93 (0.76,1.15)	0.73 (0.49,1.11)	0.72 (0.51,1.03)	0.77 (0.50,1.19)	0.62 (0.33,1.14)
0.97 (0.62,1.52)	0.79 (0.44,1.43)	1.27 (0.85,1.88)	1.29 (0.85,1.95)	0.68 (0.40,1.16)	**0.66 (0.48,0.90)**	0.75 (0.47,1.19)	0.87 (0.57,1.31)	1.18 (0.69,2.02)	interfer-on_be-ta1a_Avonex_Rebif	1.11 (0.67,1.82)	0.87 (0.56,1.35)	0.86 (0.55,1.32)	0.91 (0.57,1.44)	**0.73 (0.54,0.99)**
0.88 (0.60,1.27)	0.72 (0.42,1.21)	1.15 (0.85,1.55)	1.17 (0.61,2.22)	**0.62 (0.39,0.98)**	0.59 (0.33,1.07)	0.68 (0.46,1.00)	0.78 (0.53,1.16)	1.07 (0.87,1.31)	0.90 (0.55,1.49)	glati-ramer_ac-etate	0.78 (0.55,1.12)	0.77 (0.58,1.03)	0.82 (0.56,1.21)	0.66 (0.37,1.18)
1.12 (0.83,1.50)	0.92 (0.57,1.47)	**1.46 (1.20,1.78)**	1.49 (0.81,2.72)	0.79 (0.53,1.18)	0.76 (0.44,1.31)	0.86 (0.63,1.18)	1.00 (0.72,1.38)	1.36 (0.90,2.06)	1.15 (0.74,1.79)	1.27 (0.89,1.82)	fin-golimod	0.99 (0.76,1.29)	1.05 (0.76,1.43)	0.84 (0.49,1.44)

(Continued)

1.13 (0.85,1.50)	0.93 (0.58,1.48)	**1.48 (1.24,1.77)**	1.51 (0.83,2.75)	0.80 (0.54,1.19)	0.77 (0.45,1.32)	0.88 (0.65,1.18)	1.01 (0.74,1.38)	1.38 (0.97,1.97)	1.17 (0.76,1.80)	1.29 (0.97,1.73)	1.01 (0.78,1.32)	di-methyl-fu-marate	1.06 (0.79,1.43)	0.85 (0.50,1.45)
1.07 (0.77,1.48)	0.88 (0.53,1.44)	**1.40 (1.10,1.78)**	1.42 (0.76,2.65)	0.76 (0.49,1.16)	0.72 (0.41,1.27)	0.83 (0.59,1.17)	0.96 (0.67,1.36)	1.30 (0.84,2.02)	1.10 (0.69,1.75)	1.22 (0.83,1.79)	0.96 (0.70,1.31)	0.94 (0.70,1.27)	cladrib-ine	0.80 (0.46,1.40)
1.33 (0.77,2.30)	1.09 (0.56,2.11)	**1.74 (1.05,2.87)**	**1.77 (1.06,2.96)**	0.94 (0.51,1.73)	0.90 (0.58,1.41)	1.03 (0.59,1.80)	1.19 (0.71,2.00)	1.62 (0.87,3.02)	**1.37 (1.01,1.87)**	1.52 (0.85,2.72)	1.19 (0.69,2.04)	1.17 (0.69,2.00)	1.24 (0.71,2.17)	alem-tuzum-ab

Poser criteria

placebo_no treatment	**0.20 (0.04,0.88)**	0.68 (0.43,1.07)	0.88 (0.58,1.35)	0.76 (0.37,1.55)	0.65 (0.41,1.01)	0.60 (0.20,1.79)
5.06 (1.13,22.63)	mitoxantrone	3.42 (0.71,16.39)	4.47 (0.94,21.20)	3.85 (0.73,20.19)	3.28 (0.69,15.65)	3.06 (0.48,19.48)
1.48 (0.93,2.34)	0.29 (0.06,1.40)	interferon_beta1b_Betaferon	1.31 (0.87,1.96)	1.12 (0.48,2.64)	0.96 (0.55,1.66)	0.89 (0.27,2.91)
1.13 (0.74,1.74)	0.22 (0.05,1.06)	0.77 (0.51,1.15)	interferon_beta1a_Avonex_Rebif	0.86 (0.37,1.98)	0.73 (0.46,1.18)	0.68 (0.21,2.20)
1.32 (0.65,2.68)	0.26 (0.05,1.36)	0.89 (0.38,2.09)	1.16 (0.50,2.67)	immunoglobulins	0.85 (0.37,1.98)	0.79 (0.22,2.92)
1.54 (0.99,2.41)	0.30 (0.06,1.46)	1.04 (0.60,1.81)	1.36 (0.85,2.18)	1.17 (0.50,2.73)	glatiramer_acetate	0.93 (0.29,3.03)
1.66 (0.56,4.92)	0.33 (0.05,2.08)	1.12 (0.34,3.65)	1.46 (0.45,4.70)	1.26 (0.34,4.62)	1.07 (0.33,3.48)	azathioprine

Number of patients who discontinued treatment due to adverse events

Mc Donald criteria

placebo_no treatment	0.76 (0.37,1.54)	**1.83 (1.18,2.82)**	**5.04 (2.12,12.00)**	0.93 (0.46,1.87)	**2.00 (1.04,3.86)**	1.54 (0.79,3.03)	1.37 (0.87,2.14)	1.33 (0.83,2.13)	**3.58 (1.46,8.82)**	1.52 (0.63,3.63)	1.37 (0.92,2.03)	**1.77 (1.26,2.49)**	1.32 (0.91,1.93)	**2.38 (1.26,4.50)**	1.38 (0.46,4.19)	0.36 (0.17,0.76)
1.32 (0.65,2.69)	pegylated_interferon_beta1a	**2.41 (1.05,5.54)**	**6.66 (2.17,20.43)**	1.23 (0.57,2.65)	**2.64 (1.00,6.95)**	2.04 (0.77,5.44)	**1.81 (1.04,3.14)**	1.76 (0.80,3.86)	**4.73 (1.50,14.90)**	2.00 (0.68,5.90)	1.81 (0.86,3.81)	**2.34 (1.14,4.80)**	1.75 (0.80,3.84)	**3.14 (1.51,6.56)**	1.83 (0.49,6.81)	0.47 (0.21,1.08)
0.55 (0.35,0.85)	**0.41 (0.18,0.95)**	ozanimod	**2.76 (1.30,5.85)**	0.51 (0.22,1.16)	1.10 (0.67,1.80)	0.85 (0.38,1.89)	0.75 (0.40,1.40)	0.73 (0.38,1.38)	1.96 (0.72,5.33)	0.83 (0.31,2.20)	0.75 (0.42,1.35)	0.97 (0.56,1.69)	0.73 (0.41,1.29)	1.30 (0.60,2.82)	0.76 (0.23,2.49)	0.20 (0.08,0.47)
0.20 (0.08,0.47)	**0.15 (0.05,0.46)**	**0.36 (0.17,0.77)**	ofatumumab	**0.18 (0.06,0.56)**	0.40 (0.16,0.97)	0.31 (0.10,0.92)	0.27 (0.10,0.72)	**0.26 (0.10,0.71)**	0.71 (0.20,2.48)	0.30 (0.09,1.03)	0.27 (0.10,0.70)	0.35 (0.14,0.89)	0.26 (0.10,0.68)	0.47 (0.16,1.38)	0.27 (0.07,1.12)	0.07 (0.02,0.22)
1.07 (0.53,2.16)	0.81 (0.38,1.76)	1.96 (0.86,4.46)	**5.42 (1.78,16.50)**	ocrelizumab	2.15 (0.82,5.61)	1.66 (0.63,4.39)	1.47 (0.86,2.51)	1.43 (0.66,3.11)	**3.85 (1.23,12.03)**	1.63 (0.56,4.76)	1.47 (0.70,3.07)	1.90 (0.94,3.86)	1.42 (0.66,3.09)	**2.56 (1.24,5.28)**	1.49 (0.40,5.50)	0.38 (0.17,0.87)
0.50 (0.26,0.96)	0.38 (0.14,1.00)	0.91 (0.56,1.50)	**2.52 (1.03,6.19)**	0.47 (0.18,1.21)	natalizumab	0.77 (0.30,1.98)	0.68 (0.31,1.51)	0.67 (0.30,1.49)	1.79 (0.59,5.46)	0.76 (0.25,2.26)	0.68 (0.32,1.47)	0.88 (0.42,1.86)	0.66 (0.31,1.41)	1.19 (0.48,2.97)	0.69 (0.19,2.51)	0.18 (0.07,0.48)
0.65 (0.33,1.27)	0.49 (0.18,1.31)	1.18 (0.53,2.64)	**3.26 (1.09,9.80)**	0.60 (0.23,1.59)	1.29 (0.50,3.32)	laquinimod	0.89 (0.39,1.99)	0.86 (0.38,1.96)	2.32 (0.75,7.15)	0.98 (0.33,2.89)	0.88 (0.41,1.93)	1.15 (0.54,2.44)	0.86 (0.40,1.86)	1.54 (0.61,3.91)	0.89 (0.24,3.27)	0.23 (0.08,0.63)
0.73 (0.47,1.14)	**0.55 (0.32,0.96)**	1.33 (0.72,2.49)	**3.69 (1.39,9.79)**	0.68 (0.40,1.16)	1.46 (0.66,3.24)	1.13 (0.50,2.54)	interferon_beta_1a_1b	0.97 (0.56,1.70)	2.62 (0.96,7.16)	1.11 (0.44,2.81)	1.00 (0.60,1.65)	1.29 (0.81,2.06)	0.97 (0.55,1.70)	**1.74 (1.07,2.83)**	1.01 (0.31,3.34)	0.26 (0.14,0.48)
0.75 (0.47,1.20)	0.57 (0.26,1.25)	1.37 (0.72,2.60)	**3.79 (1.41,10.16)**	0.70 (0.32,1.52)	1.50 (0.67,3.37)	1.16 (0.51,2.64)	1.03 (0.59,1.80)	interferon_beta1b_Betaferon	2.69 (0.97,7.43)	1.14 (0.43,3.04)	1.03 (0.57,1.86)	1.33 (0.76,2.32)	1.00 (0.55,1.81)	1.79 (0.86,3.70)	1.04 (0.31,3.46)	0.27 (0.12,0.61)
0.28 (0.11,0.69)	**0.21 (0.07,0.66)**	0.51 (0.19,1.38)	1.41 (0.40,4.91)	**0.26 (0.08,0.81)**	0.56 (0.18,1.70)	0.43 (0.14,1.33)	0.38 (0.14,1.04)	0.37 (0.13,1.03)	interfer-	0.42 (0.12,1.48)	0.38 (0.14,1.02)	0.49 (0.19,1.29)	0.37 (0.14,0.98)	0.66 (0.22,2.00)	0.39 (0.09,1.61)	0.10 (0.03,0.32)

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									on_beta1a_Avonex_Rebif							
0.66 (0.28,1.58)	0.50 (0.17,1.47)	1.20 (0.45,3.20)	3.33 (0.97,11.40)	0.61 (0.21,1.80)	1.32 (0.44,3.94)	1.02 (0.35,3.00)	0.90 (0.36,2.28)	0.88 (0.33,2.34)	2.36 (0.67,8.29)	glatiramer_acetate	0.90 (0.40,2.02)	1.17 (0.48,2.82)	0.87 (0.35,2.18)	1.57 (0.56,4.41)	0.91 (0.22,3.74)	0.24 (0.08,0.72)
0.73 (0.49,1.09)	0.55 (0.26,1.17)	1.34 (0.74,2.40)	**3.69 (1.42,9.58)**	0.68 (0.33,1.42)	1.46 (0.68,3.15)	1.13 (0.52,2.46)	1.00 (0.60,1.66)	0.97 (0.54,1.76)	2.62 (0.98,7.01)	1.11 (0.50,2.48)	fingolimod	1.29 (0.84,1.99)	0.97 (0.61,1.54)	1.74 (0.88,3.44)	1.01 (0.31,3.28)	0.26 (0.12,0.58)
0.57 (0.40,0.80)	**0.43 (0.21,0.88)**	1.03 (0.59,1.79)	**2.85 (1.12,7.24)**	0.53 (0.26,1.07)	1.13 (0.54,2.37)	0.87 (0.41,1.86)	0.77 (0.49,1.23)	0.75 (0.43,1.31)	2.03 (0.77,5.31)	0.86 (0.35,2.07)	0.77 (0.50,1.19)	dimethylfumarate	0.75 (0.46,1.22)	1.35 (0.70,2.58)	0.78 (0.25,2.49)	0.20 (0.09,0.43)
0.75 (0.52,1.10)	0.57 (0.26,1.25)	1.38 (0.78,2.45)	**3.81 (1.48,9.80)**	0.70 (0.32,1.53)	1.51 (0.71,3.22)	1.17 (0.54,2.52)	1.03 (0.59,1.81)	1.00 (0.55,1.82)	**2.71 (1.02,7.18)**	1.14 (0.46,2.85)	1.03 (0.65,1.64)	1.34 (0.82,2.17)	daclizumab	1.80 (0.87,3.69)	1.04 (0.32,3.36)	0.27 (0.12,0.62)
0.42 (0.22,0.79)	**0.32 (0.15,0.66)**	0.77 (0.36,1.66)	2.12 (0.72,6.21)	**0.39 (0.19,0.81)**	0.84 (0.34,2.10)	0.65 (0.26,1.65)	0.57 (0.35,0.93)	0.56 (0.27,1.16)	1.51 (0.50,4.53)	0.64 (0.23,1.79)	0.57 (0.29,1.13)	0.74 (0.39,1.43)	0.56 (0.27,1.14)	cladribine	0.58 (0.16,2.08)	0.15 (0.07,0.33)
0.72 (0.24,2.19)	0.55 (0.15,2.04)	1.32 (0.40,4.34)	3.65 (0.89,14.90)	0.67 (0.18,2.49)	1.45 (0.40,5.25)	1.12 (0.31,4.09)	0.99 (0.30,3.27)	0.96 (0.29,3.21)	2.59 (0.62,10.80)	1.10 (0.27,4.50)	0.99 (0.30,3.21)	1.28 (0.40,4.08)	0.96 (0.30,3.09)	1.72 (0.48,6.18)	azathioprine	0.26 (0.07,0.98)
2.81 (1.32,5.97)	2.12 (0.93,4.85)	**5.12 (2.14,12.23)**	**14.15 (3.48,44.67)**	**2.61 (1.15,5.91)**	**5.61 (2.06,15.27)**	**4.33 (1.58,11.91)**	**3.84 (2.07,7.10)**	**3.74 (1.64,8.53)**	**10.06 (3.11,32.55)**	**4.25 (1.39,12.98)**	**3.84 (1.73,8.49)**	**4.96 (2.31,10.66)**	**3.72 (1.62,8.51)**	**6.68 (3.03,14.70)**	3.88 (1.02,14.82)	alemtuzumab

Poser criteria

placebo_no treatment	6.26 (0.40,97.59)	**11.01 (2.22,54.60)**	3.24 (0.90,11.72)	2.49 (0.38,16.16)	2.84 (0.78,10.31)	6.26 (0.70,56.09)
0.16 (0.01,2.49)	interferon_beta_1a_1b	1.76 (0.07,42.26)	0.52 (0.02,10.75)	0.40 (0.01,11.03)	0.45 (0.02,9.43)	1.00 (0.19,5.23)
0.09 (0.02,0.45)	0.57 (0.02,13.67)	interferon_beta1b_Betaferon	0.29 (0.06,1.51)	0.23 (0.02,2.65)	0.26 (0.05,1.39)	0.57 (0.04,8.59)
0.31 (0.09,1.11)	1.93 (0.09,40.05)	3.39 (0.66,17.38)	interferon_beta1a_Avonex_Rebif	0.77 (0.08,7.43)	0.88 (0.48,1.61)	1.93 (0.15,24.52)
0.40 (0.06,2.61)	2.51 (0.09,69.75)	4.42 (0.38,51.87)	1.30 (0.13,12.60)	immunoglobulins	1.14 (0.12,11.06)	2.51 (0.14,44.89)
0.35 (0.10,1.28)	2.20 (0.11,45.79)	3.87 (0.72,20.93)	1.14 (0.62,2.09)	0.88 (0.09,8.50)	glatiramer_acetate	2.20 (0.17,28.04)
0.16 (0.02,1.43)	1.00 (0.19,5.23)	1.76 (0.12,26.57)	0.52 (0.04,6.58)	0.40 (0.02,7.10)	0.45 (0.04,5.78)	azathioprine

Number of patients with any serious adverse events

Mc Donald criteria

teri-fluno-mid	1.07 (0.63,1.84)	0.87 (0.61,1.23)	0.93 (0.46,1.88)	1.31 (0.66,2.59)	1.31 (0.88,1.96)	0.87 (0.45,1.69)	1.07 (0.56,2.03)	0.97 (0.58,1.64)	0.75 (0.39,1.42)	1.05 (0.64,1.73)	0.76 (0.46,1.23)	0.73 (0.46,1.16)	0.88 (0.52,1.49)	1.65 (0.92,2.97)	1.20 (0.62,2.32)	1.33 (0.72,2.46)
0.93 (0.54,1.59)	pones-imod	0.80 (0.42,1.54)	0.87 (0.36,2.10)	1.22 (0.51,2.90)	1.22 (0.62,2.39)	0.81 (0.35,1.90)	1.00 (0.43,2.30)	0.91 (0.43,1.92)	0.69 (0.30,1.60)	0.98 (0.47,2.04)	0.70 (0.34,1.46)	0.68 (0.34,1.38)	0.82 (0.39,1.74)	1.53 (0.69,3.41)	1.11 (0.47,2.62)	1.24 (0.54,2.81)
1.16 (0.81,1.65)	1.24 (0.65,2.37)	place-bo_no treat-ment	1.08 (0.59,1.97)	1.51 (0.84,2.70)	1.52 (0.89,2.59)	1.01 (0.58,1.76)	1.24 (0.73,2.11)	1.13 (0.77,1.65)	0.86 (0.51,1.47)	1.22 (0.86,1.72)	0.87 (0.63,1.22)	0.85 (0.64,1.13)	1.02 (0.69,1.50)	**1.91 (1.19,3.05)**	1.39 (0.79,2.42)	1.54 (0.93,2.55)
1.07 (0.53,2.16)	1.15 (0.48,2.79)	0.93 (0.51,1.70)	pegy-lat-ed_in-terfer-on_be-ta1a	1.40 (0.61,3.25)	1.41 (0.63,3.15)	0.93 (0.41,2.13)	1.15 (0.51,2.57)	1.05 (0.51,2.14)	0.80 (0.36,1.79)	1.13 (0.56,2.27)	0.81 (0.41,1.62)	0.79 (0.40,1.54)	0.94 (0.46,1.94)	1.77 (0.82,3.81)	1.29 (0.56,2.93)	1.43 (0.65,3.13)
0.77 (0.39,1.51)	0.82 (0.34,1.96)	0.66 (0.37,1.18)	0.71 (0.31,1.65)	ozani-mod	1.00 (0.45,2.21)	0.67 (0.35,1.27)	0.82 (0.37,1.80)	0.75 (0.39,1.44)	0.57 (0.27,1.19)	0.81 (0.50,1.29)	0.58 (0.31,1.07)	0.56 (0.31,1.01)	0.67 (0.34,1.34)	1.26 (0.68,2.34)	0.92 (0.41,2.05)	1.02 (0.56,1.86)
0.76 (0.51,1.14)	0.82 (0.42,1.60)	0.66 (0.39,1.13)	0.71 (0.32,1.60)	1.00 (0.45,2.20)	ofatu-mum-ab	0.66 (0.31,1.44)	0.82 (0.38,1.74)	0.74 (0.39,1.43)	0.57 (0.27,1.21)	0.80 (0.43,1.52)	0.58 (0.31,1.09)	0.56 (0.30,1.03)	0.67 (0.35,1.30)	1.26 (0.62,2.57)	0.91 (0.42,1.98)	1.01 (0.49,2.12)
1.15 (0.59,2.22)	1.23 (0.53,2.89)	0.99 (0.57,1.73)	1.07 (0.47,2.43)	1.50 (0.79,2.86)	1.50 (0.69,3.26)	ocre-lizum-ab	1.23 (0.57,2.65)	1.12 (0.59,2.11)	0.86 (0.42,1.74)	1.21 (0.78,1.87)	0.87 (0.48,1.56)	0.84 (0.48,1.48)	1.01 (0.52,1.96)	**1.89 (1.05,3.40)**	1.37 (0.62,3.02)	1.52 (0.86,2.71)
0.93 (0.49,1.77)	1.00 (0.43,2.32)	0.81 (0.47,1.38)	0.87 (0.39,1.95)	1.22 (0.56,2.69)	1.23 (0.58,2.61)	0.81 (0.38,1.76)	natal-izum-ab	0.91 (0.47,1.75)	0.70 (0.33,1.47)	0.98 (0.52,1.86)	0.71 (0.38,1.32)	0.69 (0.37,1.25)	0.82 (0.43,1.59)	1.54 (0.76,3.14)	1.12 (0.52,2.42)	1.24 (0.60,2.59)
1.03 (0.61,1.73)	1.10 (0.52,2.33)	0.89 (0.61,1.30)	0.96 (0.47,1.95)	1.34 (0.69,2.59)	1.34 (0.70,2.59)	0.89 (0.47,1.69)	1.10 (0.57,2.11)	laquin-imod	0.77 (0.40,1.45)	1.08 (0.68,1.72)	0.78 (0.48,1.27)	0.75 (0.48,1.19)	0.90 (0.53,1.55)	1.69 (0.96,3.00)	1.23 (0.63,2.41)	1.36 (0.75,2.46)
1.34 (0.71,2.54)	1.44 (0.62,3.32)	1.16 (0.68,1.97)	1.25 (0.56,2.79)	1.75 (0.84,3.64)	1.76 (0.83,3.73)	1.17 (0.57,2.37)	1.43 (0.68,3.02)	1.31 (0.69,2.47)	inter-fer-on_be-ta1b_Betafer-on	1.41 (0.81,2.46)	1.01 (0.67,1.54)	0.98 (0.57,1.70)	1.18 (0.64,2.17)	**2.21 (1.15,4.24)**	1.60 (0.74,3.47)	1.78 (0.91,3.48)

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0.95 (0.58,1.56)	1.02 (0.49,2.12)	0.82 (0.58,1.16)	0.89 (0.44,1.78)	1.24 (0.77,1.99)	1.24 (0.66,2.35)	0.83 (0.53,1.28)	1.02 (0.54,1.92)	0.93 (0.58,1.47)	0.71 (0.41,1.24)	interferon_beta1a_Avonex_Rebif	0.72 (0.49,1.06)	**0.70 (0.49,0.99)**	0.84 (0.51,1.38)	**1.57 (1.06,2.31)**	1.14 (0.59,2.19)	1.26 (0.87,1.83)
1.32 (0.81,2.15)	1.42 (0.69,2.94)	1.14 (0.82,1.60)	1.23 (0.62,2.46)	1.73 (0.94,3.18)	1.73 (0.92,3.26)	1.15 (0.64,2.06)	1.41 (0.76,2.64)	1.29 (0.79,2.10)	0.99 (0.65,1.50)	1.39 (0.95,2.05)	glatiramer_acetate	0.97 (0.67,1.40)	1.16 (0.74,1.83)	**2.18 (1.30,3.65)**	1.58 (0.83,3.04)	**1.76 (1.03,3.00)**
1.36 (0.86,2.15)	1.47 (0.72,2.97)	1.18 (0.88,1.57)	1.27 (0.65,2.48)	1.78 (0.99,3.20)	1.79 (0.97,3.28)	1.19 (0.68,2.08)	1.46 (0.80,2.67)	1.33 (0.84,2.10)	1.02 (0.59,1.76)	**1.44 (1.01,2.04)**	1.03 (0.72,1.49)	fingolimod	1.20 (0.75,1.91)	**2.25 (1.37,3.69)**	1.63 (0.87,3.06)	**1.81 (1.09,3.02)**
1.14 (0.67,1.92)	1.22 (0.57,2.59)	0.98 (0.67,1.45)	1.06 (0.52,2.17)	1.48 (0.75,2.94)	1.49 (0.77,2.88)	0.99 (0.51,1.92)	1.21 (0.63,2.35)	1.11 (0.65,1.90)	0.85 (0.46,1.56)	1.20 (0.73,1.97)	0.86 (0.55,1.35)	0.83 (0.52,1.33)	dimethylfumarate	**1.87 (1.03,3.39)**	1.36 (0.69,2.68)	1.51 (0.81,2.80)
0.61 (0.34,1.09)	0.65 (0.29,1.45)	**0.52 (0.33,0.84)**	0.57 (0.26,1.22)	0.79 (0.43,1.47)	0.79 (0.39,1.62)	**0.53 (0.29,0.95)**	0.65 (0.32,1.32)	0.59 (0.33,1.05)	**0.45 (0.24,0.87)**	**0.64 (0.43,0.94)**	**0.46 (0.27,0.77)**	**0.44 (0.27,0.73)**	**0.53 (0.29,0.97)**	daclizumab	0.73 (0.35,1.51)	0.81 (0.47,1.38)
0.83 (0.43,1.62)	0.90 (0.38,2.11)	0.72 (0.41,1.26)	0.78 (0.34,1.77)	1.09 (0.49,2.44)	1.09 (0.50,2.37)	0.73 (0.33,1.60)	0.89 (0.41,1.93)	0.81 (0.41,1.60)	0.62 (0.29,1.35)	0.88 (0.46,1.69)	0.63 (0.33,1.21)	0.61 (0.33,1.15)	0.74 (0.37,1.45)	1.38 (0.66,2.86)	cladribine	1.11 (0.52,2.35)
0.75 (0.41,1.40)	0.81 (0.36,1.84)	0.65 (0.39,1.08)	0.70 (0.32,1.54)	0.98 (0.54,1.79)	0.99 (0.47,2.06)	0.66 (0.37,1.16)	0.80 (0.39,1.68)	0.73 (0.41,1.33)	0.56 (0.29,1.10)	0.79 (0.55,1.15)	**0.57 (0.33,0.97)**	**0.55 (0.33,0.92)**	0.66 (0.36,1.23)	1.24 (0.72,2.13)	0.90 (0.42,1.91)	alemtuzumab

Poser criteria

placebo_no treatment	0.89 (0.02,46.62)	7.67 (0.36,163.04)	7.22 (0.36,145.97)
1.12 (0.02,58.74)	mitoxantrone	8.61 (0.06,1278.49)	8.11 (0.06,1167.51)
0.13 (0.01,2.77)	0.12 (0.00,17.24)	interferon_beta1a_Avonex_Rebif	0.94 (0.55,1.62)
0.14 (0.01,2.80)	0.12 (0.00,17.75)	1.06 (0.62,1.83)	glatiramer_acetate

Significant results are bolded and underlined.

Appendix 18. Sensitivity analyses

Relapse at 12 months

Low allocation bias

teriflunomide	**1.52 (1.28,1.80)**	1.03 (0.80,1.33)	0.79 (0.61,1.02)	0.60 (0.31,1.15)	1.15 (0.93,1.41)	0.91 (0.61,1.37)	**0.71 (0.53,0.95)**	0.84 (0.61,1.16)
0.66 (0.55,0.78)	placebo_no treatment	**0.68 (0.56,0.82)**	**0.52 (0.43,0.63)**	**0.40 (0.21,0.74)**	**0.76 (0.67,0.85)**	**0.60 (0.42,0.87)**	**0.47 (0.37,0.59)**	**0.55 (0.42,0.73)**
0.97 (0.75,1.25)	**1.47 (1.22,1.78)**	pegylated_interferon_beta1a	0.77 (0.59,1.00)	0.58 (0.30,1.12)	1.11 (0.89,1.39)	0.89 (0.59,1.34)	**0.69 (0.51,0.93)**	0.82 (0.58,1.14)
1.27 (0.98,1.63)	**1.92 (1.59,2.32)**	**1.30 (1.00,1.70)**	natalizumab	0.76 (0.39,1.46)	**1.45 (1.16,1.81)**	1.15 (0.76,1.74)	0.90 (0.66,1.21)	1.06 (0.76,1.49)
1.67 (0.87,3.19)	**2.53 (1.35,4.73)**	1.72 (0.89,3.30)	1.32 (0.69,2.53)	mitoxantrone	**1.91 (1.01,3.61)**	1.52 (0.74,3.14)	1.18 (0.61,2.30)	1.40 (0.71,2.78)
0.87 (0.71,1.07)	**1.32 (1.18,1.49)**	0.90 (0.72,1.12)	**0.69 (0.55,0.86)**	**0.52 (0.28,0.99)**	interferon_beta1a_Avonex_Rebif	0.79 (0.56,1.13)	**0.62 (0.50,0.76)**	**0.73 (0.54,0.99)**
1.10 (0.73,1.64)	**1.67 (1.15,2.40)**	1.13 (0.75,1.71)	0.87 (0.57,1.31)	0.66 (0.32,1.36)	1.26 (0.89,1.78)	glatiramer_acetate	0.78 (0.59,1.03)	0.92 (0.58,1.46)
1.41 (1.06,1.88)	**2.14 (1.70,2.71)**	**1.45 (1.08,1.96)**	1.12 (0.83,1.51)	0.85 (0.43,1.65)	**1.62 (1.32,1.98)**	1.29 (0.97,1.71)	fingolimod	1.18 (0.82,1.70)
1.19 (0.86,1.65)	**1.81 (1.37,2.39)**	1.23 (0.88,1.72)	0.94 (0.67,1.32)	0.71 (0.36,1.42)	**1.37 (1.01,1.84)**	1.09 (0.69,1.72)	0.84 (0.59,1.21)	daclizumab

Low attrition bias

placebo_no treatment	**0.52 (0.43,0.63)**	**0.40 (0.21,0.74)**	1.65 (0.77,3.55)	0.69 (0.34,1.42)	**0.76 (0.68,0.85)**	**0.60 (0.47,0.79)**	**0.64 (0.55,0.75)**	**0.48 (0.40,0.58)**	0.91 (0.58,1.43)
1.93 (1.60,2.34)	natalizumab	0.76 (0.40,1.47)	**3.20 (1.46,7.02)**	1.34 (0.64,2.80)	**1.47 (1.18,1.83)**	1.17 (0.85,1.62)	1.24 (0.97,1.58)	0.93 (0.71,1.21)	**1.76 (1.08,2.87)**
2.53 (1.35,4.73)	1.31 (0.68,2.52)	mitoxantrone	**4.19 (1.56,11.24)**	1.75 (0.67,4.54)	**1.92 (1.02,3.63)**	1.53 (0.78,3.02)	1.63 (0.85,3.09)	1.21 (0.63,2.33)	**2.30 (1.06,4.99)**
0.60 (0.28,1.30)	**0.31 (0.14,0.69)**	**0.24 (0.09,0.64)**	interferon_beta_1a_1b	0.42 (0.15,1.19)	**0.46 (0.21,0.99)**	**0.37 (0.16,0.82)**	**0.39 (0.18,0.85)**	**0.29 (0.13,0.64)**	0.55 (0.30,1.02)
1.45 (0.70,2.97)	0.75 (0.36,1.57)	0.57 (0.22,1.48)	2.39 (0.84,6.84)	interferon_beta1b_Betaferon	1.10 (0.53,2.27)	0.88 (0.41,1.88)	0.93 (0.46,1.88)	0.69 (0.33,1.44)	1.32 (0.56,3.08)
1.32 (1.18,1.47)	**0.68 (0.55,0.85)**	**0.52 (0.28,0.98)**	**2.18 (1.01,4.71)**	0.91 (0.44,1.88)	interferon_beta1a_Avonex_Rebif	0.80 (0.60,1.06)	0.84 (0.71,1.01)	**0.63 (0.53,0.75)**	1.20 (0.75,1.91)
1.65 (1.27,2.15)	0.86 (0.62,1.18)	0.65 (0.33,1.29)	**2.73 (1.22,6.13)**	1.14 (0.53,2.46)	1.26 (0.95,1.67)	immunoglobulins	1.06 (0.78,1.44)	0.79 (0.57,1.10)	1.50 (0.89,2.54)
1.56 (1.34,1.81)	0.81 (0.63,1.03)	0.62 (0.32,1.17)	**2.58 (1.18,5.61)**	1.08 (0.53,2.18)	1.18 (0.99,1.41)	0.94 (0.70,1.27)	glatiramer_acetate	**0.75 (0.61,0.91)**	1.42 (0.88,2.28)
2.09 (1.73,2.52)	1.08 (0.83,1.41)	0.82 (0.43,1.58)	**3.45 (1.57,7.58)**	1.44 (0.69,3.00)	**1.59 (1.33,1.89)**	1.26 (0.91,1.74)	**1.34 (1.10,1.64)**	fingolimod	**1.90 (1.16,3.10)**
1.10 (0.70,1.73)	0.57 (0.35,0.93)	**0.43 (0.20,0.94)**	1.82 (0.98,3.36)	0.76 (0.32,1.78)	0.84 (0.52,1.33)	0.66 (0.39,1.12)	0.71 (0.44,1.14)	**0.53 (0.32,0.86)**	azathioprine

Relapse at 24 months

Low allocation bias

terifluno-mide	**0.70 (0.56,0.89)**	1.22 (0.96,1.54)	**0.68 (0.48,0.96)**	0.57 (0.31,1.05)	0.94 (0.67,1.32)	0.78 (0.49,1.23)	1.02 (0.74,1.41)	0.91 (0.59,1.39)	0.92 (0.65,1.31)	0.74 (0.55,1.00)	0.67 (0.46,0.99)
1.42 (1.13,1.80)	ponesi-mod	**1.73 (1.25,2.41)**	0.97 (0.64,1.46)	0.81 (0.42,1.57)	1.34 (0.89,2.03)	1.11 (0.67,1.85)	1.46 (0.98,2.16)	1.29 (0.79,2.10)	1.31 (0.86,2.00)	1.05 (0.72,1.54)	0.96 (0.61,1.51)
0.82 (0.65,1.04)	**0.58 (0.41,0.80)**	place-bo_notreat-ment	**0.56 (0.44,0.72)**	**0.47 (0.26,0.83)**	**0.78 (0.61,0.99)**	0.64 (0.43,0.95)	0.84 (0.67,1.05)	0.74 (0.52,1.07)	0.76 (0.58,0.99)	0.61 (0.51,0.73)	0.55 (0.41,0.75)
1.47 (1.04,2.07)	1.03 (0.68,1.56)	**1.79 (1.40,2.29)**	natalizum-ab	0.84 (0.45,1.56)	1.39 (0.98,1.96)	1.15 (0.72,1.82)	**1.50 (1.08,2.09)**	1.33 (0.86,2.06)	1.35 (0.94,1.94)	1.09 (0.80,1.48)	0.99 (0.67,1.47)
1.76 (0.95,3.25)	1.23 (0.64,2.38)	**2.14 (1.21,3.78)**	1.20 (0.64,2.22)	mitox-antrone	1.66 (0.89,3.08)	1.37 (0.69,2.74)	1.80 (0.98,3.30)	1.59 (0.81,3.12)	1.62 (0.86,3.03)	1.30 (0.72,2.37)	1.18 (0.62,2.26)
1.06 (0.76,1.49)	0.74 (0.49,1.12)	**1.29 (1.01,1.65)**	0.72 (0.51,1.02)	0.60 (0.32,1.12)	laquini-mod	0.83 (0.52,1.31)	1.08 (0.78,1.50)	0.96 (0.62,1.48)	0.98 (0.68,1.40)	0.78 (0.58,1.06)	0.71 (0.48,1.06)
1.28 (0.81,2.02)	0.90 (0.54,1.50)	**1.56 (1.05,2.31)**	0.87 (0.55,1.39)	0.73 (0.37,1.46)	1.21 (0.76,1.92)	interfer-on_be-ta1b_Betafer-on	1.31 (0.95,1.81)	1.16 (0.68,1.98)	1.18 (0.74,1.89)	0.95 (0.62,1.46)	0.86 (0.58,1.28)
0.98 (0.71,1.35)	0.69 (0.46,1.02)	1.19 (0.96,1.48)	**0.67 (0.48,0.93)**	0.56 (0.30,1.03)	0.92 (0.66,1.28)	0.76 (0.55,1.06)	interfer-on_be-ta1a_Avonex_Rebif	0.89 (0.58,1.35)	0.90 (0.64,1.27)	0.72 (0.54,0.96)	0.66 (0.53,0.82)
1.10 (0.72,1.70)	0.78 (0.48,1.26)	1.34 (0.94,1.92)	0.75 (0.49,1.16)	0.63 (0.32,1.23)	1.04 (0.67,1.61)	0.86 (0.51,1.47)	1.13 (0.74,1.72)	im-munoglob-ulins	1.02 (0.65,1.59)	0.82 (0.55,1.22)	0.74 (0.46,1.20)
1.08 (0.76,1.54)	0.76 (0.50,1.16)	**1.32 (1.01,1.72)**	0.74 (0.51,1.06)	0.62 (0.33,1.16)	1.02 (0.71,1.47)	0.85 (0.53,1.36)	1.11 (0.79,1.56)	0.98 (0.63,1.54)	glati-ramer_ac-etate	0.80 (0.62,1.05)	0.73 (0.49,1.10)
1.35 (1.00,1.82)	0.95 (0.65,1.38)	**1.64 (1.37,1.97)**	0.92 (0.68,1.25)	0.77 (0.42,1.40)	1.27 (0.94,1.73)	1.05 (0.68,1.62)	**1.38 (1.04,1.84)**	1.22 (0.82,1.83)	1.24 (0.96,1.62)	dimethyl-fumarate	0.91 (0.63,1.31)
1.48 (1.01,2.19)	1.04 (0.66,1.64)	**1.81 (1.32,2.46)**	1.01 (0.68,1.50)	0.84 (0.44,1.61)	1.40 (0.94,2.08)	1.16 (0.78,1.71)	**1.52 (1.22,1.89)**	1.34 (0.84,2.16)	1.37 (0.91,2.05)	1.10 (0.77,1.58)	alem-tuzumab

Low attrition bias

placebo_no treatment	**0.47 (0.27,0.80)**	**0.56 (0.48,0.65)**	0.90 (0.77,1.06)	0.90 (0.74,1.10)	**0.83 (0.77,0.90)**	**0.73 (0.59,0.89)**	0.88 (0.75,1.03)	0.53 (0.44,0.63)	0.77 (0.51,1.17)
2.14 (1.25,3.64)	natalizumab	1.20 (0.69,2.08)	**1.93 (1.10,3.36)**	**1.92 (1.09,3.39)**	**1.78 (1.04,3.06)**	1.55 (0.87,2.75)	**1.88 (1.08,3.28)**	1.13 (0.65,1.98)	1.65 (0.84,3.25)
1.79 (1.55,2.07)	0.84 (0.48,1.45)	mitoxantrone	**1.61 (1.30,2.00)**	**1.61 (1.26,2.05)**	**1.49 (1.27,1.76)**	**1.30 (1.01,1.67)**	**1.58 (1.27,1.95)**	0.95 (0.75,1.19)	1.38 (0.89,2.15)
1.11 (0.94,1.30)	**0.52 (0.30,0.91)**	**0.62 (0.50,0.77)**	laquinimod	1.00 (0.77,1.29)	0.93 (0.79,1.09)	0.80 (0.62,1.05)	0.98 (0.78,1.22)	0.59 (0.46,0.74)	0.86 (0.55,1.34)
1.11 (0.91,1.36)	**0.52 (0.29,0.92)**	**0.62 (0.49,0.79)**	1.00 (0.78,1.29)	interferon_beta1b_Betaferon	0.93 (0.75,1.15)	0.81 (0.60,1.08)	0.98 (0.87,1.11)	0.59 (0.45,0.77)	0.86 (0.54,1.36)
1.20 (1.11,1.29)	**0.56 (0.33,0.96)**	**0.67 (0.57,0.79)**	1.08 (0.92,1.27)	1.08 (0.87,1.33)	interferon_beta1a_Avonex_Rebif	0.87 (0.70,1.09)	1.06 (0.89,1.26)	0.63 (0.52,0.77)	0.93 (0.61,1.41)
1.38 (1.12,1.70)	0.64 (0.36,1.14)	**0.77 (0.60,0.99)**	1.24 (0.95,1.62)	1.24 (0.93,1.65)	1.15 (0.92,1.44)	immunoglobulins	1.22 (0.94,1.58)	0.73 (0.56,0.96)	1.07 (0.67,1.70)
1.13 (0.97,1.33)	**0.53 (0.30,0.92)**	**0.63 (0.51,0.78)**	1.02 (0.82,1.28)	1.02 (0.90,1.15)	0.95 (0.80,1.13)	0.82 (0.63,1.07)	glatiramer_acetate	0.60 (0.47,0.76)	0.88 (0.56,1.37)
1.89 (1.59,2.25)	0.88 (0.50,1.55)	1.06 (0.84,1.33)	**1.70 (1.35,2.16)**	**1.70 (1.31,2.21)**	**1.58 (1.31,1.91)**	**1.37 (1.04,1.80)**	**1.67 (1.32,2.11)**	cladribine	1.46 (0.93,2.29)
1.29 (0.85,1.96)	0.60 (0.31,1.19)	0.72 (0.47,1.12)	1.17 (0.75,1.82)	1.16 (0.73,1.84)	1.08 (0.71,1.64)	0.94 (0.59,1.49)	1.14 (0.73,1.78)	0.68 (0.44,1.07)	azathioprine

Disability at 24 months

Low allocation bias

teriflunomide	0.82 (0.57,1.19)	**1.31 (1.05,1.63)**	**0.71 (0.54,0.93)**	0.77 (0.56,1.07)	0.26 (0.06,1.10)	0.93 (0.64,1.35)	0.92 (0.46,1.86)	1.14 (0.79,1.66)	0.88 (0.67,1.17)
1.22 (0.84,1.77)	ponesimod	**1.60 (1.04,2.46)**	0.86 (0.54,1.37)	0.94 (0.57,1.55)	0.32 (0.07,1.41)	1.13 (0.67,1.92)	1.13 (0.51,2.49)	1.39 (0.82,2.36)	1.08 (0.68,1.72)
0.76 (0.61,0.95)	**0.63 (0.41,0.96)**	placebo_no treatment	**0.54 (0.38,0.77)**	**0.59 (0.46,0.75)**	**0.20 (0.05,0.83)**	**0.71 (0.52,0.96)**	0.71 (0.36,1.37)	0.87 (0.65,1.18)	**0.67 (0.57,0.80)**
1.41 (1.08,1.86)	1.16 (0.73,1.84)	**1.85 (1.30,2.63)**	ofatumumab	1.09 (0.71,1.68)	0.37 (0.08,1.59)	1.31 (0.82,2.09)	1.31 (0.62,2.77)	**1.61 (1.02,2.56)**	1.25 (0.84,1.85)
1.29 (0.93,1.80)	1.06 (0.65,1.74)	**1.69 (1.33,2.16)**	0.91 (0.60,1.40)	natalizumab	0.33 (0.08,1.43)	1.20 (0.81,1.77)	1.19 (0.59,2.43)	**1.48 (1.00,2.17)**	1.14 (0.84,1.54)
3.87 (0.91,16.43)	3.17 (0.71,14.12)	**5.06 (1.21,21.16)**	2.74 (0.63,11.93)	2.99 (0.70,12.76)	mitoxantrone	3.59 (0.83,15.49)	3.57 (0.74,17.31)	**4.42 (1.02,19.04)**	3.42 (0.81,14.43)
1.08 (0.74,1.57)	0.88 (0.52,1.50)	**1.41 (1.04,1.91)**	0.76 (0.48,1.21)	0.83 (0.56,1.23)	0.28 (0.06,1.20)	laquinimod	1.00 (0.48,2.07)	1.23 (0.80,1.89)	0.95 (0.67,1.35)
1.08 (0.54,2.18)	0.89 (0.40,1.96)	**1.42 (0.73,2.76)**	0.77 (0.36,1.62)	0.84 (0.41,1.70)	0.28 (0.06,1.36)	1.00 (0.48,2.09)	immunoglob-ulins	1.24 (0.60,2.57)	0.96 (0.48,1.90)
0.88 (0.60,1.27)	0.72 (0.42,1.21)	1.15 (0.85,1.55)	**0.62 (0.39,0.98)**	0.68 (0.46,1.00)	**0.23 (0.05,0.98)**	0.81 (0.53,1.25)	0.81 (0.39,1.68)	glati-ramer_ac-etate	0.77 (0.58,1.03)
1.13 (0.85,1.50)	0.93 (0.58,1.48)	**1.48 (1.24,1.77)**	0.80 (0.54,1.19)	0.88 (0.65,1.18)	0.29 (0.07,1.24)	1.05 (0.74,1.49)	1.05 (0.53,2.08)	1.29 (0.97,1.73)	dimethylfu-marate

Low attrition bias

placebo_no treatment	0.91 (0.54,1.55)	**0.59 (0.46,0.75)**	**0.20 (0.05,0.83)**	**0.61 (0.39,0.95)**	0.71 (0.46,1.11)	**0.71 (0.51,0.98)**	3.19 (0.31,33.21)	0.75 (0.41,1.37)	**0.66 (0.45,0.99)**	**0.72 (0.56,0.91)**	0.60 (0.22,1.63)
1.09 (0.65,1.85)	ocrelizum-ab	0.65 (0.36,1.15)	**0.22 (0.05,0.99)**	0.67 (0.36,1.23)	0.78 (0.39,1.55)	0.78 (0.51,1.17)	3.48 (0.32,38.47)	0.82 (0.37,1.83)	0.73 (0.38,1.40)	0.78 (0.44,1.39)	0.66 (0.21,2.03)
1.69 (1.33,2.16)	1.55 (0.87,2.76)	natalizum-ab	0.33 (0.08,1.43)	1.03 (0.63,1.71)	1.20 (0.72,2.00)	1.20 (0.80,1.80)	5.39 (0.51,56.95)	1.27 (0.66,2.44)	1.13 (0.71,1.79)	1.21 (0.86,1.71)	1.02 (0.37,2.85)
5.06 (1.21,21.16)	**4.63 (1.01,21.25)**	2.99 (0.70,12.76)	mitox-antrone	3.09 (0.69,13.80)	3.60 (0.81,16.10)	3.59 (0.83,15.57)	**16.13 (1.04,251.30)**	3.79 (0.80,17.92)	3.37 (0.76,14.84)	3.62 (0.85,15.45)	3.06 (0.54,17.45)
1.64 (1.06,2.53)	1.50 (0.81,2.77)	0.97 (0.59,1.59)	0.32 (0.07,1.44)	laquini-mod	1.16 (0.62,2.17)	1.16 (0.74,1.83)	5.21 (0.48,56.59)	1.23 (0.58,2.59)	1.09 (0.60,1.96)	1.17 (0.71,1.93)	0.99 (0.33,2.93)
1.41 (0.90,2.19)	1.29 (0.65,2.56)	0.83 (0.50,1.38)	0.28 (0.06,1.24)	0.86 (0.46,1.60)	interfer-on_be-ta1b_Betafer-on	1.00 (0.58,1.73)	4.48 (0.41,48.69)	1.05 (0.50,2.23)	0.93 (0.76,1.15)	1.01 (0.61,1.67)	0.85 (0.29,2.52)
1.41 (1.02,1.95)	1.29 (0.85,1.95)	0.83 (0.55,1.25)	0.28 (0.06,1.21)	0.86 (0.55,1.36)	1.00 (0.58,1.74)	interfer-on_be-ta1a_Avonex_Rebif	4.49 (0.42,47.84)	1.05 (0.53,2.10)	0.94 (0.56,1.56)	1.01 (0.67,1.51)	0.85 (0.30,2.42)
0.31 (0.03,3.27)	0.29 (0.03,3.17)	0.19 (0.02,1.96)	**0.06 (0.00,0.97)**	0.19 (0.02,2.08)	0.22 (0.02,2.43)	0.22 (0.02,2.37)	fingolimod	0.23 (0.02,2.65)	0.21 (0.02,2.25)	0.22 (0.02,2.37)	0.19 (0.02,1.58)
1.34 (0.73,2.45)	1.22 (0.55,2.73)	0.79 (0.41,1.52)	0.26 (0.06,1.25)	0.82 (0.39,1.72)	0.95 (0.45,2.02)	0.95 (0.48,1.89)	4.26 (0.38,47.93)	dimethyl-fumarate	0.89 (0.43,1.83)	0.96 (0.50,1.84)	0.81 (0.25,2.59)
1.50 (1.01,2.23)	1.38 (0.71,2.65)	0.89 (0.56,1.41)	0.30 (0.07,1.31)	0.92 (0.51,1.66)	1.07 (0.87,1.31)	1.07 (0.64,1.78)	4.79 (0.44,51.63)	1.13 (0.55,2.32)	cladribine	1.08 (0.68,1.71)	0.91 (0.31,2.65)
1.40 (1.10,1.78)	1.28 (0.72,2.28)	0.83 (0.59,1.17)	0.28 (0.06,1.18)	0.85 (0.52,1.41)	0.99 (0.60,1.65)	0.99 (0.66,1.49)	4.45 (0.42,47.01)	1.05 (0.54,2.01)	0.93 (0.58,1.48)	azathio-prine	0.84 (0.30,2.35)
1.66 (0.61,4.47)	1.51 (0.49,4.66)	0.98 (0.35,2.72)	0.33 (0.06,1.87)	1.01 (0.34,2.99)	1.18 (0.40,3.50)	1.17 (0.41,3.34)	5.27 (0.63,44.07)	1.24 (0.39,3.97)	1.10 (0.38,3.21)	1.18 (0.43,3.29)	alem-tuzumab

Number of patients who discontinued treatment due to adverse events

Low allocation bias

placebo_no treatment	0.67 (0.23,1.92)	**1.83 (1.09,3.07)**	**5.05 (1.87,13.66)**	0.82 (0.29,2.34)	2.00 (0.93,4.32)	1.63 (0.74,3.61)	1.21 (0.52,2.84)	1.56 (0.73,3.32)	**3.58 (1.34,9.59)**	6.06 (0.55,66.61)	3.00 (0.28,31.70)	1.14 (0.60,2.17)	1.56 (0.65,3.76)	1.26 (0.78,2.04)	2.19 (0.83,5.81)	**0.31 (0.11,0.88)**
1.49 (0.52,4.27)	pegylated_interferon_beta1a	2.73 (0.85,8.80)	**7.54 (1.77,32.04)**	1.23 (0.52,2.92)	2.99 (0.81,10.99)	2.44 (0.65,9.11)	1.81 (0.97,3.36)	2.33 (0.64,8.50)	**5.35 (1.27,22.59)**	9.04 (0.88,92.50)	4.48 (0.34,59.19)	1.70 (0.68,4.28)	2.32 (0.94,5.76)	1.89 (0.64,5.52)	**3.27 (1.37,7.82)**	0.46 (0.18,1.14)
0.55 (0.33,0.92)	0.37 (0.11,1.18)	ozanimod	**2.76 (1.18,6.46)**	0.45 (0.14,1.44)	1.10 (0.62,1.94)	0.89 (0.35,2.31)	0.66 (0.25,1.79)	0.85 (0.34,2.14)	1.96 (0.64,5.96)	3.31 (0.29,38.51)	1.64 (0.15,18.35)	0.62 (0.27,1.42)	0.85 (0.31,2.36)	0.69 (0.34,1.40)	1.20 (0.40,3.61)	**0.17 (0.05,0.55)**
0.20 (0.07,0.54)	**0.13 (0.03,0.56)**	**0.36 (0.15,0.85)**	ofatumumab	**0.16 (0.04,0.69)**	0.40 (0.14,1.10)	0.32 (0.09,1.16)	0.24 (0.06,0.89)	0.31 (0.09,1.08)	0.71 (0.18,2.88)	1.20 (0.09,16.08)	0.59 (0.05,7.68)	0.23 (0.07,0.74)	0.31 (0.08,1.16)	0.25 (0.08,0.76)	0.43 (0.11,1.75)	**0.06 (0.01,0.26)**
1.21 (0.43,3.45)	0.81 (0.34,1.94)	2.22 (0.69,7.11)	**6.13 (1.45,25.92)**	ocrelizumab	2.43 (0.67,8.89)	1.98 (0.53,7.36)	1.47 (0.80,2.70)	1.89 (0.52,6.87)	**4.35 (1.04,18.27)**	7.36 (0.72,75.00)	3.64 (0.28,48.00)	1.39 (0.56,3.45)	1.89 (0.77,4.64)	1.53 (0.53,4.45)	**2.66 (1.12,6.30)**	**0.37 (0.15,0.92)**
0.50 (0.23,1.08)	0.33 (0.09,1.23)	0.91 (0.52,1.61)	2.52 (0.91,7.01)	0.41 (0.11,1.50)	natalizumab	0.82 (0.27,2.46)	0.60 (0.19,1.90)	0.78 (0.26,2.29)	1.79 (0.51,6.24)	3.02 (0.24,37.49)	1.50 (0.13,17.89)	0.57 (0.21,1.55)	0.78 (0.24,2.50)	0.63 (0.26,1.56)	1.09 (0.32,3.78)	**0.15 (0.04,0.57)**
0.61 (0.28,1.35)	0.41 (0.11,1.53)	1.12 (0.43,2.89)	3.09 (0.87,11.04)	0.50 (0.14,1.87)	1.23 (0.41,3.70)	laquinimod	0.74 (0.23,2.38)	0.95 (0.32,2.86)	2.19 (0.62,7.77)	3.71 (0.30,46.35)	1.84 (0.15,22.11)	0.70 (0.25,1.94)	0.95 (0.29,3.12)	0.77 (0.31,1.96)	1.34 (0.38,4.72)	**0.19 (0.05,0.71)**
0.83 (0.35,1.93)	0.55 (0.30,1.03)	1.51 (0.56,4.08)	**4.17 (1.13,15.43)**	0.68 (0.37,1.25)	1.65 (0.53,5.20)	1.35 (0.42,4.32)	interferon_beta_1a_1b	1.29 (0.41,4.02)	2.96 (0.81,10.87)	5.00 (0.53,47.03)	2.48 (0.20,30.37)	0.94 (0.48,1.87)	1.29 (0.66,2.49)	1.04 (0.43,2.51)	1.81 (0.98,3.34)	**0.25 (0.13,0.49)**
0.64 (0.30,1.37)	0.43 (0.12,1.57)	1.17 (0.47,2.93)	3.24 (0.93,11.31)	0.53 (0.15,1.92)	1.28 (0.44,3.78)	1.05 (0.35,3.14)	0.78 (0.25,2.43)	interferon_beta1b_Betaferon	2.30 (0.66,7.96)	3.89 (0.31,48.01)	1.92 (0.16,22.89)	0.73 (0.27,1.98)	1.00 (0.31,3.19)	0.81 (0.33,1.99)	1.41 (0.41,4.83)	**0.20 (0.05,0.72)**
0.28 (0.10,0.75)	**0.19 (0.04,0.79)**	0.51 (0.17,1.55)	1.41 (0.35,5.71)	**0.23 (0.05,0.96)**	0.56 (0.16,1.95)	0.46 (0.13,1.61)	0.34 (0.09,1.24)	0.44 (0.13,1.51)	interferon	1.69 (0.13,22.57)	0.84 (0.07,10.77)	0.32 (0.10,1.03)	0.43 (0.12,1.63)	0.35 (0.12,1.05)	0.61 (0.15,2.44)	**0.09 (0.02,0.36)**

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										on_beta1a_Avonex_Rebif						
0.17 (0.02,1.82)	0.11 (0.01,1.13)	0.30 (0.03,3.50)	0.83 (0.06,11.17)	0.14 (0.01,1.39)	0.33 (0.03,4.10)	0.27 (0.02,3.37)	0.20 (0.02,1.88)	0.26 (0.02,3.18)	0.59 (0.04,7.90)	immunoglobulins	0.50 (0.02,14.30)	0.19 (0.02,1.96)	0.26 (0.02,2.66)	0.21 (0.02,2.32)	0.36 (0.04,3.70)	**0.05 (0.00,0.53)**
0.33 (0.03,3.52)	0.22 (0.02,2.95)	0.61 (0.05,6.81)	1.68 (0.13,21.75)	0.27 (0.02,3.62)	0.67 (0.06,7.97)	0.54 (0.05,6.55)	0.40 (0.03,4.95)	0.52 (0.04,6.18)	1.19 (0.09,15.37)	2.02 (0.07,58.28)	glatiramer_acetate	0.38 (0.03,4.38)	0.52 (0.04,6.43)	0.42 (0.04,4.67)	0.73 (0.06,9.37)	0.10 (0.01,1.36)
0.88 (0.46,1.66)	0.59 (0.23,1.47)	1.60 (0.70,3.65)	**4.42 (1.35,14.44)**	0.72 (0.29,1.80)	1.75 (0.64,4.77)	1.43 (0.52,3.97)	**1.06 (0.54,2.10)**	1.37 (0.51,3.68)	3.14 (0.97,10.16)	5.31 (0.51,55.25)	2.63 (0.23,30.25)	fingolimod	1.36 (0.70,2.65)	1.11 (0.58,2.11)	1.92 (0.80,4.60)	**0.27 (0.11,0.69)**
0.64 (0.27,1.55)	0.43 (0.17,1.07)	1.17 (0.42,3.25)	3.24 (0.86,12.23)	0.53 (0.22,1.30)	1.29 (0.40,4.14)	1.05 (0.32,3.43)	0.78 (0.40,1.51)	1.00 (0.31,3.20)	2.30 (0.61,8.62)	3.89 (0.38,40.26)	1.93 (0.16,23.86)	0.73 (0.38,1.42)	dimethylfumarate	0.81 (0.33,1.98)	1.41 (0.58,3.40)	**0.20 (0.08,0.50)**
0.79 (0.49,1.28)	0.53 (0.18,1.55)	1.45 (0.71,2.93)	**4.00 (1.32,12.06)**	0.65 (0.22,1.89)	1.59 (0.64,3.92)	1.29 (0.51,3.27)	0.96 (0.40,2.31)	1.23 (0.50,3.02)	2.84 (0.95,8.47)	4.79 (0.43,53.22)	2.37 (0.21,26.33)	0.90 (0.47,1.72)	1.23 (0.50,3.02)	daclizumab	1.74 (0.63,4.75)	**0.24 (0.08,0.72)**
0.46 (0.17,1.21)	**0.31 (0.13,0.73)**	0.83 (0.28,2.51)	2.30 (0.57,9.26)	**0.38 (0.16,0.89)**	0.91 (0.26,3.16)	0.74 (0.21,2.62)	0.55 (0.30,1.02)	0.71 (0.21,2.44)	1.63 (0.41,6.53)	2.76 (0.27,28.21)	1.37 (0.11,17.54)	0.52 (0.22,1.25)	0.71 (0.29,1.72)	0.58 (0.21,1.58)	azathioprine	**0.14 (0.06,0.35)**
3.25 (1.13,9.35)	2.18 (0.88,5.41)	**5.94 (1.83,19.26)**	**16.42 (4.85,70.07)**	**2.68 (1.09,6.59)**	**6.51 (1.76,24.05)**	**5.31 (1.42,19.92)**	**3.94 (2.02,7.67)**	**5.07 (1.38,18.60)**	**11.65 (2.75,49.38)**	**19.70 (3.90,204.13)**	9.75 (1.74,129.21)	**3.71 (1.45,9.47)**	**5.06 (2.00,12.84)**	**4.11 (1.39,12.10)**	**7.13 (2.86,17.76)**	alemtuzumab

Low attrition bias

placebo_notreatment	0.92 (0.47,1.83)	1.61 (0.94,2.77)	1.13 (0.62,2.08)	2.97 (0.28,31.41)	**3.44 (1.32,8.93)**	1.35 (0.81,2.27)	2.11 (0.39,11.45)	**3.22 (1.75,5.93)**	**2.76 (1.49,5.12)**	**2.25 (1.24,4.06)**	1.38 (0.49,3.86)	6.26 (0.70,56.07)
1.08 (0.55,2.15)	ozanimod	1.74 (0.73,4.15)	1.22 (0.59,2.54)	3.21 (0.28,37.44)	**3.72 (1.28,10.79)**	1.46 (0.93,2.30)	2.28 (0.37,14.15)	**3.49 (1.63,7.47)**	**2.98 (1.52,5.85)**	**2.43 (1.42,4.15)**	1.49 (0.43,5.14)	6.77 (0.68,67.31)
0.62 (0.36,1.07)	0.57 (0.24,1.37)	natalizumab	0.70 (0.31,1.58)	1.85 (0.16,20.75)	2.14 (0.73,6.26)	0.84 (0.40,1.77)	1.31 (0.22,7.74)	2.00 (0.90,4.48)	1.71 (0.76,3.87)	1.40 (0.63,3.10)	0.86 (0.27,2.74)	3.89 (0.41,37.22)
0.88 (0.48,1.62)	0.82 (0.39,1.70)	1.42 (0.63,3.20)	laquinimod	2.63 (0.23,29.99)	**3.04 (1.04,8.84)**	1.20 (0.67,2.13)	1.86 (0.31,11.25)	**2.85 (1.32,6.15)**	**2.44 (1.18,5.03)**	**1.99 (1.04,3.78)**	1.22 (0.37,4.03)	5.53 (0.57,53.84)
0.34 (0.03,3.56)	0.31 (0.03,3.63)	0.54 (0.05,6.09)	0.38 (0.03,4.35)	interferon_beta_1a_1b	1.16 (0.09,14.75)	0.46 (0.04,5.10)	0.71 (0.04,12.94)	1.09 (0.10,12.41)	0.93 (0.08,10.64)	0.76 (0.07,8.61)	0.47 (0.04,6.10)	2.11 (0.88,5.02)
0.29 (0.11,0.76)	**0.27 (0.09,0.78)**	0.47 (0.16,1.37)	**0.33 (0.11,0.96)**	0.86 (0.07,11.00)	interferon_beta1b_Betaferon	0.39 (0.15,1.03)	0.61 (0.09,4.28)	0.94 (0.44,2.00)	0.80 (0.32,1.99)	0.65 (0.24,1.79)	0.40 (0.10,1.63)	1.82 (0.17,19.89)
0.74 (0.44,1.24)	0.68 (0.44,1.07)	1.19 (0.56,2.50)	0.84 (0.47,1.48)	2.19 (0.20,24.52)	2.54 (0.97,6.67)	interferon_beta1a_Avonex_Rebif	1.56 (0.27,9.13)	**2.38 (1.29,4.41)**	**2.04 (1.24,3.36)**	**1.66 (1.24,2.22)**	1.02 (0.32,3.22)	4.62 (0.49,43.96)
0.47 (0.09,2.57)	0.44 (0.07,2.72)	0.76 (0.13,4.51)	0.54 (0.09,3.24)	1.41 (0.08,25.65)	1.63 (0.23,11.38)	0.64 (0.11,3.77)	immunoglobulins	1.53 (0.25,9.23)	1.31 (0.22,7.92)	1.07 (0.18,6.40)	0.66 (0.09,4.74)	2.97 (0.19,47.33)
0.31 (0.17,0.57)	**0.29 (0.13,0.61)**	0.50 (0.22,1.11)	**0.35 (0.16,0.76)**	0.92 (0.08,10.53)	1.07 (0.50,2.28)	**0.42 (0.23,0.78)**	0.65 (0.11,3.95)	glatiramer_acetate	0.86 (0.52,1.42)	0.70 (0.35,1.38)	0.43 (0.13,1.42)	1.94 (0.20,18.90)
0.36 (0.20,0.67)	**0.34 (0.17,0.66)**	0.58 (0.26,1.32)	**0.41 (0.20,0.85)**	1.08 (0.09,12.33)	1.25 (0.50,3.09)	**0.49 (0.30,0.81)**	0.76 (0.13,4.63)	1.17 (0.70,1.94)	fingolimod	0.81 (0.46,1.45)	0.50 (0.15,1.66)	2.27 (0.23,22.14)
0.45 (0.25,0.81)	**0.41 (0.24,0.70)**	0.72 (0.32,1.59)	**0.50 (0.26,0.96)**	1.32 (0.12,15.05)	1.53 (0.56,4.20)	**0.60 (0.45,0.81)**	0.94 (0.16,5.64)	1.44 (0.73,2.84)	1.23 (0.69,2.19)	daclizumab	0.62 (0.19,2.02)	2.79 (0.29,27.01)
0.72 (0.26,2.02)	0.67 (0.19,2.30)	1.16 (0.36,3.72)	0.82 (0.25,2.70)	2.15 (0.16,28.14)	2.49 (0.61,10.11)	0.98 (0.31,3.10)	1.53 (0.21,11.04)	2.33 (0.71,7.70)	2.00 (0.60,6.62)	1.62 (0.50,5.32)	cladribine	4.53 (0.40,50.99)

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0.16 (0.02,1.43)	0.15 (0.01,1.47)	0.26 (0.03,2.46)	0.18 (0.02,1.76)	0.47 (0.20,1.13)	0.55 (0.05,6.01)	0.22 (0.02,2.06)	0.34 (0.02,5.37)	0.52 (0.05,5.02)	0.44 (0.05,4.30)	0.36 (0.04,3.48)	0.22 (0.02,2.49)	azathio-prine

Number of patients with any serious adverse events

Low allocation bias

teri-fluno-mid	1.07 (0.67,1.72)	0.87 (0.64,1.17)	0.93 (0.50,1.74)	1.31 (0.62,2.75)	1.31 (0.92,1.87)	0.88 (0.43,1.81)	1.05 (0.60,1.83)	0.77 (0.01,41.00)	1.02 (0.60,1.74)	1.07 (0.58,1.95)	0.71 (0.41,1.25)	0.57 (0.30,1.10)	0.87 (0.54,1.39)	1.70 (0.92,3.17)	1.34 (0.67,2.67)
0.93 (0.58,1.49)	pones-imod	0.80 (0.46,1.41)	0.87 (0.40,1.89)	1.22 (0.51,2.92)	1.22 (0.68,2.19)	0.82 (0.35,1.94)	0.98 (0.47,2.02)	0.72 (0.01,39.21)	0.95 (0.47,1.93)	0.99 (0.46,2.13)	0.66 (0.32,1.38)	0.53 (0.24,1.19)	0.81 (0.42,1.57)	1.59 (0.73,3.45)	1.24 (0.54,2.87)
1.16 (0.85,1.56)	1.24 (0.71,2.17)	place-bo_no treat-ment	1.08 (0.63,1.86)	1.51 (0.77,2.98)	1.52 (0.95,2.41)	1.02 (0.53,1.96)	1.21 (0.76,1.94)	0.89 (0.02,46.85)	1.18 (0.77,1.83)	1.23 (0.73,2.08)	0.83 (0.52,1.32)	0.66 (0.37,1.18)	1.00 (0.70,1.43)	**1.97 (1.15,3.39)**	1.54 (0.83,2.88)
1.07 (0.58,2.00)	1.15 (0.53,2.51)	0.93 (0.54,1.60)	pegylat-ed_in-terfer-on_be-ta1a	1.40 (0.59,3.34)	1.41 (0.69,2.87)	0.94 (0.40,2.21)	1.13 (0.55,2.31)	0.83 (0.02,45.11)	1.10 (0.55,2.20)	1.14 (0.54,2.43)	0.77 (0.37,1.57)	0.61 (0.28,1.35)	0.93 (0.49,1.78)	1.83 (0.85,3.94)	1.43 (0.63,3.28)
0.76 (0.36,1.61)	0.82 (0.34,1.98)	0.66 (0.34,1.30)	0.71 (0.30,1.70)	ozani-mod	1.00 (0.44,2.28)	0.67 (0.38,1.21)	0.80 (0.35,1.83)	0.59 (0.01,32.84)	0.78 (0.35,1.75)	0.81 (0.53,1.25)	**0.55 (0.30,0.98)**	**0.44 (0.25,0.76)**	0.66 (0.33,1.34)	1.30 (0.74,2.28)	1.02 (0.59,1.76)
0.76 (0.54,1.09)	0.82 (0.46,1.47)	0.66 (0.41,1.05)	0.71 (0.35,1.45)	1.00 (0.44,2.27)	ofatu-mum-ab	0.67 (0.30,1.50)	0.80 (0.41,1.55)	0.59 (0.01,31.76)	0.78 (0.41,1.48)	0.81 (0.40,1.64)	0.54 (0.28,1.06)	**0.44 (0.21,0.92)**	0.66 (0.37,1.19)	1.30 (0.64,2.65)	1.02 (0.47,2.22)
1.14 (0.55,2.34)	1.22 (0.52,2.89)	0.98 (0.51,1.90)	1.06 (0.45,2.49)	1.49 (0.83,2.66)	1.49 (0.67,3.33)	ocre-lizum-ab	1.19 (0.53,2.67)	0.88 (0.02,48.61)	1.16 (0.53,2.56)	1.21 (0.81,1.80)	0.81 (0.46,1.42)	0.65 (0.38,1.11)	0.99 (0.50,1.96)	**1.94 (1.15,3.27)**	1.52 (0.90,2.55)
0.95 (0.55,1.67)	1.02 (0.49,2.12)	0.82 (0.52,1.32)	0.89 (0.43,1.82)	1.25 (0.55,2.84)	1.25 (0.65,2.42)	0.84 (0.37,1.88)	natal-izumab	0.73 (0.01,39.71)	0.98 (0.51,1.85)	1.02 (0.50,2.05)	0.68 (0.35,1.32)	0.54 (0.26,1.15)	0.83 (0.46,1.49)	1.62 (0.79,3.33)	1.27 (0.58,2.78)
1.30 (0.02,69.03)	1.39 (0.03,76.27)	1.12 (0.02,59.03)	1.21 (0.02,66.03)	1.70 (0.03,94.49)	1.70 (0.03,91.95)	1.14 (0.02,63.41)	1.36 (0.03,73.61)	mitox-antrone	1.33 (0.02,71.58)	1.38 (0.03,75.25)	0.93 (0.02,50.11)	0.74 (0.01,40.61)	1.13 (0.02,60.19)	2.21 (0.04,120.64)	1.73 (0.03,95.71)
0.98 (0.57,1.66)	1.05 (0.52,2.13)	0.84 (0.55,1.31)	0.91 (0.45,1.83)	1.28 (0.57,2.86)	1.28 (0.68,2.42)	0.86 (0.39,1.89)	1.02 (0.54,1.94)	0.75 (0.01,40.53)	laquin-imod	1.04 (0.53,2.06)	0.70 (0.37,1.33)	0.56 (0.27,1.15)	0.85 (0.48,1.49)	1.66 (0.83,3.34)	1.30 (0.61,2.79)
0.94 (0.51,1.72)	1.01 (0.47,2.17)	0.81 (0.48,1.37)	0.88 (0.41,1.86)	1.23 (0.80,1.89)	1.23 (0.61,2.48)	0.83 (0.56,1.23)	0.99 (0.49,1.99)	0.72 (0.01,39.40)	0.96 (0.49,1.90)	interfer-on_be-ta1a_Avonex_Rebif	0.67 (0.45,1.00)	**0.54 (0.37,0.77)**	0.81 (0.47,1.43)	**1.60 (1.14,2.25)**	1.25 (0.89,1.76)

(Continued)

1.40 (0.80,2.45)	1.51 (0.73,3.12)	1.21 (0.76,1.94)	1.31 (0.64,2.68)	**1.83 (1.02,3.28)**	1.84 (0.95,3.56)	1.23 (0.70,2.16)	1.47 (0.76,2.86)	1.08 (0.02,58.37)	1.43 (0.75,2.73)	**1.49 (1.00,2.22)**	glatiramer_acetate	0.80 (0.52,1.23)	1.22 (0.75,1.97)	**2.39 (1.46,3.90)**	**1.87 (1.11,3.15)**
1.75 (0.91,3.37)	1.88 (0.84,4.21)	1.52 (0.85,2.71)	1.63 (0.74,3.62)	**2.29 (1.31,4.00)**	**2.30 (1.09,4.84)**	1.54 (0.90,2.64)	1.84 (0.87,3.88)	1.35 (0.02,74.11)	1.80 (0.87,3.71)	**1.87 (1.30,2.69)**	1.25 (0.82,1.92)	fingolimod	1.52 (0.83,2.79)	**2.99 (1.80,4.97)**	**2.34 (1.43,3.83)**
1.15 (0.72,1.84)	1.24 (0.64,2.40)	1.00 (0.70,1.43)	1.07 (0.56,2.06)	1.51 (0.74,3.05)	1.51 (0.84,2.72)	1.01 (0.51,2.01)	1.21 (0.67,2.18)	0.89 (0.02,47.45)	1.18 (0.67,2.07)	1.23 (0.70,2.15)	0.82 (0.51,1.33)	0.66 (0.36,1.20)	dimethylfumarate	**1.96 (1.09,3.54)**	1.54 (0.80,2.96)
0.59 (0.32,1.09)	0.63 (0.29,1.37)	**0.51 (0.30,0.87)**	0.55 (0.25,1.18)	0.77 (0.44,1.34)	0.77 (0.38,1.57)	**0.52 (0.31,0.87)**	0.62 (0.30,1.26)	0.45 (0.01,24.68)	0.60 (0.30,1.21)	**0.63 (0.44,0.88)**	**0.42 (0.26,0.68)**	**0.33 (0.20,0.56)**	**0.51 (0.28,0.92)**	daclizumab	0.78 (0.48,1.28)
0.75 (0.37,1.50)	0.80 (0.35,1.86)	0.65 (0.35,1.21)	0.70 (0.31,1.60)	0.98 (0.57,1.69)	0.98 (0.45,2.14)	0.66 (0.39,1.11)	0.79 (0.36,1.72)	0.58 (0.01,31.86)	0.77 (0.36,1.64)	0.80 (0.57,1.12)	**0.53 (0.32,0.90)**	**0.43 (0.26,0.70)**	0.65 (0.34,1.25)	1.28 (0.78,2.08)	alemtuzumab

Low attrition bias

placebo_no treatment	1.29 (0.51,3.26)	1.25 (0.60,2.61)	0.89 (0.02,48.87)	0.99 (0.46,2.16)	0.82 (0.33,1.99)	1.02 (0.51,2.04)	0.78 (0.39,1.55)	0.61 (0.28,1.34)	1.77 (0.67,4.64)	1.39 (0.65,2.96)
0.77 (0.31,1.94)	ozanimod	0.97 (0.30,3.11)	0.69 (0.01,41.91)	0.76 (0.28,2.08)	0.63 (0.20,1.98)	0.79 (0.43,1.45)	0.60 (0.23,1.62)	0.47 (0.20,1.12)	1.36 (0.55,3.38)	1.07 (0.32,3.53)
0.80 (0.38,1.66)	1.03 (0.32,3.32)	natalizumab	0.71 (0.01,41.67)	0.79 (0.27,2.29)	0.65 (0.21,1.98)	0.81 (0.30,2.21)	0.62 (0.24,1.65)	0.48 (0.17,1.39)	1.41 (0.42,4.71)	1.11 (0.39,3.17)
1.12 (0.02,61.57)	1.45 (0.02,88.53)	1.41 (0.02,82.45)	mitox-antrone	1.11 (0.02,65.72)	0.91 (0.02,55.35)	1.14 (0.02,66.63)	0.88 (0.02,51.06)	0.68 (0.01,40.36)	1.98 (0.03,122.01)	1.55 (0.03,91.59)
1.01 (0.46,2.20)	1.31 (0.48,3.56)	1.27 (0.44,3.66)	0.90 (0.02,53.17)	laquinimod	0.82 (0.27,2.51)	1.03 (0.46,2.28)	0.79 (0.30,2.06)	0.61 (0.24,1.58)	1.78 (0.63,5.06)	1.40 (0.47,4.15)
1.23 (0.50,2.99)	1.59 (0.50,5.00)	1.54 (0.50,4.68)	1.09 (0.02,66.11)	1.22 (0.40,3.71)	interfer-on_be-ta1b_Betafer-on	1.25 (0.47,3.33)	0.96 (0.53,1.75)	0.74 (0.30,1.85)	2.17 (0.66,7.11)	1.70 (0.53,5.48)
0.98 (0.49,1.96)	1.27 (0.69,2.33)	1.23 (0.45,3.34)	0.87 (0.02,50.85)	0.97 (0.44,2.15)	0.80 (0.30,2.13)	interfer-on_be-ta1a_Avonex_Rebif	0.77 (0.35,1.69)	0.59 (0.31,1.13)	1.73 (0.88,3.40)	1.36 (0.49,3.79)
1.28 (0.64,2.53)	1.65 (0.62,4.44)	1.60 (0.61,4.23)	1.14 (0.02,66.18)	1.27 (0.49,3.29)	1.04 (0.57,1.90)	1.30 (0.59,2.87)	glati-ramer_ac-etate	0.78 (0.39,1.55)	2.26 (0.80,6.38)	1.77 (0.64,4.92)
1.65 (0.75,3.63)	2.13 (0.89,5.12)	2.07 (0.72,5.94)	1.47 (0.02,87.01)	1.63 (0.63,4.21)	1.34 (0.54,3.35)	1.68 (0.88,3.20)	1.29 (0.64,2.58)	fingolimod	**2.91 (1.15,7.39)**	2.28 (0.76,6.83)
0.57 (0.22,1.49)	0.73 (0.30,1.82)	0.71 (0.21,2.37)	0.50 (0.01,31.04)	0.56 (0.20,1.59)	0.46 (0.14,1.51)	0.58 (0.29,1.13)	0.44 (0.16,1.25)	**0.34 (0.14,0.87)**	daclizumab	0.78 (0.23,2.68)
0.72 (0.34,1.54)	0.93 (0.28,3.09)	0.90 (0.32,2.60)	0.64 (0.01,37.89)	0.72 (0.24,2.12)	0.59 (0.18,1.90)	0.74 (0.26,2.06)	0.56 (0.20,1.57)	0.44 (0.15,1.31)	1.28 (0.37,4.36)	cladribine

WHAT'S NEW

Date	Event	Description
4 January 2024	New search has been performed	This is an update of a previously published Cochrane review, with an updated search performed on 8 August 2022.
4 January 2024	New citation required and conclusions have changed	We included an additional 16 studies in this update (including two studies previously excluded, three previously 'Ongoing', and 11 new studies). These 16 new studies included 13,401 participants. The results of this updated review will serve as the evidence base for guidance on the use of DMTs in people with RRMS;, for this reason, when we assessed the certainty of the NMA estimates with the GRADE approach, we used a fully contextualised approach. This involved predefining quantitative thresholds to determine the magnitude of each health effect (desirable or undesirable) measured by means of each outcome. In relation to the previous review, potentially relevant interventions have increased and thus the place in therapy of the drugs included in the previous review has changed in clinical practice. Our review findings and conclusions have considered an updated and larger list of interventions.

HISTORY

Protocol first published: Issue 11, 2014
Review first published: Issue 9, 2015

CONTRIBUTIONS OF AUTHORS

- Conception of the review: Francesco Nonino (FN), Silvia Minozzi (SM), Graziella Filippini (GF), Elisa Baldin (EB), Ben Ridley (BR)
- Design of the review: SM, Cinzia Del Giovane (CDG), FN, GF
- Co-ordination of the review: FN, BR, SM, Marien Gonzalez-Lorenzo (MGL)
- Search and selection of studies for inclusion in the review: FN, Irene Tramacere (IT), EB, Matteo Foschi (MF), BR, Guy Peryer (GP)
- Collection of data for the review: SM, MGL, BR, IT, FN
- Assessment of the risk of bias in the included studies: SM, MGL
- Analysis of data: CDG
- Assessment of the certainty in the body of evidence: SM, MGL
- Interpretation of data: FN, SM, MGL, CDG, EB, GP, BR, GF, MF, TP (Thomas Piggott)
- Writing the review: MGL, BR, SM, FN, EB, CDG, GF, GP, MF, TP
- Checking the review: MGL, BR, SM, FN, EB, CDG, GF, GP, MF, TP, MGL

All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

DECLARATIONS OF INTEREST

MGL: none known.

GF: no relevant interests; Joint Co-ordinating Editor of Cochrane Multiple Sclerosis and Rare Disease of the CNS (not involved in the editorial process of this review); involved with MAIN 2014 - Azathioprine versus beta interferons for relapsing-remitting multiple sclerosis: a multicentre randomized non-inferiority trial. PLoS One 2014;9(11):e113371. Funding: AIFA (Italian Medicines Agency)). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Trial Registration: EudraCT 2006-004937-13. This study was approved by ethics committees in the co-ordinating centre (Careggi University Hospital, Ethics Committee, Florence) and each of the participating centres (Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano; Clinica Neurologica, Novara; Universita ''La Sapienza'', Roma; Policlinico ''G. Rodolico'' Azienda Ospedaliero-Universitaria, Catania; Clinica Neurologica 2,

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CDG: Multiple Sclerosis International Federation (grant/contract).

BR: no relevant interests; Managing Editor of Cochrane Multiple Sclerosis and Rare Diseases of the CNS (not involved in the editorial process of this review).

FN: no relevant interests; epidemiologist and neurologist within the public Italian Health Service (at the IRCCS Istituto delle Scienze Neurologiche di Bologna); Co-ordinating Editor of Cochrane Multiple Sclerosis and Rare Disease of the CNS (not involved in the editorial process of this review).

SM: no relevant interests; Joint Co-ordinating Editor and Methods Editor of Cochrane Drugs and Alcohol.

GP: Bristol-Myers Squibb (consultation); Multiple Sclerosis International Federation (patient representative and consultant); Multiple Sclerosis Society (patient representative and consultant); National Institute for Health Research (patient representative); published 'Celani MG, Nonino F, Mahan K, Orso M, Ridley B, Baldin E, et al. Identifying unanswered questions and setting the agenda for future systematic research in Multiple Sclerosis. A worldwide, multi-stakeholder Priority Setting project. Mult Scler Relat Disord. 2022;60:103688'; 'Li V, Leurent B, Barkhof F, Braisher M, Cafferty F, Ciccarelli O, et al. Designing Multi-arm Multistage Adaptive Trials for Neuroprotection in Progressive Multiple Sclerosis. Neurology. 2022;98(18):754-764' and 'Alexander S, Peryer G, Gray E, Barkhof F, Chataway J. Wearable technologies to measure clinical outcomes in multiple sclerosis: A scoping review. Mult Scler. 2021;27(11):1643-1656'; volunteered for the UK MS Society; acted as a peer reviewer for Cochrane.

TP: Multiple Sclerosis International Federation (grant/contract).

MF: Novartis, Merck, (travel); published an opinion paper on dalfampridine - see Foschi M, Lugaresi A. Evaluating dalfampridine for the treatment of relapsing-remitting multiple sclerosis: does it add to the treatment armamentarium? Expert Opinion on Pharmacotherapy, 2019 Jun; Consultant Neurologist at S. Maria delle Croci Hospital of Ravenna, AUSL Romagna, Ravenna, Italy.

EB: no relevant interests; author of a manuscript on ponesimod for the treatment of relapsing multiple sclerosis; Neurologist IRCCS Istituto delle Scienze Neurologiche di Bologna; Affiliated Researcher of Cochrane Multiple Sclerosis and Rare Disease of the CNS (not involved in the editorial process of this review).

IT: none known

SOURCES OF SUPPORT

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- IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

  Salary provision

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- Multiple Sclerosis International Federation, MSIF, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the original review (Tramacere 2015) and this update:

The electronic search for the update did not include CINHAL, LILACS, or US FDA.

Study selection was conducted with the Rayyan platform (https://rayyan.ai/) in accordance with the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021).

A number of additional interventions were considered for inclusion: cladribine; cyclophosphamide; diroximel fumarate; fludarabine; interferon beta 1-a and beta 1-b; leflunomide; methotrexate; minocycline; mycophenolate mofetil; ofatumumab; ozanimod; ponesimod; rituximab; siponimod; steroids.

Inclusion criteria were amended to permit studies with mixed populations provided more than 80% of the sampled population was affected by relapsing forms of multiple sclerosis.

In this update, we did not include open-label studies and only considered studies with a follow-up of 12 months or longer.

We excluded the route of administration of treatments (oral, subcutaneous, intravenous) from the effect modifiers that were possible sources of inconsistency or heterogeneity, since it was not clinically expected.

We included two studies (Etemadifar 2006; Knobler 1993) that were excluded in Tramacere 2015 that, with further information, were found to meet inclusion criteria.

In this update, some studies excluded at full-text review included five that were previously included in Tramacere 2015 for insufficient follow-up duration (Comi 2001; Fazekas 2008; OWIMS 1999; TENERE 2014) and incorrect comparator (EVIDENCE 2007), as well as four included in Filippini 2013 for wrong intervention (SENTINEL 2006), wrong publication type (Ghezzi 1989) and mixed populations where < 80% were people with relapsing MS (British and Dutch 1988; Milanese 1993).

Treatment discontinuation due to adverse events is regarded as a primary safety outcome in this update, whereas it was classified as a primary acceptability outcome in the previous version.

In this update, evidence for both primary efficacy outcomes (relapses, disability worsening) and primary safety outcomes (treatment discontinuation, SAEs) were graded, compared to just primary efficacy outcomes in the previous version.

We considered serious adverse events (SAEs) as a primary, instead of secondary, outcome since the multi-stakeholder MEMP panel informing the selection and prioritisation of outcomes voted SAEs as of “critical” importance, according to the GRADE methodology (Guyatt 2011).

Among the secondary outcomes, we considered the following: cognitive decline, quality of life impairment, new or enlarging T2-weighted magnetic resonance imaging, new gadolinium-enhancing positive T1-weighted MRI lesions, and mortality. We decided to add such outcomes to this latest update because the multi-stakeholder MEMP panel informing the selection and prioritisation of outcomes voted them as of “critical” importance, according to the GRADE methodology (Guyatt 2011), and because new evidence on them has been accumulating since the publication of the previous review.

Regarding the risk of bias assessment, we deleted some comments in the 'Other bias' section, as we judged that they were not relevant for the risk of bias evaluation of the outcomes considered in the review. We did not measure an overall risk of bias as it was not necessary to assess the certainty of evidence following the approach suggested by the GRADE working group. We did not express a judgement of risk of bias related to the method associated with the monitoring and reporting of adverse events.

The certainty of the evidence for this NMA was assessed using a fully contextualised approach. A fully contextualised approach is important in an NMA to incorporate the value of individual outcomes in the overall interpretation of the results (Schünemann 2022b). This involved predefining quantitative thresholds to determine the magnitude of each health effect (desirable or undesirable) measured by means of each outcome.

We did not consider the definition of relapse as lasting 48 hours rather than 24 hours as a potential effect modifier and source of inconsistency or heterogeneity and, therefore, we did not perform a subanalysis based on such a distinction. We made such a decision because most of the studies included in the review adopted the 24-hour criterion and because the latest 2017 revision of the McDonald diagnostic criteria for the diagnosis of MS, widely used in research and clinical practice and published after the previous review, recommend considering a duration of at least 24 hours in the definition of relapse (Thompson 2018).

We did not consider the pre-trial relapse rate and the number of years over which the pre-trial relapse rate was calculated as an effect modifier and a potential source of inconsistency or heterogeneity and, therefore, we did not perform a subanalysis based on such a distinction. We made such a decision because relapse rate may be dependent on other patient-specific factors, such as age at onset and time from onset (Tremlett 2008) and because, in clinical practice, a low relapse rate *per se*, without MRI data, is not a sufficient criterion to decide to start treatment with DMTs (e.g. in a person with RRMS and no relapse in the previous 2 years, MRI data may be enough to establish disease activity and foster treatment with DMTs) (Thompson 2018). Moreover, clinical characteristics of relapse, in terms of topography, functional impairment, and relation to previous relapses, may be important in treatment decisions (Van Wijmeersch 2022).

We did not perform sensitivity analysis excluding studies that did not provide complete and clear reporting of dropout data because this issue has already been captured in the evaluation of risk of bias of attrition bias, for which we performed sensitivity analysis.

Finally, in the previous NMA, the relative effects of treatments were not affected by any of the hypothesised effect modifiers (Tramacere 2015).

INDEX TERMS

Medical Subject Headings (MeSH)

Immunologic Factors [*therapeutic use]; Immunosuppressive Agents [*therapeutic use]; Multiple Sclerosis, Relapsing-Remitting [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans