Disease-modifying Drugs for Multiple Sclerosis

Systematic Review

May 2020

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Executive Summary

Background

Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system.[1] In 2017, nearly 1 million adults were estimated to be living with MS in the United States.[2] Evidence suggests that the prevalence of MS has been increasing over the past 5 decades and that occurrence of this disease is higher in women than in men.[2] MS typically presents in early adulthood, with patients experiencing 1 or more clinically distinct episodes of neurological dysfunction that partially resolve.[3]

MS occurs when the body's immune system attacks the fatty tissue myelin, which surrounds and insulates neurons and allows for efficient transmission of nerve impulses.[4] In MS, this abnormal immune response causes the degradation of myelin, leading to neurologic dysfunction.[4] Symptoms of MS include sensory issues such as numbness, muscle weakness or spasms, vision problems, dizziness, and trouble walking or speaking.[5] The pattern and course of MS is categorized by 4 clinical subtypes of MS and the initial event, which are detailed in Table 1.

Table 1. Clinical Subtypes of MS

Clinical Subtype	Definition
Clinically Isolated Syndrome (CIS)	First attack of multiple sclerosis (MS)
Relapsing-remitting MS (RRMS)	Clearly defined attacks with full or incomplete recovery
Secondary Progressive MS (SPMS)	Progressive worsening from relapsing-remitting MS; with or without occasional relapses, minor remissions, and plateaus in severity
Primary Progressive MS (PPMS)	Progressive accumulation of disability from disease onset with occasional plateaus in severity, temporary minor improvements, or acute relapses
Progressive Relapsing MS (PRMS)	An older term, that has now been superseded. People who were previously diagnosed with progressive-relapsing MS would now be considered primary progressive: **active** (at the time of relapses or new MRI lesions) or **not active**.

Sources. Olek and Howard, 2019[3]; National MS Society, 2020.[6]

Approximately 85% to 90% of MS cases are of the relapsing-remitting type (RRMS) at onset, and the majority of cases eventually move into a secondary progressive MS (SPMS) phase, often over the course of decades.[3] However, 10% of patients have steadily progressing neurological disability independent of relapses; this is considered primary progressive MS (PPMS).[3]

Disease-modifying drugs for MS largely consist of treatments targeted to patients with relapsing forms of the disease, in an effort to reduce the progression of disease by preventing relapses and clinical exacerbations.[7,8] Disease-modifying drugs are also prescribed for people diagnosed with CIS, which is considered likely to progress to clinically definite MS, with the goal of delaying a second attack.[9] There are 10 FDA-approved therapies for all relapsing forms of MS, including CIS, RRMS, and active SPMS. There are an additional 2 therapies which are recommended for patients who have had an inadequate response to, or are unable to tolerate, other disease-modifying therapies; neither therapy is approved for patients with CIS.[10,11] There is 1 other

therapy FDA-approved for the relapsing forms of MS as well as PPMS; this therapy is the only one FDA-approved for PPMS.

Drug Effectiveness Review Project (DERP) participants are interested in an update of the prior report on disease-modifying drugs for MS[12], including new published evidence for all FDA-approved drugs (Table 2) and 1 pipeline drug.

PICOS and Key Questions

This report identifies comparative randomized controlled trials (RCTs), placebo-controlled trials for interventions without comparative RCTs, and cohort studies that evaluated the effectiveness and harms of FDA-approved disease-modifying therapies for the treatment of MS and CIS. Outcomes of interest are measures of relapse and disease progression, functional capacity, adverse events, serious adverse events, and other health outcome measures. This report also evaluated the effectiveness and harms (compared to placebo) of 1 selected pipeline MS therapy.

This review addresses 4 key questions:
1. What is the effectiveness of disease-modifying treatments for MS?

2. What is the effectiveness of disease-modifying treatments for patients with CIS?

3. Do disease-modifying treatments differ in harms by indication (MS or CIS)?

4. Do the effectiveness and harms vary by subgroup (e.g. patient characteristics, use of prior disease-modifying therapies for MS, subtype of MS, presence of comorbidities, antibody status)?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE and the Cochrane Library from January 1, 2016 up to October 15, 2019, and several other websites to identify eligible studies. For new drugs not included in the previous DERP reports, we searched from database inception. We also reran the Ovid MEDLINE search on February 3, 2020 to capture any studies published since our initial search in October 2019. We checked the included studies from the previous DERP reports[12-16] and from relevant systematic reviews published since the last update report[12] against our updated inclusion and exclusion criteria. We searched the ClinicalTrials.gov and the International Standard Randomised Controlled Trials Number (ISRCTN) registry for ongoing studies through March 31, 2020. We rated the methodological quality of eligible studies using standard instruments adapted from national and international quality standards.[17-21] We rated the quality of the body of evidence for each comparison and indication (MS and CIS) for major outcomes (i.e., relapse, disability progression, change in disability, persistence, and serious adverse events) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[22,23]

Key Findings

People with MS

Relapse

When compared directly, the following therapies were significantly more effective in reducing relapses than the active comparator:

- Alemtuzumab compared with interferon beta-1a (moderate quality of evidence [QoE]; meta-analysis of 3 RCTs)
- Fingolimod compared with interferon beta-1a (low QoE; 1 RCT), and although fingolimod compared with interferon beta-1b reduced relapse rates numerically, the statistical significance is not clear (low-QoE; 1 RCT)
- Glatiramer acetate in combination with interferon beta-1a compared with interferon beta-1a (low QoE; 1 RCT)
- Cladribine in combination with interferon beta, compared with interferon beta alone (moderate QoE; 1 RCT)
- Ocrelizumab compared with interferon beta-1a (low QoE; 3 RCTs)
- Ozanimod compared with interferon beta-1a (low QoE; 2 RCTs)
- Teriflunomide 7 mg compared with interferon beta-1a (low QoE; 1 RCT)

When compared directly, the following therapies were not significantly different for relapse:

- Dimethyl fumarate and glatiramer acetate (very low QoE; 1 RCT)
- Fingolimod and injectable disease-modifying therapies (low QoE; 1 RCT)
- Glatiramer acetate and interferon beta-1b (low QoE; 2 RCTs)
- Glatiramer acetate and interferon beta-1a (low QoE; 2 RCTs)
- Glatiramer acetate plus interferon beta-1a and glatiramer acetate (low QoE; 1 RCT)
- Interferon beta-1b and interferon beta-1a (very low QoE; meta-analysis of 3 RCTs)
- Teriflunomide 14 mg and interferon beta-1a (low QoE; 1 RCT)

When compared with placebo, the following therapies were significantly more effective in reducing relapse:

- Cladribine (low QoE; 1 RCT)
- Peginterferon beta-1a (low QoE; 1 RCT)
- Siponimod (moderate QoE; 2 RCTs)

When compared with placebo, ozanimod was not significantly different for relapse (low QoE; 1 RCT).

Different dosing schedules were not significantly different for relapse with:

- Dimethyl fumarate (low QoE; 2 RCTs)
- Interferon beta-1a (very low QoE; 3 RCTs)
- Peginterferon beta-1a (low QoE; 1 RCT)

Disability Progression

When compared directly, the following therapies were significantly more effective in reducing disability progression than the active comparator:

- Alemtuzumab compared with interferon beta-1a (low QoE; meta-analysis of 3 RCTs)
- Ocrelizumab compared with interferon beta-1a (low QoE; pooled analysis of 2 RCTs)

When compared directly, the following therapies were not significantly different in disability progression:

- Dimethyl fumarate and glatiramer acetate (very low QoE; 1 RCT)
- Fingolimod and interferon beta-1a (low QoE; 1 RCT)
- Fingolimod and interferon beta-1b (low QoE; 1 RCT)
- Glatiramer acetate and interferon beta-1a (very low QoE; 2 RCTs)
- Glatiramer acetate in combination with interferon beta-1a compared with interferon beta-1a or glatiramer acetate alone (low QoE; 1 RCT)
- Interferon beta-1b and interferon beta-1a (very low QoE; meta-analysis of 2 RCTs)
- Cladribine plus interferon beta and interferon beta alone (low QoE; 1 RCT)
- Ozanimod and interferon beta-1a (low QoE; 2 RCTs)

When compared with placebo, the following therapies were significantly more effective in reducing disability progression:

- Cladribine (low QoE; 1 RCT)
- Peginterferon beta-1a (moderate QoE; 1 RCT)
- Siponimod (low QoE; 1 RCT)

Different dosing schedules were not significantly different in disability progression with:

- Dimethyl fumarate 240 mg (low QoE; 2 RCTs)
- Interferon beta-1a (very low QoE; 1 RCT)
- Peginterferon beta-1a (low QoE; 1 RCT)

Change in Disability

When compared directly, alemtuzumab was significantly more effective in reducing disability, measured using the Expanded Disability Status Scale (EDSS), than interferon beta-1a; however, the differences were small and are unlikely to be clinically meaningful (low QoE; meta-analysis of 3 RCTs).

When compared directly, the following therapies were not significantly different in reducing disability, measured using the EDSS:

- Fingolimod and interferon beta-1b (low QoE; 1 RCT)
- Fingolimod and interferon beta-1a (low QoE; 1 RCT)
- Glatiramer acetate and interferon beta-1a (low QoE; 1 RCT)
- Interferon beta-1b and interferon beta-1a (moderate QoE; meta-analysis of 4 RCTs)

Different dosing schedules of interferon beta-1a were not significantly different in reducing disability, measured using the EDSS (moderate QoE; 2 RCTs),

Change in Function

When compared directly, the following therapies were significantly more effective in improving function, measured using the MS Functional Composite (MSFC), than the active comparator:

- Alemtuzumab compared with interferon beta-1a, but the clinical importance of the improvement is not clear (moderate QoE; meta-analysis of 2 RCTs)
- Ocrelizumab compared with interferon beta-1a, but the clinical importance of the difference is not clear (moderate QoE; meta-analysis of 2 RCTs)

- Ozanimod 0.5 mg compared with interferon beta-1a, but the clinical importance of the difference is not clear (very low QoE; 2 RCTs)

Interferon beta-1b compared with interferon beta-1a, improved function, as measured by the Paced Auditory Serial Addition Test (PASAT) component of the MSFC, but the clinical importance of the difference is not clear (very low QoE; 1 RCT)

When compared directly, the following therapies were not significantly different in improving function, measured using the MSFC:
- Fingolimod and interferon beta-1a (low QoE; 1 RCT)
- Glatiramer acetate and interferon beta-1a (low QoE; 1 RCT)
- Ozanimod 1 mg and interferon beta-1a (very low QoE; 2 RCTs)
- Glatiramer acetate in combination with interferon beta-1a and interferon beta-1a 30 μg or glatiramer acetate 20 mg alone (low QoE; 1 RCT)

When compared with placebo, siponimod was not significantly different in improving function, measured using the MSFC (very low QoE; 1 RCT).

Persistence

When compared directly, the following therapies were significantly more effective in improving persistence than the active comparator:
- Alemtuzumab compared with interferon beta-1a (low QoE; meta-analysis of 3 RCTs)
- Fingolimod compared with interferon beta-1b (moderate QoE; 1 RCT)
- Fingolimod compared with injectable disease-modifying therapies (low QoE; 1 RCT)
- Glatiramer compared with interferon beta-1a (low QoE; meta-analysis of 3 RCTs)
- Ocrelizumab compared with interferon beta-1a at 24 months, but not at 6 months (low QoE; meta-analysis of 3 RCTs)
- Teriflunomide 7 mg, compared with interferon beta-1a but the difference is only marginal for teriflunomide 14 mg (very low QoE; 1 RCT)

Glatiramer acetate in combination with interferon beta-reduced persistence compared with glatiramer acetate alone (low QoE; 1 RCT), but not compared with interferon beta-1a 30 μg alone (low QoE; 1 RCT). Cladribine in combination with interferon beta also reduced persistence compared with interferon beta alone (low QoE; 1 RCT)

When compared directly, the following therapies were not significantly different in disability progression:
- Dimethyl fumarate and glatiramer acetate (moderate QoE; 1 RCT)
- Fingolimod and interferon beta-1a (moderate QoE; 1 RCT)
- Glatiramer acetate and interferon beta-1b (moderate QoE; meta-analysis of 2 RCTs)
- Interferon beta-1b and interferon beta-1a (moderate QoE; meta-analysis of 4 RCTs)
- Ozanimod and interferon beta-1a (moderate QoE; meta-analysis of 2 RCTs)

When compared with placebo, cladribine increased persistence (moderate QoE; 1 RCT) and peginterferon beta-1a reduced persistence (moderate QoE; 1 RCT).

When compared with placebo, the following therapies were not significantly different in persistence:
- Ozanimod (moderate QoE; 1 RCT)
- Siponimod (low QoE; 2 RCTs)

Different dosing schedules were not significantly different for persistence with:
- Dimethyl fumarate (moderate QoE; 2 RCTs)
- Glatiramer acetate (moderate QoE; 2 RCTs)
- Interferon beta-1a (low QoE; 3 RCTs)
- Peginterferon beta-1a (moderate QoE; 1 RCT)

Serious Adverse Events

Fingolimod, compared with injectable disease-modifying therapies, significantly increased serious adverse events (low QoE; 1 RCT).

When compared directly, the following therapies were not significantly different for serious adverse events:
- Alemtuzumab and interferon beta-1a (very low QoE; meta-analysis of 3 RCTs)
- Dimethyl fumarate and glatiramer acetate (low QoE; 1 RCT)
- Fingolimod and interferon beta-1b (low QoE; 1 RCT)
- Fingolimod and interferon beta-1a (low QoE; 1 RCT)
- Glatiramer acetate and interferon beta-1b (low QoE; 1 RCT)
- Glatiramer acetate and interferon beta-1a (very low QoE; meta-analysis of 2 RCTs)
- Glatiramer acetate in combination with interferon beta-1a and interferon beta-1a or glatiramer acetate alone (low QoE; 1 RCT)
- Cladribine in combination with interferon beta and interferon beta alone (low QoE; 1 RCT)
- Ocrelizumab and interferon beta-1a (low QoE; meta-analysis of 3 RCTs)
- Ozanimod and interferon beta-1a (very low QoE; meta-analysis of 2 RCTs)
- Teriflunomide and interferon beta-1a (very low QoE; 1 RCT)

When compared with placebo, the following therapies were not significantly different in persistence:
- Cladribine (very low QoE; 1 RCT)
- Ozanimod (very low QoE; 1 RCT)
- Peginterferon beta-1a (low QoE; 1 RCT)
- Siponimod (very low QoE; 2 RCTs)

Different dosing schedules were not significantly different for serious adverse events with:
- Dimethyl fumarate (low QoE; 2 RCTs)
- Interferon beta-1a (low QoE; 1 RCT)
- Peginterferon beta-1a (low QoE; 1 RCT)

Serious adverse events varied by different dosing schedules of glatiramer acetate, but there was no clear association with dose (very low QoE; 2 RCTs).

People with CIS

Conversion to MS

When compared with placebo, the following therapies significantly reduced conversion to MS:
- Cladribine (moderate QoE; 1 RCT)
- Glatiramer acetate (moderate QoE; 1 RCT)
- Interferon beta-1b (moderate QoE; 1 RCT)
- Interferon beta-1a (low QoE; meta-analysis of 4 RCTs)
- Teriflunomide (low QoE; 1 RCT)

Different dosing schedules of interferon beta-1a did not differ significantly for conversion to MS (very low QoE; 1 RCT).

Progression in Disability

Teriflunomide and placebo did not differ significantly for disability progression (very low QoE; 1 RCT).

Change in Disability

Interferon beta-1a and placebo did not differ significantly for disability, as measured by the EDSS (low QoE; 1 RCT).

Teriflunomide compared with placebo significantly improved disability, as measured by the EDSS (low QoE; 1 RCT).

Change in Function

Teriflunomide and placebo did not differ significantly for function, as measured by the MSFC (low QoE; 1 RCT).

Persistence

When compared with placebo, cladribine significantly reduced persistence (low QoE; 1 RCT).

When compared with placebo, the following therapies were not significantly different in persistence:
- Glatiramer acetate (low QoE; 1 RCT)
- Interferon beta-1b (low QoE; 1 RCT)
- Interferon beta-1a (moderate QoE; 2 RCTs)
- Teriflunomide (low QoE; 1 RCT)

Different dosing schedules of interferon beta-1a did not differ significantly for persistence (moderate QoE; 1 RCT).

Serious Adverse Events

When compared with placebo, the following therapies were not significantly different for serious adverse events:
- Cladribine (low QoE; 1 RCT)
- Glatiramer acetate (low QoE; 1 RCT)
- Interferon beta-1b (very low QoE; 1 RCT)
- Interferon beta-1a (very low QoE; meta-analysis of 4 RCTs)

- Teriflunomide (low QoE; 1 RCT)

Different dosing schedules of interferon beta-1a did not differ significantly for persistence (low QoE; 1 RCT)

Conclusions

Overall, this update includes 42 RCTs and 30 observational studies. Evidence from the RCTs comprises:
- 11 head-to-head comparisons in MS evaluated in 23 RCTs
- 4 comparisons of different dosing schedules in MS evaluated in 9 RCTs
- 5 placebo-controlled comparisons in MS evaluated in 5 RCTs
- 1 comparison of different dosing schedules in CIS evaluated in 1 fair-methodological RCT
- 5 placebo-controlled comparisons in CIS evaluated in 8 RCTs

All the RCTs were assessed as being fair- or poor-methodological quality.

When comparing the disease-modifying therapies directly, alemtuzumab, fingolimod, ocrelizumab, and teriflunomide significantly reduce relapses and are not associated with increased serious adverse events compared with other disease-modifying therapies assessed in the eligible trials. However, we did not identify head-to-head trials for every possible comparison of the relevant interventions, so we are not able to state conclusively that other therapies are not any more or less effective overall.

The newer drugs with FDA approval, cladribine and siponimod, are significantly more effective than placebo for MS, although cladribine is highlighted as having some safety concerns with a black box warning related to malignancies and teratogenicity.[10] However, ozanimod 0.5 mg and 1 mg (currently not approved by the FDA) does not appear to be an effective treatment for MS.

The presence of neutralizing antibodies does not appear to be associated with a reduction in the effectiveness of treatment. Patient factors, such as age and prior treatment, may change the effectiveness of treatment, but subgroup analyses are not reported consistently across studies, limiting our ability to draw robust conclusions.

For CIS, each of the active therapies reviewed (cladribine, glatiramer acetate, interferon beta-1b, interferon beta-1b, and teriflunomide) significantly reduced conversion to MS compared with placebo and did not appear to be associated with more serious adverse events. As with therapies for MS, subgroup analyses are not reported consistently across studies, but there is some evidence that women may benefit more than men with glatiramer acetate and interferon beta-1a for CIS.

We did not identify any eligible RCTs comparing diroximel fumarate with placebo. The FDA approval in 2019 was based on bioavailability studies comparing oral dimethyl fumarate delayed release capsules to diroximel fumarate delayed-release capsules and 2 placebo-controlled trials of dimethyl fumarate.[24] Since FDA-approval, we found 1 ongoing study and 1 published RCT evaluating the efficacy and safety of diroximel fumarate; however, neither study met our inclusion criteria for this report.

Disease-modifying therapies do have adverse events and they differ in their safety profile. From the cohort studies, treatment discontinuations or switches appear to be significantly lower with fingolimod and dimethyl fumarate. The route of administration (oral or injectable) is also likely to affect patient adherence, and therefore clinical outcomes. However, the evidence is not consistent in which therapies are compared, limiting our ability to draw conclusions. Overall, the risk of specific adverse events is higher with some disease-modifying therapies:

- The risk of liver injury was higher for alemtuzumab, teriflunomide, and fingolimod.
- The risk of progressive multifocal leukoencephalopathy was higher with fingolimod and dimethyl fumarate.
- The risk of infection was lower with interferon beta and glatiramer acetate.

Disease-modifying therapies do not appear to be associated with an increased risk of cancer. However, the evidence is from only 1 retrospective study in a specific population, and may not be generalizable to the U.S. Medicaid population. Different dosing schedules are unlikely to show benefit in effectiveness and safety, based on the evidence reviewed in this report. In summary, the choice of disease-modifying therapy might depend on the values and preferences of the patient and the prescriber.

List of Brand Names and Generics

Table 2. Included Interventions by Date of FDA Approval

Generic Name	Brand Name	Dose, Route of Administration, Frequency	FDA Approval Date
FDA-approved Drugs			
Diroximel Fumarate	**Vumerity**	**462 mg orally twice daily (maintenance)**	**10/30/2019**
Cladribine	**Mavenclad**	**Cumulative dose of 3.5 mg/kg, orally in 2 treatment courses**	**3/29/2019**
Siponimod	**Mayzent**	**2 mg orally once daily (maintenance)** **1 mg orally once daily (maintenance) for patients with a CYP2C9*1/*3 or *2/*3 genotype**	**3/27/2019**
Ocrelizumab	Ocrevus	600 mg intravenous infusion every 6 months (maintenance)	3/28/2017
Glatiramer Acetate	Glatopa (branded generic)	20 mg subcutaneously daily 40 mg subcutaneously 3 times a week	4/16/2015
Peginterferon Beta-1a	Plegridy	125 µg subcutaneously every 14 days	8/15/2014
Dimethyl Fumarate	Tecfidera	240 mg orally twice daily (maintenance)	3/27/2013
Teriflunomide	Aubagio	7 mg or 14 mg orally once daily	9/12/2012
Fingolimod	Gilenya	0.5 mg orally once daily	9/21/2010
Interferon Beta-1a	Rebif	22 µg or 44 µg subcutaneously 3 times a week	3/7/2002
Alemtuzumab	Lemtrada	12 mg/day by intravenous infusion for 5 days, then 12 mg/day for 3 consecutive days 12 months after the first treatment course	5/7/2001
Glatiramer Acetate	Copaxone	20 mg subcutaneously daily 40 mg subcutaneously 3 times a week	12/20/1996
Interferon Beta-1a	Avonex	30 µg intramuscularly once a week	5/17/1996
Interferon Beta-1b	Betaseron Extavia	250 µg subcutaneously every other day	7/23/1993
Pipeline Drugs			
Ozanimod (RPC1063)	N/A	Oral	N/A

Note. Bold text indicates newly approved drugs for multiple sclerosis. Abbreviations. µg: microgram; FDA: U.S. Food and Drug Administration; kg: kilogram; mg: milligram; N/A: not applicable.

Background

Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system.[1] In 2017, nearly 1 million adults were estimated to be living with MS in the United States.[2] Evidence suggests that the prevalence of MS has been increasing over the past 5 decades and that the occurrence of this disease is higher in women than in men.[2] MS typically presents in early adulthood, with patients experiencing 1 or more clinically distinct episodes of neurological dysfunction that partially resolve.[3]

MS occurs when the body's immune system attacks the fatty tissue myelin, which surrounds and insulates neurons and allows for efficient transmission of nerve impulses.[4] In MS, this abnormal immune response causes the degradation of myelin, leading to neurologic dysfunction.[4] Symptoms of MS include sensory issues such as numbness, muscle weakness or spasms, vision problems, dizziness, and trouble walking or speaking.[5] The pattern and course of MS is categorized by 4 clinical subtypes of MS and the initial event, which are detailed in Table 3.

Table 3. Clinical Subtypes of MS

Clinical Subtype	Definition
Clinically Isolated Syndrome (CIS)	First attack of multiple sclerosis (MS)
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Approximately 85% to 90% of MS cases are of the relapsing-remitting type (RRMS) at onset, and the majority of cases eventually move into a secondary progressive MS (SPMS) phase, often over the course of decades.[3] However, 10% of patients have steadily progressing neurological disability independent of relapses, which is considered primary progressive MS (PPMS).[3]

Disease-modifying drugs for MS largely consist of treatments targeted to patients with relapsing forms of the disease, in an effort to reduce the progression of disease by preventing relapses and clinical exacerbations.[7,8] Disease-modifying drugs are also prescribed for people diagnosed with clinically isolated syndrome (CIS) that is considered likely to progress to clinically definite MS, with the goal of delaying a second attack.[9] There are 10 FDA-approved therapies for all relapsing forms of MS, including CIS, RRMS, and active SPMS. There are another 2 therapies recommended for patients who have had an inadequate response to, or are unable to tolerate, other disease-modifying therapies; neither of these therapies are approved for patients with CIS. There is also 1 therapy which is FDA-approved for the relapsing forms of MS and PPMS; this is the only therapy FDA-approved for PPMS.

Drug Effectiveness Review Project (DERP) participants are interested in an update of the prior report on disease-modifying drugs for MS,[12] including new published evidence for all FDA-approved drugs (Table 2) and 1 pipeline drug.

PICOS

Population

- Adult outpatients (age ≥ 18 years) with MS
  - RRMS
  - SPMS
  - PPMS
  - Progressive relapsing MS
- Adult outpatients with CIS (also known as a "first demyelinating event," the first clinical attack suggestive of MS, or monosymptomatic presentation)

Interventions

- Disease-modifying drugs with FDA approval for the treatment of MS and CIS, and select pipeline drugs likely to be approved soon (Table 2)

Comparators

- Another listed intervention (head-to-head comparison)
- Placebo (interventions that lack head-to-head comparisons, and for pipeline drugs)

Outcomes

- Health outcomes
  - Disability
  - Clinical exacerbation/relapse
  - Quality of life (QoL)
  - Functional outcomes (e.g., wheelchair use, time lost from work)
  - Persistence (discontinuation rates)
  - For CIS: progression to MS diagnosis
- Harms
  - Overall adverse events
  - Serious adverse events
  - Withdrawals due to adverse events
  - Specific adverse events (e.g., hepatotoxicity)

Study Designs

- Randomized controlled trials (RCTs)
  - ≥ 12 weeks study duration
- Placebo-controlled trials
  - ≥ 12 weeks study duration
  - For interventions that do not have head-to-head studies and pipeline drugs
- Retrospective and prospective cohort studies comparing an intervention type to another for outcomes on harms
  - ≥ 12 weeks study duration
  - Minimum total sample size of 1,000

Key Questions

1. What is the effectiveness of disease-modifying treatments for MS?

2. What is the effectiveness of disease-modifying treatments for patients with CIS?

3. Do disease-modifying treatments differ in harms by indication (MS or CIS)?

4. Do the effectiveness and harms vary by subgroup (e.g. patient characteristics, use of prior disease-modifying therapies for MS, subtype of MS, presence of comorbidities, antibody status)?

5. What are the characteristics of ongoing studies of disease-modifying treatments for MS?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, the Cochrane Library, and several other websites to identify eligible studies from January 1, 2016 through October 15, 2019. For new drugs not included in the previous DERP reports, we searched from database inception. We also reran the Ovid MEDLINE search on February 3, 2020 to capture any studies published since our initial search in October 2019. We checked the studies included in the previous DERP reports[12-16] and the 37 relevant systematic reviews[25-58] published since the last update report[12] against our updated inclusion and exclusion criteria. We searched the ClinicalTrials.gov and the International Standard Randomised Controlled Trials Number (ISRCTN) registry for ongoing studies through March 31, 2020. We rated the methodological quality of eligible studies using standard instruments adapted from national and international quality standards.[17-21] We calculated risk ratios where possible for persistence and serious adverse events, if these were not reported in the trial report, using Review Manager.[59] We also combined data in meta-analyses for major outcomes (i.e., relapse, disability progression, change in disability, persistence, and serious adverse events) using Review Manager.[59] We rated the quality of the body of evidence for each comparison and indication (MS and CIS) for major outcomes (i.e., relapse, disability progression, change in disability, persistence, and serious adverse events) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[22,23]

Findings

Overall, this update includes 42 RCTs and 30 observational studies (Figure 1). Evidence from the RCTs includes:
- 11 head-to-head comparisons in MS
- 4 comparisons of different dosing schedules in MS
- 5 placebo-controlled comparisons in MS
- 1 comparison of different dosing schedules in CIS
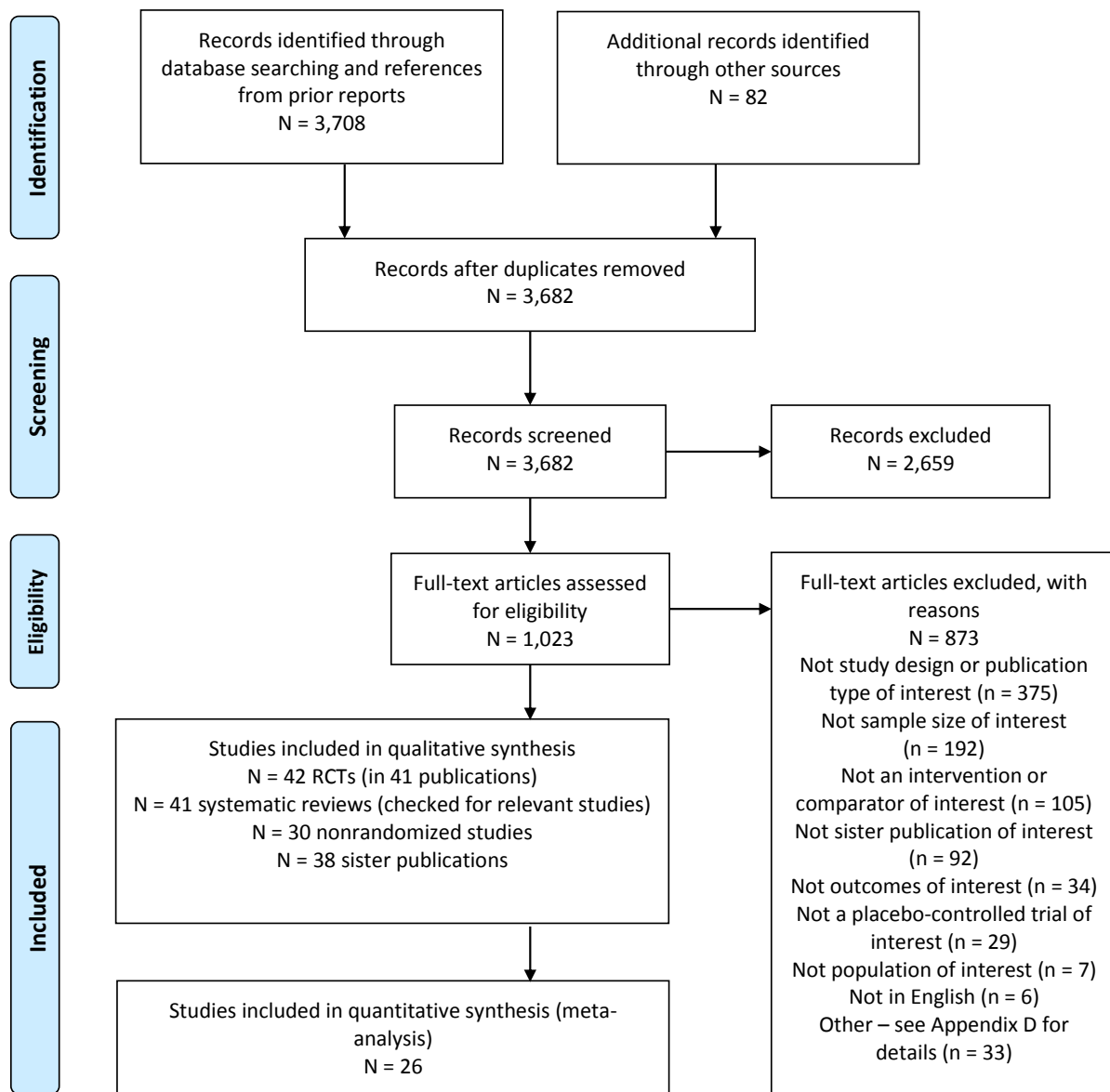- 5 placebo-controlled comparisons in CIS

Figure 1. PRISMA Diagram

Identification

| Records identified through database searching and references from prior reports N = 3,708 | Additional records identified through other sources N = 82 |

Records after duplicates removed
N = 3,682

Screening

Records screened
N = 3,682

Records excluded
N = 2,659

Eligibility

Full-text articles assessed for eligibility
N = 1,023

Full-text articles excluded, with reasons
N = 873
Not study design or publication type of interest (n = 375)
Not sample size of interest (n = 192)
Not an intervention or comparator of interest (n = 105)
Not sister publication of interest (n = 92)
Not outcomes of interest (n = 34)
Not a placebo-controlled trial of interest (n = 29)
Not population of interest (n = 7)
Not in English (n = 6)
Other – see Appendix D for details (n = 33)

Included

Studies included in qualitative synthesis
N = 42 RCTs (in 41 publications)
N = 41 systematic reviews (checked for relevant studies)
N = 30 nonrandomized studies
N = 38 sister publications

Studies included in quantitative synthesis (meta-analysis)
N = 26

For this update we included 14 new head-to-head or placebo-controlled RCTs (in 13 publications[60-71]) on the comparative effectiveness and harms of disease-modifying therapies for MS or CIS. We carried forward 28 RCTs[72-99] from the prior update report for a total of 42 RCTs in this update.

We also included 22 new cohort studies reported in 23 publications[100-122] providing comparative evidence of harms. We carried forward 8 cohort studies[123-130] from the prior update report for a total of 30 cohort studies in this update.

We also identified a further 38 publications[131-167] that reported on differences in effectiveness or harms by subgroup (Key Question 3), on extension studies or longer-term outcomes of the initial RCT, or on other outcomes of relevance. Appendix D provides the bibliography of studies identified in our search but that were excluded at full-text review stage.

Overview of Key Outcome Measures

The Canadian Agency for Drugs and Technologies in Health (CADTH) has produced a number of reports evaluating disease-modifying therapies for MS and CIS.[28-31,168-171] Some of the reports include an appendix summarizing the characteristics of the MS-related outcome measures, including validity, reliability, and the minimal important difference.[28-30,171] In this section, we have used information from the relevant CADTH reports to provide an overview of key outcome measures we use in this update report (Table 4).

Table 4. Overview of Key Outcome Measures

Measure	Description	Interpretation of Score	Evidence of Validity	Minimal Important Difference
EDSS	An ordinal scale that incorporates functional system grades as well as the degree of functional disability and ambulation	0 to 10 (in increments of 0.5); lower scores are better	Yes	• 1.0 point change when the score is between 0 and 5.5 • 0.5 point change when the score is between 5.4 to 8.5
MSFC	A composite score assessing different clinical dimensions: arm (9-HPT, time to insert and remove nine pegs), leg (T25FW), and cognition (PASAT, number of correct additions)	Transformed scores, with no defined range; increased scores are better	Yes	None defined

Source. Adapted from CADTH, 2018[30] and CADTH, 2018.[29] Abbreviations. 9-HPT: 9-hole peg test; CADTH: Canadian Agency for Drugs and Technologies in Health; EDSS: Expanded Disability Status Score; MSFC: Multiple Sclerosis Functional Composite; PASAT: Paced Auditory Serial Addition Test; T25FW: timed 25-foot walk.

Summary of Findings from RCTs for MS

Alemtuzumab 12 mg (milligram) vs. Interferon Beta-1a 44 µg (microgram)

- Alemtuzumab significantly reduced the proportion of relapses at 24 months (risk ratio [RR], 0.65; 95% confidence interval [CI], 0.48 to 0.88) and at 36 months (RR, 0.52; 95% CI, 0.34 to 0.80; moderate quality of evidence [QoE]; meta-analysis of 3 RCTs; Table 5)
- Alemtuzumab significantly reduced the proportion of disability progression at 24 months (RR, 0.73; 95% CI, 0.54 to 0.99) and at 36 months (RR, 0.33; 95% CI, 0.15 to 0.70; low QoE; meta-analysis of 3 RCTs; Table 5)
- Alemtuzumab significantly improved disability, as measured by the Expanded Disability Status Score (EDSS), at 36 months (mean difference, -0.07; 95% CI, -1.04 to -0.36), but not at 24 months (mean difference, -0.20; 95% CI, -0.60 to 0.20; low QoE; meta-analysis of 3 RCTs; Table 5). However, the differences were small and are unlikely to be clinically meaningful
- Alemtuzumab significantly improved function, as measured by the Multiple Sclerosis Functional Composite (MSFC), at 24 months (mean difference, 0.10; 95% CI, 0.05 to 0.16)

but the clinical importance of the improvement is not clear (moderate QoE; meta-analysis of 2 RCTs; Table 5)
- Alemtuzumab significantly increased persistence at 36 months (RR, 1.37; 95% CI, 1.15 to 1.63) but not at 24 months (RR, 1.16; 95% CI, 0.98 to 1.37; low QoE; meta-analysis of 3 RCTs; Table 5)
- No significant difference in serious adverse events at 24 months or 36 months (very low QoE; meta-analysis of 3 RCTs; Table 5)

Dimethyl Fumarate 240 mg vs. Glatiramer Acetate 20 mg
- No significant difference in relapse rates between dimethyl fumarate compared with glatiramer acetate (very low QoE; 1 RCT; Table 5)
- No significant difference in disability progression (very low QoE; 1 RCT; Table 6)
- No significant difference in persistence (moderate QoE; 1 RCT; Table 6)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 6)
- Changes in disability (EDSS) and function (MSFC) were not evaluated

Fingolimod 0.5 mg vs. Interferon Beta-1b 250 μg
- Fingolimod reduced relapse rates numerically, but the statistical significance is not clear (annualized relapse rate [ARR], 0.12 vs. 0.39; *P* value not reported; low QoE; 1 RCT; Table 7)
- No significant difference in disability as measured by the EDSS (mean increase of 0.12 vs. 0.19; *P* value not reported; low QoE; 1 RCT; Table 7). Differences are small and are unlikely to be clinically meaningful
- Fingolimod significantly increased persistence (RR, 1.56; 95% CI, 1.23 to 1.97; moderate QoE; 1 RCT; Table 7)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 7)
- Disability progression and changes in function (MSFC) were not evaluated

Fingolimod 0.5 mg vs. Interferon Beta-1a 30 μg
- Fingolimod significantly reduced relapse rates (ARR, 0.16 vs. 0.33; *P* < .001; low QoE; 1 RCT; Table 8)
- No significant difference in disability progression (low QoE; 1 RCT; Table 8)
- No significant difference in disability as measured by the EDSS (low QoE; 1 RCT; Table 8)
- No significant difference in function as measured by the MSFC (low QoE; 1 RCT; Table 8)
- No significant difference in persistence (moderate QoE; 1 RCT; Table 8)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 8)

Fingolimod 0.5 mg vs. Injectable Disease-modifying Therapies
- No significant difference in relapse (low QoE; 1 RCT; Table 9)
- Fingolimod significantly increased persistence (RR, 1.11; 95% CI, 1.04 to 1.18; low QoE; 1 RCT; Table 9)
- Fingolimod significantly increased serious adverse events (RR, 1.91; 95% CI, 1.04 to 3.51; low QoE; 1 RCT; Table 9)
- Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated

Glatiramer Acetate 20 mg vs. Interferon Beta-1b 250 µg

- No significant difference in relapse between glatiramer acetate and interferon beta-1b (low QoE; 2 RCTs; Table 10)
- No significant difference in disability progression (low QoE; 1 RCT; Table 10)
- No significant difference in persistence (moderate QoE; meta-analysis of 2 RCTs; Table 10)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 10)
- Changes in disability (EDSS) and function (MSFC) were not evaluated

Glatiramer Acetate 20 mg vs. Interferon Beta-1a 30 µg or 44 µg

- No significant difference in relapse between glatiramer acetate and interferon beta-1a at 24 or 36 months, although the proportion was numerically lower with glatiramer acetate at 36 months (20% vs. 26%; low QoE; 2 RCTs; Table 11)
- No significant difference in disability progression (very low QoE; 2 RCTs; Table 11)
- No significant difference in disability as measured by the EDSS (low QoE; 1 RCT; Table 11)
- No significant difference in function as measured by the MSFC (low QoE; 1 RCT; Table 11)
- Glatiramer acetate significantly increased persistence at 24 months (RR, 1.08; 95% CI, 1.02 to 1.15) and at 36 months (RR, 1.08; 95% CI, 1.01 to 1.16; low QoE; meta-analysis of 3 RCTs; Table 11)
- No significant difference in serious adverse events (very low QoE; meta-analysis of 2 RCTs; Table 11)

Interferon Beta-1b 250 µg vs. Interferon Beta-1a (different doses)

- No significant difference in relapse at 24 months (very low QoE; meta-analysis of 3 RCTs; Table 12)
- No significant difference in disability progression (very low QoE; meta-analysis of 2 RCTs; Table 12)
- No significant difference in disability, as measured by the EDSS, at 12 or 24 months (moderate QoE; meta-analysis of 4 RCTs; Table 12)
- Interferon beta-1b significantly increased the level of function (a difference between groups of 9.04), as measured by the Paced Auditory Serial Addition Test (PASAT) component of the MSFC, and the clinical importance of the difference is unclear (very low QoE; 1 RCT; Table 12)
- No significant difference in persistence at 24 months (moderate QoE; meta-analysis of 4 RCTs; Table 12)
- Serious adverse events were not evaluated

Ocrelizumab 600 mg vs. Interferon Beta-1a 30 µg or 44 µg

- Ocrelizumab significantly reduced relapse (ARR of 0.13 and 0.16 vs. 0.36 and 0.29; low QoE; 3 RCTs; Table 13)
- Ocrelizumab significantly reduced disability progression (hazard ratio [HR], 0.60; 95% CI, 0.45 to 0.81; low QoE; pooled analysis of 2 RCTs; Table 13)
- Ocrelizumab significantly improved functioning (mean difference, 0.07; 95% CI, 0.02 to 0.13), as measured by the MSFC, but the clinical importance of the difference is not clear (moderate QoE; meta-analysis of 2 RCTs; Table 13)

- Ocrelizumab significantly increased persistence at 24 months (RR, 1.10; 95% CI, 1.05 to 1.15), but not at 6 months (low QoE; meta-analysis of 3 RCTs; Table 13)
- No significant difference in serious adverse events (low QoE; meta-analysis of 3 RCTs; Table 13)
- Change in disability (EDSS) was not evaluated

Ozanimod 0.5 mg and 1 mg vs. Interferon Beta-1a 30 μg

- Ozanimod significantly reduced relapse (rate ratio, ozanimod 0.5 mg vs. interferon beta-1a, 0.69; 95% CI, 0.55 to 0.86; rate ratio, ozanimod 1 mg vs. interferon beta-1a, 0.52; 95% CI, 0.41 to 0.66; and RR, ozanimod 0.5 mg vs. interferon beta-1a, 0.79; 95% CI, 0.65 to 0.96; RR, ozanimod 1 mg vs. interferon beta-1a, 0.62; 95% CI, 0.51 to 0.77); low QoE; 2 RCTs; Table 14)
- No significant difference in disability progression (low QoE; 2 RCTs; Table 14)
- Ozanimod 0.5 mg significantly improved function as measured by the MSFC (mean difference interferon beta-1a, 0.10; 95% CI, 0.01 to 0.19), but no significant difference with ozanimod 1 mg. The clinical importance of the difference is not clear (very low QoE; 2 RCTs; Table 14)
- No significant difference in persistence (moderate QoE; meta-analysis of 2 RCTs; Table 14)
- No significant difference in serious adverse events (very low QoE; meta-analysis of 2 RCTs; Table 14)
- Change in disability (EDSS) was not evaluated

Teriflunomide 7 mg and 14 mg vs. Interferon Beta-1a

- Teriflunomide 7 mg significantly reduced relapse rates (ARR, 0.41 vs. 0.22; *P* = .03), but no significant differences with teriflunomide 14 mg (low QoE; 1 RCT; Table 15)
- Teriflunomide 7 mg significantly increased persistence (RR, 1.20; 95% CI, 1.02 to 1.40), but the difference is only marginal with teriflunomide 14 mg (RR, 1.17; 95% CI, 1.00 to 1.38; very low QoE; 1 RCT; Table 15)
- Teriflunomide 7 mg increased the number of serious adverse events but the difference is not significant (RR, 1.57; 95% CI, 0.64 to 3.84), and no significant differences with teriflunomide 14 mg (very low QoE; 1 RCT; Table 15)
- Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated

Cladribine 3.5 mg/kg (kilogram) vs. Placebo

- Cladribine significantly reduced relapse (ARR, 0.14 vs. 0.33; *P* < .001; low QoE; 1 RCT; Table 16)
- Cladribine significantly reduced disability progression (HR, 0.67; 95% CI, 0.48 to 0.93; low QoE; 1 RCT; Table 16)
- Cladribine significantly increased persistence (RR, 1.06; 95% CI, 1.01 to 1.11; moderate QoE; 1 RCT; Table 16)
- No significant difference in serious adverse events (very low QoE; 1 RCT; Table 16)
- Changes in disability (EDSS) and function (MSFC) were not evaluated

Cladribine 3.5 mg/kg Plus Continued Interferon Beta vs. Placebo Plus Continued Interferon Beta

- Cladribine plus interferon beta significantly reduced relapse (RR, 0.37; 95% CI 0.22 to 0.63) (moderate QoE; 1 RCT; Table 17)
- No significant difference in disability progression (low QoE; 1 RCT; Table 17)
- Cladribine plus interferon beta significantly reduced persistence (RR, 0.79; 95% CI, 0.66 to 0.96; low QoE; 1 RCT; Table 17)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 17)
- Changes in disability (EDSS) and function (MSFC) were not evaluated

Diroximel Fumarate vs. Placebo

We did not identify any eligible studies.

Ozanimod 0.5 mg and 1 mg vs. Placebo

- No significant difference in relapse with ozanimod (low QoE; 1 RCT; Table 18)
- No significant difference in persistence (moderate QoE; 1 RCT; Table 18)
- No significant difference in serious adverse events (very low QoE; 1 RCT; Table 18)
- Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated

Peginterferon Beta-1a 125 µg Every 2 Weeks vs. Placebo

- Peginterferon beta-1a significantly reduced relapse (ARR, 0.26 vs. 0.40; rate ratio, 0.64; 95% CI, 0.50 to 0.83; low QoE; 1 RCT; Table 19)
- Peginterferon beta-1a significantly reduced disability progression (HR, 0.62; 95% CI, 0.40 to 0.97; moderate QoE; 1 RCT; Table 19)
- Peginterferon beta-1a significantly reduced persistence (RR, 0.94; 95% CI, 0.90 to 0.98; moderate QoE; 1 RCT; Table 19)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 19)
- Changes in disability (EDSS) and function (MSFC) were not evaluated

Siponimod 2 mg vs. Placebo

- Siponimod significantly reduced relapse in RRMS (ARR ratio, 0.45; 95% CI, 0.34 to 0.59) and in SPMS (ARR, 0.20 vs. 0.58; *P* = .04) (moderate QoE; 2 RCTs; Table 20)
- Siponimod significantly reduced disability progression (HR, 0.79; 95% CI, 0.65 to 0.95; low QoE; 1 RCT; Table 20)
- No significant difference in function, as measured by the MSFC (very low QoE; 1 RCT; Table 20)
- No significant difference in persistence (low QoE; 2 RCTs; Table 20)
- No significant difference in serious adverse events (very low QoE; 2 RCTs; Table 20)
- Change in disability (EDSS) was not evaluated

Different Dosing Schedule for Dimethyl Fumarate

- No significant difference in relapse with dimethyl fumarate 240 mg twice a day (low QoE; 2 RCTs; Table 21)
- No significant difference in disability progression (low QoE; 2 RCTs; Table 21)
- No significant difference in persistence (moderate QoE; 2 RCTs; Table 21)

- No significant difference in serious adverse events (low QoE; 2 RCTs; Table 21)
- Changes in disability (EDSS) and function (MSFC) were not evaluated

Different Dosing Schedule for Glatiramer Acetate

- No significant difference in persistence with glatiramer acetate 40 mg (moderate QoE; 2 RCTs; Table 22)
- No clear association with serious adverse events (results were mixed; very low QoE; 2 RCTs; Table 22)
- Relapse, disability progression, and changes in disability (EDSS) and function (MSFC) were not evaluated

Different Dosing Schedule for Interferon Beta-1a

- No clear association with relapse for subcutaneous interferon beta-1a 44 µg 3 times a week (very low QoE; 3 RCTs; Table 23)
- No significant difference in disability progression (very low QoE; 1 RCT; Table 23)
- No significant difference in disability, as measured by the EDSS (moderate QoE; 2 RCTs; Table 23)
- No significant difference in persistence (low QoE; 3 RCTs; Table 23)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 23)
- Change in function (MSFC) was not evaluated

Different Dosing Schedule for Peginterferon Beta-1a

- No significant difference in relapse with peginterferon beta-1a 125 µg every 2 weeks (low QoE; 1 RCT; Table 24)
- No significant difference in disability progression (low QoE; 1 RCT; Table 24)
- No significant difference in persistence (moderate QoE; 1 RCT; Table 24)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 24)
- Changes in disability (EDSS) and function (MSFC) were not evaluated

Combination of Glatiramer Acetate 20 mg Plus Interferon Beta-1a 30 µg

- Glatiramer acetate plus interferon beta-1a reduced relapse compared with interferon beta-1a alone (ARR, 0.12 vs. 0.16; *P* = .02), but no significant difference with glatiramer acetate 20 mg alone (low QoE; 1 RCT; Table 25)
- No significant difference in disability progression, compared with interferon beta-1a or glatiramer acetate alone (low QoE; 1 RCT; Table 25)
- No significant difference in function (MSFC) compared with interferon beta-1a or glatiramer acetate alone (low QoE; 1 RCT; Table 25)
- Glatiramer acetate plus interferon beta-1a reduced persistence (RR, 0.92; 95% CI, 0.86 to 0.99) compared with glatiramer acetate alone, but not with interferon beta-1a alone (low QoE; 1 RCT; Table 25)
- No significant difference in serious adverse events compared with interferon beta-1a alone or glatiramer acetate alone (low QoE; 1 RCT; Table 25)
- Change in disability (EDSS) was not evaluated

GRADE Summary of Findings for MS
Alemtuzumab 12 mg vs. Interferon Beta-1a 44 μg

Table 5. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (3 RCTs with 1,472 total participants[74,78,86])	⊕⊕⊕◯ MODERATE	Lower at 24 and 36 months with alemtuzumab compared with interferon beta-1a	Downgraded 1 level for risk of bias
Disability Progression (3 RCTs with 1,472 total participants[74,78,86])	⊕⊕◯◯ LOW	Lower at 24 and 36 months with alemtuzumab compared with interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision
Change in Disability (as measured by the EDSS) 3 RCTs with 1,414 total participants[74,78,86])	⊕⊕◯◯ LOW	Greater improvements at 36 months with alemtuzumab compared with interferon beta-1a, but not at 24 months; changes were small and unlikely to be clinically important	Downgraded 1 level each for risk of bias and imprecision
Change in Function (as measured by the MSFC) (2 RCTs with 1,191 total participants[74,78])	⊕⊕⊕◯ MODERATE	Greater improvements at 24 months with alemtuzumab compared with interferon beta-1a; changes were small and the clinical importance is not known	Downgraded 1 level for risk of bias
Persistence 3 RCTs with 1,472 total participants[74,78,86])	⊕⊕◯◯ LOW	Higher completion rates at 36 months with alemtuzumab compared with interferon beta-1a, but not at 24 months	Downgraded 1 level each for risk of bias and imprecision
Serious Adverse Events 3 RCTs with 1,415 total participants[74,78,86])	⊕◯◯◯ VERY LOW	No difference at 24 and 36 months between alemtuzumab and interferon beta-1a	Downgraded 1 level for risk of bias and 2 levels for imprecision

Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Dimethyl Fumarate 240 mg vs. Glatiramer Acetate 20 mg

Table 6. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 709 participants[79])	⊕◯◯◯ VERY LOW	No difference between dimethyl fumarate and glatiramer acetate	Downgraded 1 level for risk of bias and 2 levels for imprecision
Disability Progression (1 RCT with 709 participants[79])	⊕◯◯◯ VERY LOW	No difference between dimethyl fumarate and glatiramer acetate	Downgraded 1 level for risk of bias and 2 levels for imprecision
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Change in Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (1 RCT with 709 participants[79])	⊕⊕⊕◯ MODERATE	No difference between dimethyl fumarate and glatiramer acetate	Downgraded 1 level for risk of bias
Serious Adverse Events (1 RCT with 709 participants[79])	⊕⊕◯◯ LOW	No difference between dimethyl fumarate and glatiramer acetate	Downgraded 1 level each for risk of bias and imprecision[a]

Note. [a] Imprecision was not assessable. Also, inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Fingolimod 0.5 mg vs. Interferon Beta-1b 250 µg

Table 7. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 157 participants[172])	⊕⊕◯◯ LOW	Lower with fingolimod compared with interferon beta-1b	Downgraded 1 level each for risk of bias and imprecision[a]
Disability Progression No RCTs	Not reported		
Change in Disability (as measured by the EDSS) (1 RCT with 157 participants[172])	⊕⊕◯◯ LOW	No difference between fingolimod and interferon beta-1b	Downgraded 1 level each for risk of bias and imprecision[a]
Change in Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (1 RCT with 157 participants[172])	⊕⊕⊕◯ MODERATE	Higher completion rates with fingolimod compared with interferon beta-1b	Downgraded 1 level for risk of bias
Serious Adverse Events (1 RCT with 151 participants[172])	⊕⊕◯◯ LOW	No difference between fingolimod and interferon beta-1b	Downgraded 1 level each for risk of bias and imprecision[a]

Note. [a] Imprecision was not assessable. Also, inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Fingolimod 0.5 mg vs. Interferon Beta-1a 30 μg

Table 8. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 860 participants[95])	⊕⊕◯◯ LOW	Lower rates with fingolimod compared with interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision[a]
Disability Progression (1 RCT with 860 participants[95])	⊕⊕◯◯ LOW	No difference between fingolimod and interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision[a]
Change in Disability **(as measured by the EDSS)** (1 RCT with 860 participants[95])	⊕⊕◯◯ LOW	No difference between fingolimod and interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision[a]
Change in Function **(as measured by the MSFC)** (1 RCT with 860 participants[95])	⊕⊕◯◯ LOW	No difference between fingolimod and interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision[a]
Persistence (1 RCT with 866 participants[95])	⊕⊕⊕◯ MODERATE	No difference between fingolimod and interferon beta-1a	Downgraded 1 level for risk of bias
Serious Adverse Events (1 RCT with 860 participants[95])	⊕⊕◯◯ LOW	No difference between fingolimod and interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision

Note. [a] Imprecision was not assessable. Also, inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Fingolimod 0.5 mg vs. Injectable Disease-modifying Therapies

Table 9. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 861 participants[69])	⊕⊕◯◯ LOW	No difference between fingolimod and injectable therapies (interferon beta-1a, interferon beta-1b, and glatiramer acetate)	Downgraded 1 level each for risk of bias and imprecision
Disability Progression (No RCTs)	Not reported		
Change in Disability **(as measured by the EDSS)** (No RCTs)	Not reported		
Change in Function **(as measured by the MSFC)** (No RCTs)s	Not reported		
Persistence (1 RCT with 875 participants[69])	⊕⊕◯◯ LOW	Higher with fingolimod compared with injectable therapies (interferon beta-1a, interferon beta-1b, and glatiramer acetate)	Downgraded 1 level each for risk of bias and imprecision

Outcome	Quality of the Evidence	Relationship	Rationale
Serious Adverse Events (1 RCT with 861 participants[69])	⊕⊕○○ LOW	Higher with fingolimod compared with injectable therapies (interferon beta-1a, interferon beta-1b, and glatiramer acetate)	Downgraded 1 level each for risk of bias and imprecision

Note. Inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Glatiramer Acetate 20 mg vs. Interferon Beta-1b 250 µg

Table 10. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (2 RCTs with 1,420 total participants[82,85])	⊕⊕○○ LOW	No difference between glatiramer acetate and interferon beta-1b	Downgraded 1 level each for risk of bias and imprecision[a]
Disability Progression (1 RCT with 1,345 participants[85])	⊕⊕○○ LOW	No difference between glatiramer acetate and interferon beta-1b	Downgraded 1 level each for risk of bias and imprecision[a]
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Change in Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (2 RCTs with 1,420 total participants[82,85])	⊕⊕⊕○ MODERATE	No difference between glatiramer acetate and interferon beta-1b	Downgraded 1 level for risk of bias
Serious Adverse Events (1 RCT with 1,333 participants[85])	⊕⊕○○ LOW	No difference between glatiramer acetate and interferon beta-1b	Downgraded 1 level each for risk of bias and imprecision

Note. Imprecision was not assessable. If there is only 1 trial for an outcome, inconsistency was not assessable. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Glatiramer Acetate 20 mg vs. Interferon Beta-1a 30 µg or 44 µg

Table 11. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (2 RCTs with 1,273 total participants[72,75])	⊕⊕○○ LOW	No difference between glatiramer acetate and interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision
Disability Progression (2 RCTs with 1,273 total participants[72,75])	⊕○○○ VERY LOW	No difference between glatiramer acetate and interferon beta-1a	Downgraded 1 level for risk of bias and 2 levels for imprecision

Outcome	Quality of the Evidence	Relationship	Rationale
Change in Disability (as measured by the EDSS) (1 RCT with 141 participants[80])	⊕⊕◯◯ LOW	No difference between glatiramer acetate and interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision[a]
Change in Function (as measured by the MSFC) (1 RCTs with 423 participants[75])	⊕⊕◯◯ LOW	No difference between glatiramer acetate and interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision[a]
Persistence (3 RCTs with 1,687 total participants[72,75,80])	⊕⊕◯◯ LOW	Higher at 24 and 36 months with glatiramer acetate compared with interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision
Serious Adverse Events (2 RCTs with 1,265 total participants[72,75])	⊕◯◯◯ VERY LOW	No difference between glatiramer acetate and interferon beta-1a	Downgraded 1 level for risk of bias and 2 levels for imprecision

Note. [a] Imprecision was not assessable. If there is only 1 trial for an outcome, inconsistency was not assessable. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Interferon Beta-1b 250 µg vs. Interferon Beta-1a (different doses)

Table 12. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (4 RCTs with 648 total participants[76,77,83,84])	⊕◯◯◯ VERY LOW	No difference between interferon beta-1b and interferon beta-1a	Downgraded 1 level each for risk of bias, inconsistency, and imprecision
Disability Progression (2 RCTs with 489 total participants[76,84])	⊕◯◯◯ VERY LOW	No difference between interferon beta-1b and interferon beta-1a	Downgraded 1 level each for risk of bias, inconsistency, and imprecision
Change in Disability (as measured by the EDSS) (4 RCTs with 407 total participants[76,77,81,83])	⊕⊕⊕◯ MODERATE	No difference between interferon beta-1b and interferon beta-1a at 12 or 24 months	Downgraded 1 level each for risk of bias
Change in Function (as measured by the MSFC) (1 RCT with 63 participants[77])	⊕◯◯◯ VERY LOW	Higher levels with interferon beta-1a compared with interferon beta-1b	Downgraded 1 level each for risk of bias, imprecision[a], and indirectness (i.e., only assessed 1 component of the MSFC)
Persistence (4 RCTs with 648 total participants[76,77,83,84])	⊕⊕⊕◯ MODERATE	No difference between interferon beta-1b and interferon beta-1a	Downgraded 1 level for risk of bias
Serious Adverse Events (No RCTs)	Not reported		

Note. [a] Imprecision was not assessable. If there is only 1 trial for an outcome, inconsistency was not assessable. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Ocrelizumab 600 mg vs. Interferon Beta-1a 30 µg or 44 µg

Table 13. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (3 RCTs with 1,765 total participants[60,73])	⊕⊕◯◯ LOW	Lower with ocrelizumab compared with interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision[a]
Disability Progression (2 RCTs with 1,656 total participants[60])	⊕⊕◯◯ LOW	Lower with ocrelizumab compared with interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Change in Function (as measured by the MSFC) (2 RCTs with 1,656 total participants[60])	⊕⊕⊕◯ MODERATE	Higher levels with ocrelizumab compared with interferon beta-1a, but the clinical importance of the difference is not known	Downgraded 1 level for risk of bias
Persistence (3 RCTs with 1,767 total participants[60,73])	⊕⊕◯◯ LOW	Higher at 24 months with ocrelizumab compared with interferon beta-1a, but not at 6 months	Downgraded 1 level each for risk of bias and inconsistency
Serious Adverse Events (3 RCTs with 1,760 total participants[60,73])	⊕⊕◯◯ LOW	No difference between ocrelizumab and interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision

Note. [a] Imprecision was not assessable. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Ozanimod 0.5 mg and 1 mg vs. Interferon Beta-1a 30 µg

Table 14. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (2 RCTs with 2,659 total participants[66,67])	⊕⊕◯◯ LOW	Lower with ozanimod compared with interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision
Disability Progression (2 RCTs with 2,659 total participants[66,67])	⊕⊕◯◯ LOW	No difference between ozanimod and interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision[a]
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (2 RCTs with 2,659 total participants[66,67])	⊕◯◯◯ VERY LOW	Some higher levels with ozanimod 0.5 mg compared with interferon beta-1a, but the results were mixed	Downgraded 1 level each for risk of bias, inconsistency, and imprecision[a]
Persistence (2 RCTs with 2,666 total participants[66,67])	⊕⊕⊕◯ MODERATE	No difference between ozanimod and interferon beta-1a	Downgraded 1 level for risk of bias

Outcome	Quality of the Evidence	Relationship	Rationale
Serious Adverse Events (2 RCTs with 2,658 total participants[66,67])	⊕○○○ VERY LOW	No difference between ozanimod and interferon beta-1a	Downgraded 1 level for risk of bias, inconsistency and 2 levels for imprecision

Note. [a] Imprecision was not assessable. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Teriflunomide 7 mg and 14 mg vs. Interferon Beta-1a 44 µg

Table 15. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 324 participants[99])	⊕⊕○○ LOW	Lower with teriflunomide 7 mg compared with interferon beta-1a, but not with teriflunomide 14 mg	Downgraded 1 level each for risk of bias and imprecision[a]
Disability Progression (No RCTs)	Not reported		
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (1 RCT with 324 participants[99])	⊕○○○ VERY LOW	Higher with teriflunomide 7 mg compared with interferon beta-1a, but not with teriflunomide 14 mg	Downgraded 1 level each for risk of bias, inconsistency, and imprecision[a]
Serious Adverse Events (1 RCT with 321 participants[99])	⊕○○○ VERY LOW	Higher with teriflunomide 7 mg compared with interferon beta-1a and teriflunomide 14 mg	Downgraded 1 level each for risk of bias, inconsistency, and imprecision

Note. [a] Imprecision was not assessable. Inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; mg: milligram; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Cladribine 3.5 mg/kg vs. Placebo

Table 16. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 870 participants [148])	⊕⊕○○ LOW	Lower with cladribine compared with placebo	Downgraded 1 level each for risk of bias and imprecision[a]
Disability Progression (1 RCT with 870 participants[148])	⊕⊕○○ LOW	Lower with cladribine compared with placebo	Downgraded 1 level each for risk of bias and imprecision

Outcome	Quality of the Evidence	Relationship	Rationale
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (1 RCT with 870 participants[148])	⊕⊕⊕◯ MODERATE	Higher with cladribine compared with placebo	Downgraded 1 level for risk of bias
Serious Adverse Events (1 RCT with 870 participants[148])	⊕◯◯◯ VERY LOW	No difference with cladribine compared with placebo	Downgraded 1 level each for risk of bias and 2 levels for imprecision

Note. ᵃ Imprecision was not assessable. Inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Cladribine 3.5 mg/kg Plus Continued Interferon Beta vs. Placebo Plus Continued Interferon Beta

Table 17. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 172 participants[70])	⊕⊕⊕◯ MODERATE	Lower with cladribine plus interferon beta compared with interferon alone	Downgraded 1 level for risk of bias
Disability Progression (1 RCT with 172 participants[70])	⊕⊕◯◯ LOW	No difference between cladribine plus interferon beta compared with interferon alone	Downgraded 1 level each for risk of bias and imprecision[a]
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (1 RCT with 172 participants[70])	⊕⊕◯◯ LOW	Lower with cladribine plus interferon beta compared with interferon alone	Downgraded 1 level each for risk of bias and imprecision
Serious Adverse Events (1 RCT with 172 participants[70])	⊕⊕◯◯ LOW	No difference between cladribine plus interferon beta compared with interferon alone	Downgraded 1 level each for risk of bias and imprecision[a]

Note. ᵃ Imprecision was not assessable. Inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Diroximel Fumarate vs. Placebo

We did not identify any eligible RCTs.

Ozanimod 0.5 mg and 1 mg vs. Placebo

Table 18. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 258 participants[62])	⊕⊕◯◯ LOW	No difference between ozanimod and placebo	Downgraded 1 level each for risk of bias and imprecision
Disability Progression (No RCTs)	Not reported		
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (1 RCT with 258 participants[62])	⊕⊕⊕◯ MODERATE	No difference between ozanimod and placebo	Downgraded 1 level for risk of bias
Serious Adverse Events (1 RCT with 258 participants[62])	⊕◯◯◯ VERY LOW	No difference between ozanimod and placebo	Downgraded 1 level for risk of bias and 2 levels for imprecision

Note. Inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Peginterferon Beta-1a 125 μg Every 2 Weeks vs. Placebo

Table 19. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 1,012 participants[98])	⊕⊕◯◯ LOW	Lower with peginterferon beta-1a compared with placebo	Downgraded 1 level each for risk of bias and imprecision
Disability Progression (1 RCT with 1,012 participants[98])	⊕⊕⊕◯ MODERATE	Lower with peginterferon beta-1a compared with placebo	Downgraded 1 level for risk of bias
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (1 RCT with 1,012 participants[98])	⊕⊕⊕◯ MODERATE	Lower with peginterferon beta-1a compared with placebo	Downgraded 1 level for risk of bias
Serious Adverse Events (1 RCT with 1,012 participants[98])	⊕⊕◯◯ LOW	No difference between peginterferon beta-1a and placebo	Downgraded 1 level each for risk of bias and imprecision[a]

Note. [a] Imprecision was not assessable. Inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Siponimod 2 mg vs. Placebo

Table 20. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (2 RCTs with 1,756 total participants[61])	⊕⊕⊕◯ MODERATE	Lower rates with siponimod compared with placebo	Downgraded 1 level for risk of bias
Disability Progression (1 RCT with 1,645 participants[61])	⊕⊕◯◯ LOW	Lower rates with siponimod compared with placebo	Downgraded 1 level each for risk of bias and imprecision
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (1 RCT with 1,645 participants[61])	⊕◯◯◯ VERY LOW	No difference between siponimod and placebo	Downgraded 1 level each for risk of bias, indirectness, and imprecision
Persistence (2 RCTs with 1,721 total participants[61,71])	⊕⊕◯◯ LOW	No difference between siponimod and placebo for RRMS and SPMS, although there was a tendency for higher persistence in SPMS	Downgraded 1 level each for risk of bias and inconsistency
Serious Adverse Events (2 RCTs with 1,755 total participants[61,71])	⊕◯◯◯ VERY LOW	No difference between siponimod and placebo	Downgraded 1 level for risk of bias and 2 levels for imprecision

Note. If there is only 1 trial for an outcome, inconsistency was not assessable. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MS: multiple sclerosis; MSFC; Multiple Sclerosis Functional Composite; RRMS: relapsing-remitting MS; SPMS: secondary progressive MS; RCT: randomized controlled trial.

Different Dosing Schedule for Dimethyl Fumarate

Table 21. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (2 RCTs with 1,530 total participants[79,92])	⊕⊕◯◯ LOW	No difference between dimethyl fumarate 240 mg twice a day and dimethyl fumarate 240 mg 3 times a day	Downgraded 1 level each for risk of bias and imprecision[a]
Disability Progression (2 RCTs with 1,530 total participants[79,92])	⊕⊕◯◯ LOW	No difference between dimethyl fumarate 240 mg twice a day and dimethyl fumarate 240 mg 3 times a day	Downgraded 1 level each for risk of bias and imprecision[a]
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (No RCTs)	Not reported		

Outcome	Quality of the Evidence	Relationship	Rationale
Persistence (2 RCTs with 1,545 total participants[79,92])	⊕⊕⊕○ MODERATE	No difference between dimethyl fumarate 240 mg twice a day and dimethyl fumarate 240 mg 3 times a day	Downgraded 1 level for risk of bias
Serious Adverse Events (2 RCTs with 1,529 total participants[79,92])	⊕⊕○○ LOW	No difference between dimethyl fumarate 240 mg twice a day and dimethyl fumarate 240 mg 3 times a day	Downgraded 1 level each for risk of bias and imprecision[a]

Note. [a] Imprecision was not assessable. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; mg: milligram; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Different Dosing Schedule for Glatiramer Acetate

Table 22. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (No RCTs)	Not reported		
Disability Progression (No RCTs)	Not reported		
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (2 RCTs with 1,070 total participants[68,93])	⊕⊕⊕○ MODERATE	No difference between glatiramer acetate 40 mg and glatiramer acetate 20 mg	Downgraded 1 level for risk of bias
Serious Adverse Events (2 RCTs with 1,066 total participants[68,93])	⊕○○○ VERY LOW	No clear association between rate and dosing schedule of glatiramer acetate	Downgraded 1 level each for risk of bias, inconsistency, and imprecision[a]

Note. [a] Imprecision was not assessable. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; mg: milligram; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial. Different Dosing Schedule for Interferon Beta-1a

Table 23. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (3 RCTs with 860 total participants[80,81,88])	⊕○○○ VERY LOW	No clear association with dosing schedule of interferon beta-1a	Downgraded 1 level each for risk of bias, imprecision[a], and inconsistency

Outcome	Quality of the Evidence	Relationship	Rationale
Disability Progression (1 RCTs with 677 participants[88])	⊕○○○ VERY LOW	No difference between subcutaneous interferon beta-1a 44 μg 3 times a week and intramuscular interferon beta-1a 30 μg once a week	Downgraded 1 level each for risk of bias and 2 levels for imprecision
Change in Disability (as measured by the EDSS) (2 RCTs with 103 total participants[77,81])	⊕⊕⊕○ MODERATE	No difference between subcutaneous interferon beta-1a 44 μg 3 times a week and intramuscular interferon beta-1a 30 μg once a week	Downgraded 1 level for risk of bias
Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (3 RCTs with 833 total participants[77,80,88])	⊕⊕○○ LOW	No difference between subcutaneous interferon beta-1a 44 μg 3 times a week and intramuscular interferon beta-1a 30 μg once a week	Downgraded 1 level each for risk of bias and imprecision
Serious Adverse Events (1 RCTs with 677 participants[88])	⊕⊕○○ LOW	No difference between subcutaneous interferon beta-1a 44 μg 3 times a week and intramuscular interferon beta-1a 30 μg once a week	Downgraded 1 level each for risk of bias and imprecision[a]

Note. [a] Imprecision was not assessable. If there is only 1 trial for an outcome, inconsistency was not assessable. Abbreviations. μg: microgram; EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Different Dosing Schedule for Peginterferon Beta-1a

Table 24. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 1,012 participants[98])	⊕⊕○○ LOW	No difference between peginterferon beta-1a 125 μg every 2 weeks and peginterferon beta-1a 125 μg every 4 weeks	Downgraded 1 level each for risk of bias and imprecision[a]
Disability Progression (1 RCT with 1,012 participants[98])	⊕⊕○○ LOW	No difference between peginterferon beta-1a 125 μg every 2 weeks and peginterferon beta-1a 125 μg every 4 weeks	Downgraded 1 level each for risk of bias and imprecision[a]
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		

Outcome	Quality of the Evidence	Relationship	Rationale
Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (1 RCT with 1,012 participants[98])	⊕⊕⊕◯ MODERATE	No difference between peginterferon beta-1a 125 µg every 2 weeks and peginterferon beta-1a 125 µg every 4 weeks	Downgraded 1 level for risk of bias
Serious Adverse Events (1 RCT with 1,012 participants[98])	⊕⊕◯◯ LOW	No difference between peginterferon beta-1a 125 µg every 2 weeks and peginterferon beta-1a 125 µg every 4 weeks	Downgraded 1 level each for risk of bias and imprecision[a]

Note. [a] Imprecision was not assessable. Inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. µg: microgram; EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Combination of Glatiramer Acetate 20 mg Plus Interferon Beta-1a 30 µg
Table 25. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Relapse (1 RCT with 1,008 participants[75])	⊕⊕◯◯ LOW	Lower with glatiramer acetate plus interferon beta-1a compared with interferon beta-1a alone, but not with glatiramer acetate alone	Downgraded 1 level each for risk of bias and imprecision[a]
Disability Progression (1 RCT with 1,008 participants[75])	⊕⊕◯◯ LOW	No difference between glatiramer acetate plus interferon beta-1a and glatiramer acetate or interferon beta-1a alone	Downgraded 1 level each for risk of bias and imprecision[a]
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (1 RCT with 1,008 participants[75])	⊕⊕◯◯ LOW	No difference between glatiramer acetate plus interferon beta-1a and glatiramer acetate or interferon beta-1a alone	Downgraded 1 level each for risk of bias and imprecision[a]
Persistence (1 RCT with 1,008 participants[75])	⊕⊕◯◯ LOW	Lower with glatiramer acetate plus interferon beta-1a compared with glatiramer acetate alone, but not with interferon beta-1a alone	Downgraded 1 level for risk of bias and imprecision

Outcome	Quality of the Evidence	Relationship	Rationale
Serious Adverse Events (1 RCT with 1,008 participants[75])	⊕⊕◯◯ LOW	No difference for glatiramer acetate alone or interferon beta-1a alone compared with glatiramer acetate plus interferon beta-1a	Downgraded 1 level each for risk of bias and imprecision

Note. [a] Imprecision was not assessable. Inconsistency was not assessable for any outcome as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Effectiveness and Harms of Disease-modifying Treatments for MS

Alemtuzumab vs. Interferon Beta-1a

Study Characteristics

We identified 3 eligible RCTs comparing alemtuzumab and interferon beta-1a in adults with RRMS (Table 26).[74,78,86] All 3 RCTs (N = 581, CARE-MS I; N = 334, CAMMS223; N = 667, CARE-MS II) randomized participants to an initial intravenous infusion of alemtuzumab 12 mg for 5 days, then for 3 days at 12 months, compared with subcutaneous injections of interferon beta-1a 44 μg 3 times a week.[74,78,86] The CARE-MS II trial also randomized 173 participants to alemtuzumab 24 mg, which is not an FDA-approved dose.[74] We assessed each of the trials as fair-methodological quality because of the lack of blinding, some high and differential loss to follow-up, author conflicts of interest, and funding by industry.

Participants in the CARE-MS trials could continue in extension studies with alemtuzumab retreatment as needed for relapse or magnetic resonance imaging (MRI) activity.[140,152]

Table 26. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Trial Duration
Alemtuzumab vs. Interferon Beta-1a				
Cohen et al., 2012[78] 101 sites in 16 countries, including the U.S. NCT00530348 CARE-MS I	• Adults with RRMS • Total N = 581 randomized; n = 386, alemtuzumab; n = 195, interferon beta-1a	Alemtuzumab 12 mg IV, 5 days initially, then 3 days at 12 months	Interferon beta-1a 44 μg SC, 3 times a week	24 months
Coles et al., 2008[86] 49 sites in Europe and the U.S. NCT00050778 CAMMS223	• Adults with RRMS • Total N = 334 randomized; n = 113, alemtuzumab 12 mg; n = 110, alemtuzumab 24 mg; n = 111, interferon beta-1a	Alemtuzumab 12 or 24 mg IV, 5 days initially, then 3 days at 12 and 24 months	Interferon beta-1a 44 μg SC, 3 times a week	36 months

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Trial Duration

Coles et al., 2012[74]
194 sites in 23 countries, including the U.S.
NCT00548405
CARE-MS II
	• Adults with RRMS
	• Total N = 840 randomized;
	   n = 436, alemtuzumab 12 mg;
	   n = 173, alemtuzumab 24 mg;
	   n = 231, interferon beta-1a
		Alemtuzumab 12 or 24 mg IV, 5 days initially, then 3 days at 12 months	Interferon beta-1a 44 µg SC, 3 times a week	24 months

Abbreviations. µg: microgram; IV: intravenous; mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous.

Disability

Participants in the alemtuzumab 12 mg groups had significantly lower rates of disability progression at 24 months in the two CARE-MS trials and at 36 months in the CAMMS223 trial (Figure 2).[74,78,86]
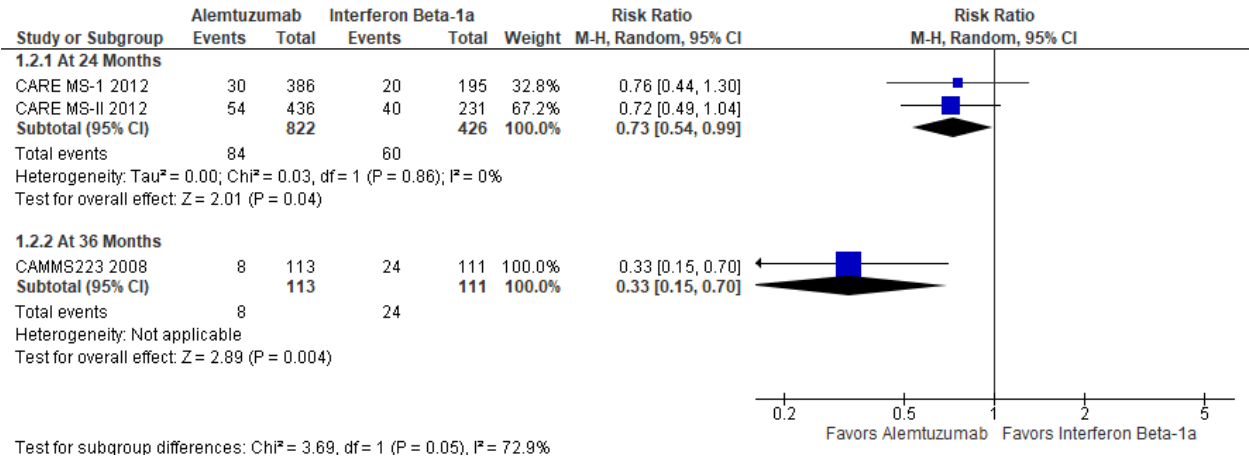

Figure 2. Alemtuzumab 12 mg vs. Interferon Beta-1a. Confirmed Disability Progression.

Participants in the alemtuzumab 12 mg groups had a reduced level of disability at 36 months in the CAMMS223 trial, but not at 24 months in the two CARE-MS trials (Figure 3).[74,78,86] However the significant changes in EDSS were small and are unlikely to be clinically meaningful.
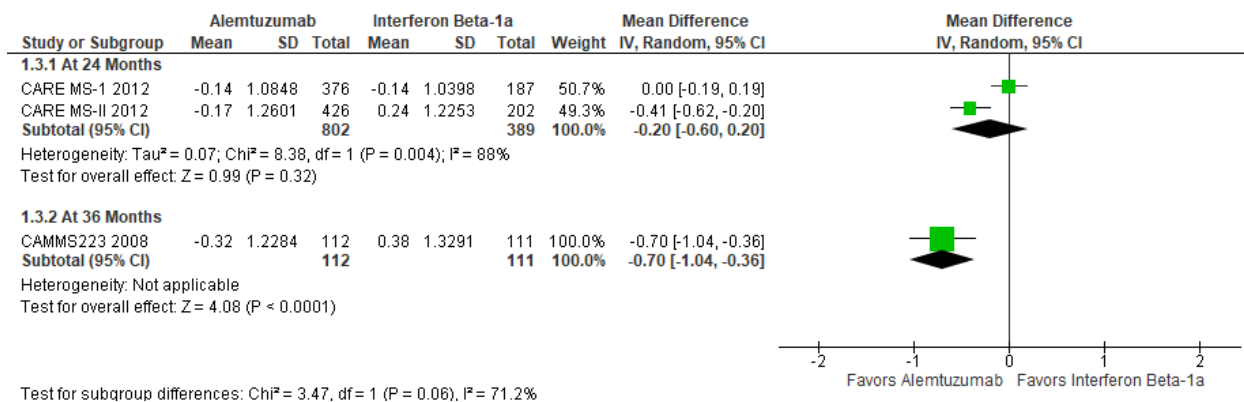
Figure 3. Alemtuzumab 12 mg vs. Interferon Beta-1a. Change in Disability (EDSS).

In the extended CARE-MS I trial, 68.5% of the participants received no alemtuzumab retreatment.[152] Over 5 years, the majority of patients from CARE-MS I who continued in the extension study had improved or stable levels of disability (22.2% improved EDSS score, vs. 60.0% stable EDSS score, vs. 17.8% worsened EDSS score).[152]

In the extended CARE-MS II trial, 59.8% of the participants received no alemtuzumab retreatment.[140] Over 5 years, the majority of patients from CARE-MS II who continued in the extension study had improved or stable levels of disability (24.9% improved EDSS score, vs. 51.7% stable EDSS score, vs. 23.4% worsened EDSS score).[140]

Clinical Exacerbation or Relapse

Participants in the alemtuzumab 12 mg groups had significantly lower rates of relapse at 24 months in the two CARE-MS trials and at 36 months in the CAMMS223 trial (Figure 4).[74,78,86]
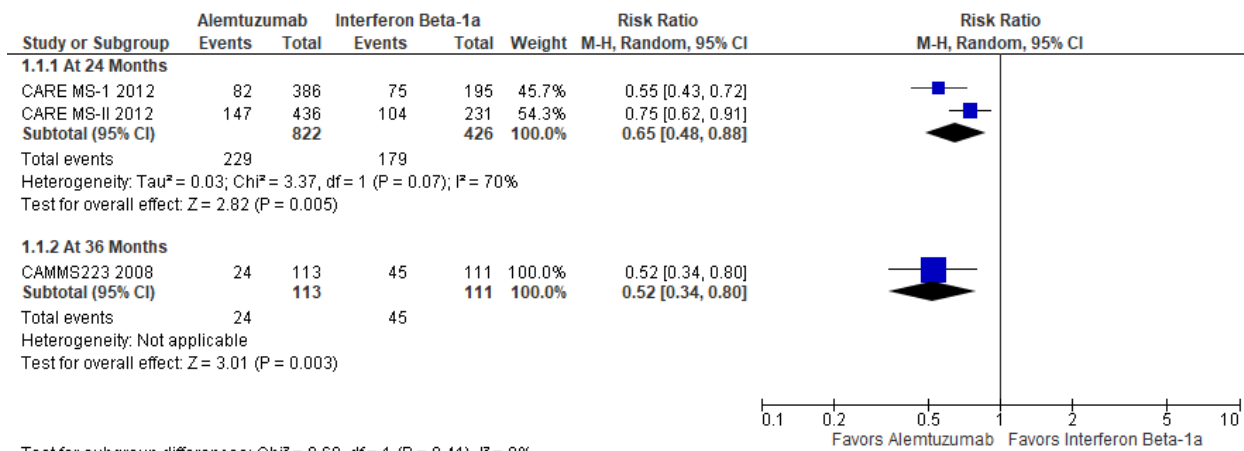

Figure 4. Alemtuzumab 12 mg vs. Interferon Beta-1a. Relapse.

ARRs were lower in the alemtuzumab groups compared with the interferon beta-1a groups:
- At 24 months, ARRs in the CARE-MS I trial were 0.18 in the alemtuzumab group and 0.39 in the interferon beta-1a group (*P* value not reported)[78]
- At 24 months, ARRs in the CARE-MS II trial were 0.26 in the alemtuzumab group and 0.52 in the interferon beta-1a group (*P* value not reported)[74]

- At 36 months, ARRs in the CAMMS223 trial were 0.11 in the alemtuzumab group and 0.36 in the interferon beta-1a group[86]

Over 5 years, patients from the two CARE-MS trials who continued in the extension study had low ARR (0.18 in years 0 to 2, vs. 0.16 in years 3 to 5, CARE-MS I; 0.28 in years 0 to 2, vs. 0.21 in years 3 to 5, CARE-MS II).[140,152] The numbers of patients who were relapse-free remained stable or increased over time (from 89% in the first 2 years to 88% in year 5 of CARE-MS I; 79% in the first 2 years to 85% in year 5 of CARE-MS II).[152]

Functional Outcomes

In the two CARE-MS trials, participants in the alemtuzumab groups had greater improvements in functioning (MSFC) at 24 months compared with the interferon beta-1a groups (Figure 5).[74,78] However, changes were small and the clinical importance is not known.
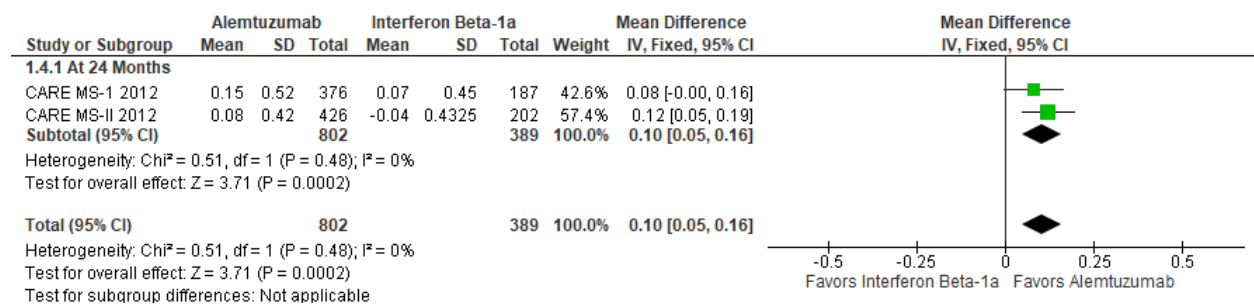

Figure 5. Alemtuzumab 12 mg vs. Interferon Beta-1a. Change in Function (MSFC).

Persistence

Participants in the alemtuzumab 12 mg groups also had higher levels of study completion at 24 months in the two CARE-MS trials, and 36 months in the CAMMS223 trial, but this was not significantly different to that of the interferon beta-1a group at 24 months (Figure 6).[74,78,86]
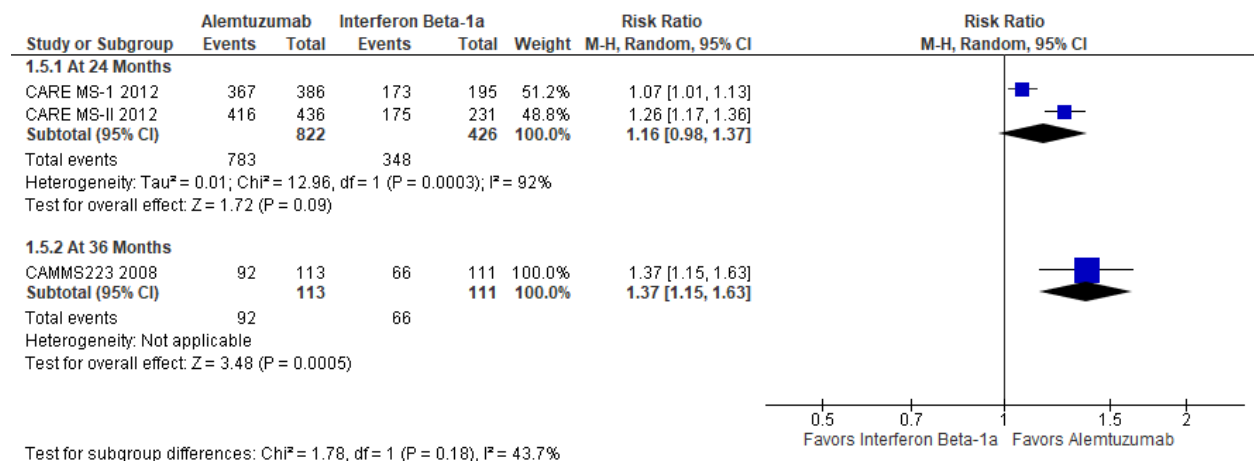

Figure 6. Alemtuzumab 12 mg vs. Interferon Beta-1a. Completed Study.

Other Outcomes of Effectiveness

In the two CARE-MS trials, patients in the alemtuzumab groups had improvements in physical, mental, and emotional QoL from baseline, measured using both disease-specific and general

measures of QoL at 24 months.[134] Participants from the CARE-MS II trial were followed-up for a further 4 years.[135] Over 6 years, alemtuzumab-treated RRMS patients with inadequate response to prior treatment reported improvement or stabilization in health-related QoL compared with baseline.[135] However, the improvements were small and did not meet the threshold for clinical importance.[135]

Effectiveness by Subgroup

In the CARE-MS II trial,[74] alemtuzumab 12 mg was more effective in lowering the relapse rate compared with interferon beta 1a in all subgroups (previous therapy with or without interferon beta, treatment at any time with interferon beta 1a or glatiramer acetate; Appendix B). Results were also unchanged by the presence of anti-interferon antibodies at baseline or month 24.[74] Similar results were seen in the CARE-MS I trial, with alemtuzumab remaining more effective than interferon beta 1a in reducing relapse, regardless of the presence of antibodies at month 24.[78]

Over 6 years, patients with highly active disease and an inadequate response to prior treatment who were treated with alemtuzumab reported an improvement or stabilization in health-related QoL compared with baseline.[135] However, the improvements were small and did not meet the threshold for clinical importance.[135]

In the two CARE-MS trials and the extension study, 4% of participants were of African descent and received alemtuzumab in the 2-year core or in the 6-year extension.[162] Patients of African descent in the alemtuzumab group experienced significantly lower ARRs at year 2 (0.09 vs. 0.42; P = 0.04) than patients of African descent in the interferon beta-1a group.[162] Patients of African descent in the alemtuzumab group also experienced improved disability scores and lower rates of disability progression than patients of African descent in the interferon beta-1a group; however, no P values were reported.[162] The safety profile of alemtuzumab was consistent with the overall CARE MS population (the majority of whom identified as non-Hispanic white), although the sample size was small and may have prevented the detection of known rarer adverse events.[162] The effectiveness of alemtuzumab was sustained over the 8 year study, with an ARR of 0.30 at year 8 in the patients who continued with alemtuzumab.[162]

A pooled analysis of the two CARE MS trials and the extension studies aimed to evaluate the efficacy and safety by the number of additional alemtuzumab courses.[141] In the additional-course groups, patients who had 3 and 4 courses of alemtuzumab had a reduced ARR (ARR, 0.73 in the 12 months before treatment, vs. 0.07 in the 12 months after treatment).[141] For 36 months, 89% of patients after 3 courses and 92% of patients after 4 courses were free of disability progression, with 20% and 26% achieving 6-month confirmed disability improvement.[141] Safety was similar across groups; serious events occurred irrespective of the number of courses.

A post hoc analysis was conducted for patients in the two CARE MS trials who enrolled in the extension study, to evaluate outcomes in patients who relapsed between alemtuzumab courses 1 and 2 (classified as early relapse).[164] Patients classified as having early relapse had more relapses in the 1 to 2 years pre-alemtuzumab treatment and a higher mean baseline EDSS score than patients without relapse. Over 6 years, patients who had an early relapse but completed the

2 courses of alemtuzumab had improved disability outcomes, despite a clinical relapse after the first course.[164]

In the CAMMS223 trial,[86] alemtuzumab was more effective than interferon beta-1a regardless of study-site location, baseline EDSS score, sex, race, and age of patients (details were not reported).

Adverse Events

Participants in both groups withdrew because of adverse events, but the proportions varied across the trials:

- 1% of participants in the alemtuzumab and 6% in the interferon beta-1a groups in the CARE-MS I trial[78]
- 3% of participants in the alemtuzumab and 7% in the interferon beta-1a groups in the CARE-MS II trial[74]
- 1.4% of participants in the alemtuzumab and 12.1% in the interferon beta-1a groups in the CAMMS223 trial withdrew because of adverse events ($P < .001$).[86] The safety population in CAMMS223 included participants who received alemtuzumab 12 mg and alemtuzumab 24 mg, which is not an FDA-approved dose.[86]

The rates of serious adverse events were similar at 24 months in the two CARE-MS trials and 36 months in the CAMMS223 trial for alemtuzumab and interferon beta-1a (Figure 7).
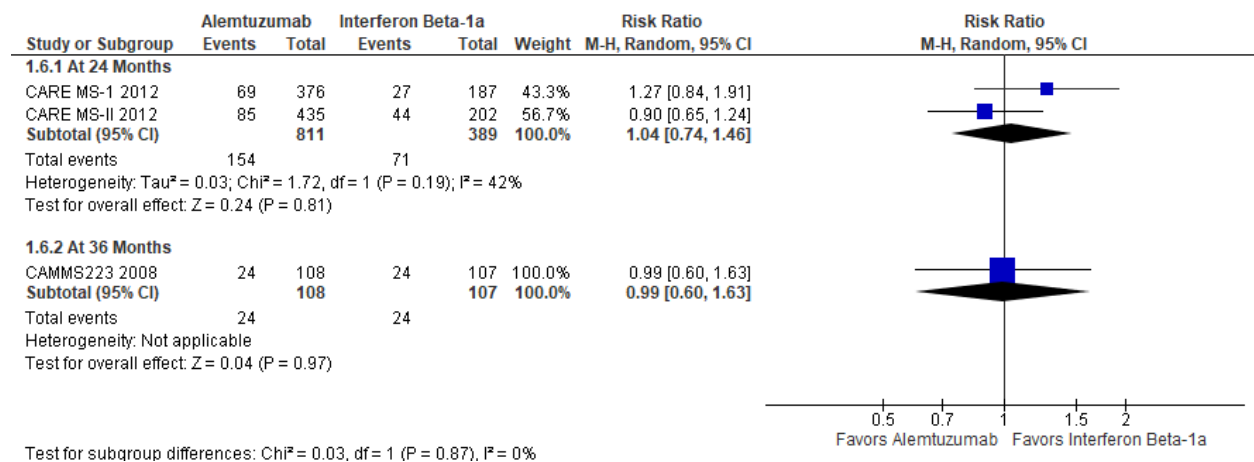

Figure 7. Alemtuzumab 12 mg vs. Interferon Beta-1a. Serious Adverse Events.

Overall, across the 3 RCTs, 6 patients died in the alemtuzumab group (including 1 death related to immune thrombocytopenic purpura) and no patients died in the interferon beta-1a group.[74,78,86]

Over 5 years, patients from the two CARE-MS trials who continued in the extension study had lower rates of adverse events in the follow-up period (705.2 in the first 2 years of the core trial, vs. 133.6 adverse events per 100 person-years for CARE-MS I; 871.3 in the first 2 years of the core trial, vs. 201.5 adverse events per 100 person-years for CARE-MS II).[140,152]

The 3 RCTs reported the same commonly experienced adverse events. For alemtuzumab, patients reported headache (43% to 61%), nausea (14% to 24%), rash (39% to 91%), and fever related to the infusion (16% to 37%).[74,78,86] In the alemtuzumab group, patients also reported nasopharyngitis (20% to 29%), urinary tract infections (11% to 21%), herpes viral infections (8% to 16%), and upper respiratory tract infections (15% to 59%).[74,78,86] In the interferon beta-1a group, patients reported influenza-like illness (8% to 27%), injection-site erythema (25%), headache (19% to 63%), and relapse (33% to 39%).[74,78,86]

Liver toxicity was lower in the alemtuzumab groups:
- 4% of participants in the alemtuzumab group, vs. 17% in the interferon beta-1a group in the CARE-MS I trial (*P* value not reported[78]
- 4% of participants in the alemtuzumab group, vs. 6% in the interferon beta-1a group in the CARE-MS II trial (*P* value not reported[74]
- 2.3% of participants in the alemtuzumab group, vs. 15.0% in the interferon beta-1a group in the CAMMS223 trial had abnormal liver tests (*P* < .001).[86] The safety population in CAMMS223 included participants who received alemtuzumab 12 mg and alemtuzumab 24 mg, which is not an FDA-approved dose.[86]

In the CARE-MS I trial,[78] neutralizing anti-interferon beta antibodies were present in 13% of patients treated with interferon beta-1a at 24 months.[78] In the CARE-MS II trial, neutralizing anti-interferon beta antibodies were present in 18% of patients receiving interferon beta-1 at baseline and 13% of these patients at 24 months.[74]

Overall, in the alemtuzumab groups (including patients who received alemtuzumab 24 mg), 10 patients were diagnosed with cancer (3 thyroid cancer, 2 basal cell carcinoma, 1 vulval cancer, 1 colon cancer, 1 Burkitt's lymphoma, 1 breast cancer, and 1 cervical cancer).[74,78,86] In the interferon beta-1a groups, 3 patients were diagnosed with cancer (1 basal cell carcinoma, 1 acute myeloid leukemia, and 1 colon cancer).[74,78,86]

In 2017, Baker et al.[136] extracted data on neutrophils from the regulatory submission of alemtuzumab to the European Medicines Agency in the two CARE-MS trials. In year 1, 8.9% of patients treated with alemtuzumab developed neutropenia (i.e., having an abnormally low count of neutrophils, a type of white blood cell, which might lead to an increased risk of infection), rising to 14.4% in year 2.[136] The degree of neutropenia was generally mild, with 0.6% of patients in year 1 and 1.5% of people in in year 2 developing grade 3–4 toxicity.[136] Overall, 2 participants developed severe neutropenia-related adverse events.[136]

A pooled analysis[166] of the two CARE-MS trials, the CAMMS223 trial, and the extension study found that infections occurred more frequently with alemtuzumab 12 mg than with interferon beta-1a:
- In years 1 and 2, the rates of infection were 58.7% and 52.6% respectively in the alemtuzumab group, vs. 41.3% and 37.7% respectively in the interferon beta-1a group.

The rates of adverse events declined in the alemtuzumab groups over years 3 to 6 (46.6% in year 3, 42.8% in year 4, 40.9% in year 5, and 38.1% in year 6).[166] Similarly, rates of serious infections were higher with alemtuzumab 12 mg than with interferon beta-1a (range, 1.0% to 1.9% per year vs. 0.4 to 0.7 per year).[166] Infections in both groups were predominantly (95% and over) mild to

moderate and included upper respiratory tract infections, urinary tract infections, and mucocutaneous herpetic infections.[166]

An analysis of the full clinical program development cohort of participants of the CARE-MS trials, the CAMMS223 trial, and the extension study found that 2.2% of participants treated with alemtuzumab had immune thrombocytopenia (2.0% alemtuzumab 12 mg vs. 3.3% alemtuzumab 24 mg) over a median follow-up of 6.1 years after the first infusion.[144] All cases occurred within 48 months of the last alemtuzumab infusion.[144]

Harms by Subgroup

In the CARE-MS I trial,[78] alemtuzumab-binding antibodies were detected in 29% of patients treated with alemtuzumab immediately before the second course and in 86% of patients 1 month after the second course. In the CARE-MS II trial,[74] 29% of patients had alemtuzumab-binding antibodies before the second treatment compared with 81% 1 month after treatment. The presence and concentration of anti-alemtuzumab antibodies was not associated with any impact on lymphocyte depletion or repopulation, efficacy, or safety.[74,78]

In the CAMMS223 trial,[86] alemtuzumab-binding antibodies were detected in 0.5% of patients at 12 months and in 26.3% at 24 months. The presence of these antibodies was not associated with any changes in efficacy, infusion-associated reactions, lymphocyte depletion, or repopulation.[86]

A pooled analysis of the two CARE-MS trials and the extension studies aimed to evaluate the efficacy and safety by the number of additional alemtuzumab courses.[141] Adverse events were similar across groups, and serious events occurred irrespective of the number of courses.[141]

Dimethyl Fumarate vs. Glatiramer Acetate
Study Characteristics

We identified 1 eligible RCT comparing dimethyl fumarate and glatiramer acetate in adults with RRMS (Table 27).[79] In the CONFIRM trial,[79] 1,430 participants were randomized for 24 months to dimethyl fumarate 240 mg twice daily, dimethyl fumarate 240 mg 3 times daily, daily subcutaneous injections of 20 mg of glatiramer acetate, or placebo. We assessed the CONFIRM trial as being of poor methodological quality because of concerns about author conflicts of interest, funding by industry, and the potential for unblinding in the dimethyl fumarate groups (a flushing reaction is known to be an adverse effect associated with dimethyl fumarate). Although the RCT was not designed to test the superiority or noninferiority of dimethyl fumarate compared with glatiramer acetate, the authors conducted a post hoc evaluation of a direct comparison of dimethyl fumarate and glatiramer acetate.[79] The statistical testing for the direct comparison should be considered exploratory, and not definitive.[79]

Table 27. Summary Table of Included RCTs for MS

Citation Location NCT Number Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Dimethyl Fumarate vs. Glatiramer Acetate				

Fox et al., 2012[79]
 	
200 sites in 28 countries, including the U.S.
 	
NCT00451451
 	
CONFIRM
	• Adults with RRMS
	• Total N = 1,430 randomized; n = 362, dimethyl fumarate twice daily;
	n = 345, dimethyl fumarate 3 times daily;
	n = 360, glatiramer acetate;
	n = 363, placebo
		Dimethyl fumarate 240 mg oral, twice daily; dimethyl fumarate 240 mg oral, 3 times daily	Glatiramer acetate 20 mg SC, once daily; placebo	24 months

Abbreviations. mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous

Disability

At 2 years, the rate of disability progression (confirmed at 3 weeks) was similar between dimethyl fumarate 240 mg twice daily and placebo (HR, 0.79; 95% CI, 0.52 to 1.19) and between glatiramer acetate 20 mg daily and placebo (HR, 0.93; 95% CI, 0.63 to 1.37).[79] In the direct post hoc comparison, participants in the dimethyl fumarate 240 mg twice daily group and glatiramer acetate 20 mg daily group had similar rates of disability progression at 2 years (HR, 0.85; 95% CI, 0.56 to 1.29).[79] No difference in disability was seen for the non-FDA approved dosage of dimethyl fumarate 240 mg 3 times daily compared with glatiramer acetate 20 mg daily (P = .37).[79]

Clinical Exacerbation or Relapse

At 2 years, participants in both the dimethyl fumarate 240 mg twice daily group and glatiramer acetate 20 mg daily group had lower ARRs than participants in the placebo group (a reduction of 44.0%; 95% CI, 26.0 to 57.7 for dimethyl fumarate; a reduction of 28.6%; 95% CI, 6.9 to 45.2 for glatiramer acetate).[79] In the direct post hoc comparison, participants in the dimethyl fumarate 240 mg twice daily and glatiramer acetate 20 mg daily groups had similar ARRs at 2 years (rate ratio, 0.78; 95% CI, 0.59 to 1.05).[79] However the non-FDA approved dosage of dimethyl fumarate 240 mg 3 times daily was associated with a lower ARR when compared with glatiramer acetate 20 mg daily (rate ratio, 0.69; 95% CI, 0.51 to 0.94).[79]

Participants in the dimethyl fumarate and glatiramer acetate groups also experienced fewer relapses at 2 years than participants in the placebo group (P < .01).[79] When compared directly, similar number of participants in the dimethyl fumarate and glatiramer acetate groups relapsed, with no statistically significant difference between the dimethyl fumarate 240 mg twice daily group and glatiramer acetate 20 mg daily group (HR, 0.92; 95% CI, 0.70 to 1.22) or the dimethyl fumarate 240 mg 3 times daily and glatiramer acetate 20 mg daily group (HR, 0.78 95% CI, 0.58 to 1.04).[79]

Functional Outcomes

No functional outcomes were reported in the CONFIRM trial.[79]

Persistence

Overall, 80% of participants completed the 24-month trial (284 of 362, 78.5% dimethyl fumarate 240 mg twice daily; 273 of 345, 79.1% dimethyl fumarate 240 mg 3 times daily; 292 of 360, 81.1% glatiramer acetate 20 mg daily; 278 of 363, 76.6% placebo), with no significant difference between the dimethyl fumarate 240 mg twice and day and glatiramer acetate groups.[79] The numbers of participants who discontinued the study drug was higher in the placebo group (36%) than in the other groups (30% dimethyl fumarate 240 mg twice daily; 28% dimethyl fumarate 240 mg 3 times daily; 25% glatiramer acetate 20 mg daily; no *P* value reported).[79]

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the CONFIRM trial.[79]

Effectiveness by Subgroup

We did not identify any evidence on the effectiveness by subgroup in the CONFIRM trial.[79]

Adverse Events

Overall, participants in all groups experienced similar numbers of adverse events leading to discontinuation of the study drug (12% dimethyl fumarate 240 mg twice daily; 12% dimethyl fumarate 240 mg 3 times daily; 10% glatiramer acetate 20 mg daily; 10% placebo; no *P* value reported).[79] Participants in all groups also experienced similar numbers of serious adverse events (17% dimethyl fumarate 240 mg twice daily; 16% dimethyl fumarate 240 mg 3 times daily; 17% glatiramer acetate 20 mg daily; 22% placebo; no *P* value reported).[79] Overall, 3 participants died during the trial or within 30 days after trial withdrawal.[79] In the dimethyl fumarate 240 mg 3 times daily group, 1 patient died from complications after an MS relapse; in the glatiramer acetate 20 mg daily group, 1 patient died from suicide; and in the placebo group, 1 patient died from a stroke.[79]

The most common adverse events experienced by participants in the dimethyl fumarate groups experienced were relapse (31%) and flushing (31%).[79] Although participants in all groups experienced similar numbers of MS relapse (a range of 25% to 43%), more participants in the dimethyl fumarate groups than in the other 2 groups experienced flushing (24% and 31% vs. 2% and 4%).[79] In the glatiramer acetate group, the most commonly experienced adverse events were relapse (34%) and nasopharyngitis (15%), although participants in all groups reported similar levels of nasopharyngitis (15% to 18%).[79] Participants in the glatiramer acetate group also reported higher injection-related events (injection-related pain, 8%; injection-related erythema, 9%).[79]

The incidence of serious infections was low and similar (1 to 2%) across all groups and no participant reported opportunistic infections during the trial.[79] No participants in the dimethyl fumarate groups reported any malignant neoplasms.[79] However, 1 patient was diagnosed with breast cancer in the placebo group and 4 patients in the glatiramer acetate group were diagnosed with cancer (1 case of basal-cell carcinoma, 1 of cervical carcinoma, 1 of endometrial cancer, and 1 of thyroid cancer).[79] Participants in all groups experienced similar rates of raised aminotransferase levels (defined as at least 3 times the upper limit of the normal range) and no elevations were concurrent with raised bilirubin levels (defined as more than twice the upper limit of the normal range).[79]

Harms by Subgroup

We did not identify any evidence on the harms by subgroup in the CONFIRM trial.[79]

Fingolimod vs. Interferon Beta-1b

Study Characteristics

We identified 1 eligible RCT comparing fingolimod and interferon beta-1b in adults with RRMS (Table 28).[172] In the GOLDEN trial,[172] 157 participants were randomized to fingolimod 0.5 mg once daily or subcutaneous injections of interferon beta-1b 250 μg every other day for 18 months. We assessed the GOLDEN trial as of poor methodological quality because of a lack of reporting of key trial components, including randomization, high and differential losses to follow-up, and author conflicts of interest. The authors designed the GOLDEN trial to provide pilot evidence for the effect of fingolimod and interferon beta-1b on cognitive, MRI and clinical outcomes, and a direct comparison between fingolimod and interferon beta-1b was not a prespecified objective.[172]

Table 28. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Fingolimod vs. Interferon Beta-1b				
Comi et al., 2017[172] 36 sites in Italy and Germany NCT01333501 GOLDEN	• Adults with RRMS • Total N = 157 randomized; n = 106, fingolimod; n = 51, interferon beta-1b	Fingolimod 0.5 mg, oral, once daily	Interferon beta-1b 250 μg SC injection, every other day	18 months

Abbreviations. μg: microgram; mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous.

Disability

At 18 months, the EDSS scores in both treatment groups remained relatively stable, with only small increases over the study period (mean increase of 0.12; 95% CI, -0.07 to 0.31, fingolimod; mean increase of 0.19; 95% CI, -0.03 to 0.40, interferon beta-1b; *P* value between groups not reported).[172]

Clinical Exacerbation or Relapse

At 18 months, patients in the fingolimod groups experienced lower rates of relapse (ARR, 0.12) than patients in the interferon beta-1b group (ARR, 0.39; *P* value between groups not reported).[172] The number of people with at least 1 relapse was also significantly lower in the fingolimod group compared with the interferon beta-1a group (15.38% vs. 31.91%; *P* = .02).[172]

Functional Outcomes

No functional outcomes were reported in the GOLDEN trial.[172]

Persistence

Overall, significantly more participants randomized to fingolimod completed the 18-month trial compared with those randomized to interferon beta-1b (97 of 106, vs. 30 of 51; 91.5% vs. 58.8%; *P* < .001).[172]

Other Outcomes of Effectiveness

Participants in the fingolimod and interferon beta-1b groups showed improvements in cognitive functioning at 18 months, as measured by the PASAT-2 and PASAT-3 tests, but there were no significant differences between the treatment groups.[172]

Effectiveness by Subgroup

We did not identify any evidence on the effectiveness by subgroup in the GOLDEN trial.[172]

Adverse Events

Participants in both the fingolimod group and the interferon beta-1b group discontinued the trial because of adverse events (4.81% vs. 6.38%; *P* = .69).[172] Participants in both groups also experienced similar rates of serious adverse events (8.65% vs. 2.13%; *P* = .14).[172] No deaths were observed during the study period.[172]

Overall, patients in the fingolimod groups reported more adverse events than patients in the interferon beta-1b group (79.81% vs. 59.57%; *P* = .009).[172] The most commonly reported adverse events, by organ class, in the fingolimod group were infections and infestations (28%, primarily nasopharyngitis and influenza) and investigations (25%, primarily alanine aminotransferase, cholesterol and transaminase increases).[172] In the interferon beta-1b group, the most commonly reported adverse events were nervous system disorders (26%, primarily MS relapses) and general disorders and administration-site conditions (21%, primarily fever, fatigue and influenza-like illnesses).[172]

In the fingolimod group, 1 patient experienced second-degree atrioventricular block after the first dose, and this event was suspected of being related to the study treatment.[172]

Harms by Subgroup

We did not identify any evidence on the harms by subgroup in the GOLDEN trial.[172]

Fingolimod vs. Interferon Beta-1a
Study Characteristics

We identified 1 eligible RCT comparing fingolimod and interferon beta-1a in adults with RRMS (Table 29).[95] In the TRANSFORMS trial,[95] 1,292 participants were randomized to fingolimod 0.5 mg daily, fingolimod 1.25 mg daily, or intramuscular injections of interferon beta-1a 30 μg once a week for 12 months. We assessed the TRANSFORMS trial as of fair methodological quality due to concerns about the potential for unblinding because of adverse events, author conflicts of interest, and funding by industry.

Patients in the TRANSFORMS trial were eligible to continue in an extension study.[156] Patients in the fingolimod groups continued with the same treatment and patients interferon beta-1a 30 μg

once a week were rerandomized to fingolimod 0.5 mg daily or fingolimod 1.25 mg daily for an additional 12 months.[156]

Table 29. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Fingolimod vs. Interferon Beta-1a				
Cohen et al., 2010[95] 172 sites in 18 countries, the U.S. NCT00340834 TRANSFORMS	• Adults with RRMS • Total N = 1,292 randomized; n = 431, fingolimod 0.5 mg; n = 426, fingolimod 1.25 mg; n = 435, interferon beta-1a	Fingolimod 0.5 mg oral daily; fingolimod 1.25 mg oral daily	Interferon beta-1a 30 µg IM injection, once a week	12 months

Abbreviations. IM: intramuscular; µg: microgram; mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis.

Disability

At 12 months, levels of disability for patients in the fingolimod 0.5 mg daily and in the interferon beta-1a group remained relatively stable, and there was no significant difference between the groups (P = .06).[95] Patients in the fingolimod 1.25 mg group, a dose which is not FDA-approved, did experience greater improvements in disability compared with interferon beta-1a, but this was not considered as statistically significant because of the prespecified hierarchical testing plan.[95] The rates of participants who had no disability progression were similar between the fingolimod 0.5 mg daily and interferon beta-1a groups (94.1% vs. 92.1%; P = .25), and between the non-FDA-approved dose of fingolimod 1.25 mg and interferon beta-1a groups (93.3% vs. 92.1%; P = .50).[95]

In the extension study,[156] the time to first confirmed disability progression did not differ between patients in the continuous fingolimod and the switch groups.[156]

Clinical Exacerbation or Relapse

At 12 months, the ARR was lower in the fingolimod 0.5 mg daily group compared with the interferon beta-1a group (0.16 vs. 0.33; P < .001).[95] More patients in the fingolimod 0.5 mg daily group had no relapses compared with the interferon beta-1a group (82.6% vs. 69.3%; P < .001).[95] In the fingolimod 0.5 mg daily group, patients also experienced a longer time to relapse compared with interferon beta-1a (P < .001).[95] Similar results were seen for the non-FDA-approved dose of fingolimod 1.25 mg compared with interferon beta-1a.[95]

In the extension study,[156] patients who continued with fingolimod had sustained low ARRs (0.12 in months 0 to 12, vs. 0.11 in months 13 to 24; P = .08).[156] Patients who switched from interferon beta-1a to fingolimod had a lower ARR after switching (0.31 in months 0 to 12 vs. 0.22 in months 13 to 24; P = .049).[156] At up to 4.5 years, patients who continued with fingolimod had a sustained reduction in relapse compared with patients who switched from interferon beta-1a (0.17 vs. 0.27; HR, 0.65; P < .001).[167]

Functional Outcomes

At 12 months functional ability, as measured using the MSFC, was relatively unchanged from baseline and there were no differences between groups.[95]

Persistence

Overall, 1,153 of 1,292 patients (89%) completed the 12-month trial, with 1,123 (87%) remaining on the study drug.[95] The rates of study completion were similar across the 3 treatment groups (398 of 431, 92.3% fingolimod 0.5 mg; 369 of 426, 86.6% fingolimod 1.25 mg; 386 of 435, 88.7% interferon beta-1a), although fingolimod was marginally statistically higher when compared with interferon beta-1a .[95]

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the TRANSFORMS trial.[95]

Effectiveness by Subgroup

Khatri et al.[157] conducted a post hoc analysis of TRANSFORMS data, among patient subgroups defined by prior treatment history. Patients in the fingolimod 0.5 mg group had lower ARRs than patients in the interferon beta-1a group in the following subgroups[157]:
- Prior interferon beta or glatiramer acetate treatment (0.23 vs. 0.54; $P < .001$)
- Naïve to interferon beta treatment (0.19 vs. 0.33; $P = .009$)
- Naïve to glatiramer acetate treatment (0.17 vs. 0.40; $P < .001$)
- Discontinued prior treatment due to unsatisfactory therapeutic effect (0.26 vs. 0.62; $P = .03$)
- Reason other than discontinued prior treatment due to unsatisfactory therapeutic effect (0.20 vs. 0.41; $P < .001$)
- Reason other than discontinued prior treatment due to adverse events (0.18 vs. 0.41; $P < .001$)
- No prior treatment (0.14 vs. 0.31; $P = .002$)
- More than 1 year to 3 years of prior treatment (0.23 vs. 0.50; $P = .01$)
- More than 3 years of prior treatment (0.31 vs. 0.59; $P = .008$)

Patients in the fingolimod 0.5 mg group had similar ARRs to patients in the interferon beta-1a group in the following subgroups[157]:
- Prior glatiramer acetate treatment (0.45 vs. 0.62; $P = .28$)
- Discontinued prior treatment due to adverse events (0.40 vs. 0.57; $P = .28$)
- 1 year of prior treatment or less (0.22 vs. 0.46; $P = .06$)

Adverse Events

Participants in the non-FDA-approved dose group (fingolimod 1.25 mg) had the highest rates of adverse events leading to discontinuation (10.0%), compared with 5.6% in the fingolimod 0.5 mg group and 3.7% in the interferon beta-1a group.[95] A similar pattern was seen for serious adverse events (7.0% fingolimod 0.5 mg, 10.7% fingolimod 1.25 mg, 5.8% interferon beta-1a; P value not reported).[95] During the study period, 2 people in the fingolimod 1.25 mg group died; 1 from disseminated varicella zoster infection and 1 from herpes simplex encephalitis.[95]

In both fingolimod groups, the most commonly reported adverse events were nasopharyngitis (21% and 22%) and headache (23%).[95] In the interferon beta-1a group, participants reported

influenza-like illnesses (37%) most commonly, with nasopharyngitis (20%) and headache (20%) being the next most commonly reported adverse events.[95]

Rates of serious infection were low across all groups (range of 0.2% to 1.7%).[95] Overall, 14 patients were diagnosed with cancer (3 basal cell carcinomas, 3 melanomas, and 2 breast cancers in the fingolimod 0.5 mg group; 2 basal cell carcinomas and 2 breast cancers in the fingolimod 1.25 mg group; 1 basal cell carcinoma; and 1 squamous cell carcinoma in the interferon beta-1a group).[95] Patients in the fingolimod groups experienced higher rates of raised alanine aminotransferase levels (defined as 3 times the upper limit of the normal range) compared with the interferon-beta 1a group (8% and 7% vs. 2%).[95]

Harms by Subgroup

Patients had similar rates of adverse events and serious adverse events in the subgroups of prior disease-modifying therapy, reasons for discontinuation of prior therapy, and duration of prior therapy.[157] None of the subgroups were associated with an increased incidence of serious adverse events related to increased liver enzymes, macular edema, or infections.[157]

Fingolimod vs. Injectable Disease-modifying Therapies

Study Characteristics

We identified 1 eligible RCT comparing fingolimod with injectable disease-modifying therapies, specifically interferon beta-1a, interferon beta-1b, and glatiramer acetate, in adults with RRMS (Table 30).[69] In the PREFERMS trial,[69] 875 participants were randomized to oral fingolimod 0.5 mg once daily or to injectable disease-modifying therapies for 48 weeks. We assessed the PREFERMS trial as of poor methodological quality due to concerns about the lack of blinding, high and differential loss to follow-up, author conflicts of interest, and funding by industry.

Table 30. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Fingolimod vs. Injectable MS Therapies				
Cree et al., 2018[69] 117 sites in the U.S. NCT01623596 PREFERMS	• Adults with RRMS • Total N = 875 randomized; n = 436, fingolimod; n = 439, injectable DMT	Fingolimod 0.5 mg, oral daily	Injectable DMTs (interferon beta-1a, interferon beta-1b, or glatiramer acetate)	48 weeks

Abbreviations. DMT: disease-modifying therapy; mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis.

Disability

No disability outcomes were reported in the PREFERMS trial.[69]

Clinical Exacerbation or Relapse

At 28 weeks, participants in the fingolimod and injectable DMT groups had similar ARRs of relapse (ARR, 0.22 vs. 0.31; rate ratio, 0.70; 95% CI, 0.47 to 1.05).[69]

Functional Outcomes

No functional outcomes were reported in the PREFERMS trial.[69]

Persistence

Overall, 81.5% of the randomized participants completed the 48-week trial with significantly higher rates of persistence in the fingolimod group (374 of 436, 85.8% fingolimod; 339 of 439, 77.2% injectable DMT).[69] More people in the fingolimod group continued on the study drug compared with the injectable DMT group (81.3% vs. 29.2%; 52.1% absolute group difference; 95% CI, 46.4% to 57.8%).[69]

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the PREFERMS trial.[69]

Effectiveness by Subgroup

In PREFERMS, 141 of 875 patients (16.1%) randomized identified as African American.[138] Overall, African American participants in the fingolimod group were more likely to be retained in the trial at 48 weeks than patients in the injectable DMT group (80.6% vs. 30.4%; $P < .001$).

Adverse Events

Fewer participants in the fingolimod group discontinued because of adverse events when compared with the injectable DMT group (9.2% vs. 23.4%).[69] However, more serious adverse events were reported in the fingolimod group than in the injectable DMT group (6.7% vs. 3.5%).[69] Overall, 3 patients died; 1 of myocardial infarction during screening, 1 of metastatic small-cell lung carcinoma (the patient started on an injectable DMT and then switched to fingolimod), and 1 from cardiopulmonary arrest in the injectable DMT group.[69] Deaths were assessed as being unrelated to study medications.[69]

In the fingolimod group, the most commonly reported adverse events leading to discontinuation, were nervous system disorders (0.02 adverse events per patient year) and general disorders and administration site conditions (e.g., nonspecific disorders that impact several body systems or sites; 0.01 adverse events per patient year).[69] The most commonly reported adverse events in the injectable DMT group were general disorders and administration site conditions, which included injection-site reactions (specifically injection-site pain, erythema, and itching; 0.42 adverse events per patient year) and fatigue.[69]

In the fingolimod group, 3 total patients experienced serious adverse events, with 2 patients experiencing pneumonia, dehydration, and suicidal ideation, and 1 patient reporting anxiety.[69] In the injectable DMT group, 2 patients also reported anxiety as a serious adverse event.[69] No patients experienced serious opportunistic infections (e.g., progressive multifocal leukoencephalopathy).[69] Small numbers of participants in both groups discontinued treatment because of hepatic side effects, although rates were higher in the fingolimod group than in the injectable DMT group (2.46% vs. 0.35%).[69]

Harms by Subgroup

We did not identify any evidence on the harms by subgroup in the PREFERMS trial.[69]

Glatiramer Acetate vs. Interferon Beta-1b

Study Characteristics

We identified 2 eligible RCTs (BECOME and BEYOND) comparing glatiramer acetate with interferon beta-1b in adults with RRMS (Table 31).[82,85] The BECOME trial[82] also included people with CIS. In the BECOME trial,[82] 75 participants were randomized to subcutaneous injections of glatiramer acetate 20 mg once a day or to subcutaneous injections of interferon beta-1b 250 µg every other day for up to 2 years. In the BEYOND trial,[85] 2,244 participants were randomized to subcutaneous injections of glatiramer acetate 20 mg once a day, subcutaneous injections of interferon beta-1b 500 µg every other day, or subcutaneous injections of interferon beta-1b 250 µg every other day, for up to 3.5 years. We assessed the BECOME trial as of poor methodological quality because of the lack of blinding, the small sample size, author conflict of interests, and funding by industry. We assessed the BEYOND trial as of fair methodological quality because of concerns about the method of analysis (per-protocol), author conflict of interests, and funding by industry.

Table 31. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Glatiramer Acetate vs. Interferon Beta-1b				
Cadavid et al., 2009[82] 2 sites in the U.S. NCT00176592 BECOME	• Adults with RRMS • Total N = 75 randomized; n = 39, glatiramer acetate; n = 36, interferon beta-1b	Glatiramer acetate 20 mg once daily, SC injection	Interferon beta-1b 250 µg SC injection, every other day	Up to 2 years
O'Connor et al., 2009[85] 198 sites in 26 countries, including in the U.S. NCT00099502 BEYOND	• Adults with RRMS • Total N = 2,244 randomized; n = 448, glatiramer acetate; n = 899, interferon beta-1b 500 µg; n = 897, interferon beta-1b 250 µg	Glatiramer acetate 20 mg once daily, SC injection; interferon beta-1b 500 µg, SC injection every other day	Interferon beta-1b 250 µg SC injection, every other day	Up to 3.5 years

Abbreviations. µg: microgram; mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous.

Disability

Only the BEYOND trial evaluated disability progression and neither trial evaluated changes in EDSS. In BEYOND, at 2 years, participants in the glatiramer acetate and interferon beta-1b 250 µg groups experienced similar rates of disability progression (20% vs. 21%; *P* = .68).[85] The change in time to confirmed progression was also similar between the glatiramer acetate and interferon beta-1b 250 µg groups (268 days vs. 274 days; *P* = .35).[85] Similar results were seen for the dose of interferon beta-1b 500 µg, which is not the standard recommended dose for MS.[85] There were also no differences in disability outcomes between the 2 doses of interferon beta-1b.[85]

Clinical Exacerbation or Relapse

In the BECOME trial at 18 months (Figure 8),[82] patients in the glatiramer acetate and interferon beta-1b groups experienced similar rates of being relapse-free (72% vs. 53%; *P* = .10; ARRs, 0.33 vs. 0.37; *P* = .68) and time to first relapse (121 days vs. 123 days; *P* = .12).[82]

In the BEYOND trial at 24 months (Figure 8), similar proportions of patients in the glatiramer acetate and interferon beta-1b 250 μg groups were relapse-free (59% vs. 58%; *P* = .72; Figure 8).[85] The ARR was also similar between the glatiramer acetate and interferon beta-1b 250 μg groups (0.34 vs. 0.36; *P* = 0.79), as was the risk of relapse (HR interferon beta-1a vs. glatiramer acetate, 1.06; 95% CI, 0.89 to 1.26).[85] Patients in both the glatiramer acetate and interferon beta-1b 250 μg groups had a similar time to the first relapse (271 days vs. 283 days; *P* = .75).[85]
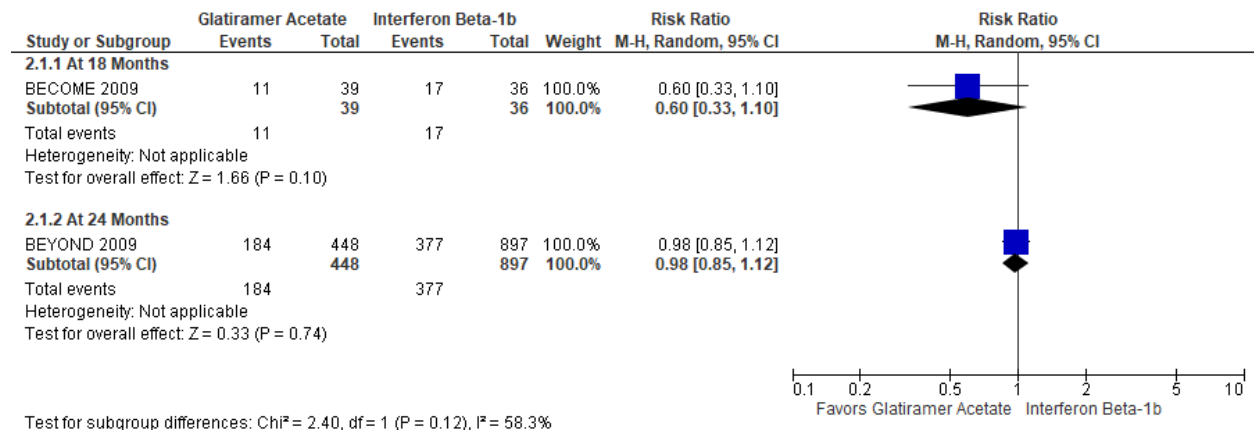
Figure 8. Glatiramer Acetate vs. Interferon Beta-1b 250. Relapse.

Similar results were seen for the dose of interferon beta-1b 500 μg, which is not the standard recommended dose for MS.[85] There were also no differences in relapse outcomes between the 2 doses of interferon beta-1b.[85]

Functional Outcomes

Functional outcomes were not reported in the BECOME and BEYOND trials.[82,85]

Persistence

In the BECOME trial, 89.7% of participants in the glatiramer acetate group and 80.6% of participants in the interferon beta-1b group completed the 2-year trial (Figure 9).[82] In the BEYOND trial at 24 months, 82.6% of participants in the glatiramer acetate group, 87.4% in the interferon beta-1b 250 μg group, and 80.8% in the interferon beta-1b 500 μg group completed the trial, with a longest duration of follow-up of 3.5 years (Figure 9).[85]
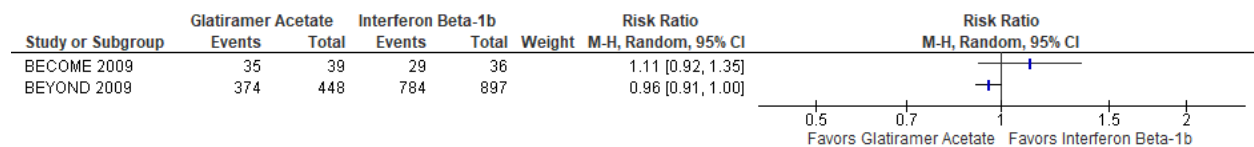
Figure 9. Glatiramer Acetate vs. Interferon Beta-1b 250. Completed Study.

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the BECOME and BEYOND trials.[82,85]

Effectiveness by Subgroup

In the BECOME trial,[85] there were no differences between glatiramer acetate and interferon beta-1b in relapse-based or disability-based outcomes in any subgroups, stratified by baseline disease activity, severity, or duration.

Adverse Events

In the BECOME trial,[82] 4 patients in each group discontinued because of adverse events (4 in the glatiramer acetate group because of trial failure, and 1 patient with skin necrosis and 3 because of treatment failures in the interferon beta-1b group). No further details of adverse events were reported.[82]

In the BEYOND trial,[85] 1.8% of the participants in the glatiramer acetate group, 2.3% in the interferon beta-1b 250 μg group, and 1.5% in the interferon beta-1b 500 μg withdrew because of adverse events. Rates of serious adverse events were 13% in the glatiramer acetate group, 11% in the interferon beta-1b 250 μg group, and 16% in the interferon beta-1b 500 μg.[85] Overall, 4 participants died during the trial (1 patient in the glatiramer acetate group and 3 patients in the interferon beta-1b 500 μg; no details on cause of death were reported).[85]

The most commonly reported events in the glatiramer acetate group were injection-site reactions (58%), headache (27%), fatigue (21%), and nasopharyngitis (24%).[85] In the interferon beta-1b groups, the most commonly reported adverse events were influenza-like illness (40% to 45%), injection-site reactions (48% to 55%), headache (32% to 33%), fatigue (22 to 24%), and nasopharyngitis (18% to 20%).[85] Of the most commonly reported adverse events:

- Patients in the interferon beta-1b group experienced higher rates of influenza-like illness (40% interferon beta-1b 250 μg, vs. 45% interferon beta-1b 500 μg, vs. 6% glatiramer acetate; $P < .001$).[85]
- Patients in the interferon beta-1b 250 μg group experienced lower rates of injection-site reactions (48% interferon beta-1b 250 μg, vs. 55% interferon beta-1b 500 μg, vs. 58% glatiramer acetate; $P < .001$).[85]
- Patients in the interferon beta-1b 250 μg group experienced lower rates of nasopharyngitis (18% interferon beta-1b 250 μg, vs. 20% interferon beta-1b 500 μg, vs. 24% glatiramer acetate; $P = .01$).[85]

Patients in the interferon beta-1b groups experienced higher rates of abnormal liver function (raised alanine aminotransferase, 11% interferon beta-1b 250 μg, vs. 16% interferon beta-1b 500 μg, vs. 4% glatiramer acetate; $P < .001$; raised aspartate aminotransferase, 9% interferon beta-1b 250 μg, vs. 13% interferon beta-1b 500 μg, vs. 2% glatiramer acetate; $P < .001$).[85]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the BECOME and BEYOND trials.[82,85]

Glatiramer Acetate vs. Interferon Beta-1a

Study Characteristics

We identified 3 eligible RCTs comparing glatiramer acetate and interferon beta-1a in adults with RRMS (Table 32).[72,75,80]

- In the trial by Calabrese et al.,[80] 165 participants were randomized to subcutaneous injections of glatiramer acetate 20 mg once a day, subcutaneous interferon beta-1a 44 μg 3 times a week, and intramuscular interferon beta-1a 30 μg once a week.
- In the CombiRx trial,[75] 509 participants were randomized to subcutaneous injections of glatiramer acetate 20 mg daily or intramuscular injections of interferon beta-1a 30 μg once a week. A further 499 participants were randomized to subcutaneous injections of glatiramer acetate 20 mg daily plus intramuscular injections of interferon beta-1a 30 μg once a week, and the results for the combined therapy are presented later in the report (Combination of Glatiramer Acetate Plus Interferon Beta-1a).[75]
- In the REGARD trial,[72] 764 participants were randomized to subcutaneous injections of glatiramer acetate 20 mg once a day or subcutaneous interferon beta-1a 44 μg 3 times a week.

We assessed the CombiRx trial as of fair methodological quality due to concerns about high loss to follow-up and author conflicts of interest. We assessed Calabrese et al., 2012 and the REGARD trial as of poor methodological quality because of concerns about randomization and blinding, high and differential loss to follow-up (in REGARD), author conflicts of interest, and funding by industry.[72]

Table 32. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Glatiramer Acetate vs. Interferon Beta-1a				
Calabrese et al., 2012[80] Single site in Italy Not reported Not reported	• Adults with RRMS • Total N = 165 randomized; n = 55, glatiramer acetate; n = 55, interferon beta-1a SC; n = 36, interferon beta-1a IM	Glatiramer acetate 20 mg SC, once daily	Interferon beta-1a 44 μg SC, 3 times a week; interferon beta-1a 30 μg IM, once a week	24 months
Lublin et al., 2013[75] 68 sites in the U.S. and Canada NCT00211887 CombiRx	• Adults with RRMS • Total N = 1,008 randomized; n = 259, glatiramer acetate; n = 250, interferon beta-1a; n = 499, combination	Glatiramer acetate 20 mg SC, once daily with placebo once a week	Interferon beta-1a 30 μg IM, once a week, with daily placebo; glatiramer acetate 20 mg plus interferon beta-1a 30 μg	36 months
Mikol et al., 2008[72] 81 sites in 14 countries, including the U.S.	• Adults with RRMS • Total N = 764 randomized; n = 378, glatiramer acetate; n = 386, interferon beta-1a	Glatiramer acetate 20 mg SC, once daily	Interferon beta-1a 44 μg SC 3 times a week	96 weeks

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
NCT00078338 REGARD				

Disability

Patients in the glatiramer acetate and interferon beta-1a groups experienced similar rates of progression to disability at 24 months in the REGARD trial and at 36 months in the CombiRx trial (Figure 10).[72,75]

Figure 10. Glatiramer Acetate vs. Interferon Beta-1a. Confirmed Disability Progression.

Participants in the glatiramer acetate and interferon beta-1a groups had similar increases in disability, as measured by the EDSS (0.3 glatiramer acetate, vs. 0.2 subcutaneous interferon beta-1a, vs. 0.2 intramuscular interferon beta-1a; $P > .05$).[80]

Clinical Exacerbation or Relapse

Patients in the glatiramer acetate and interferon beta-1a groups experienced similar rates of relapse at 24 months in the REGARD trial and at 36 months in the CombiRx trial (Figure 11).[72,75]
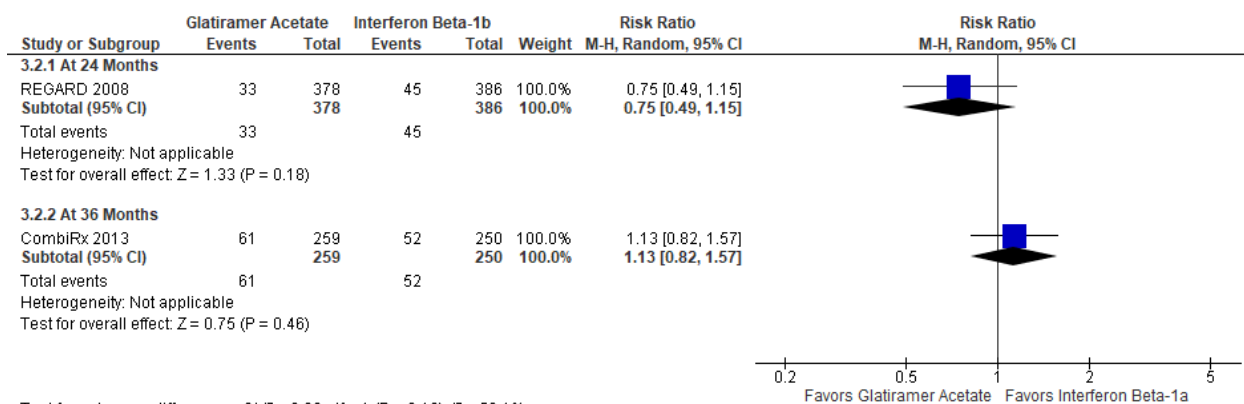
| | Glatiramer Acetate | | Interferon Beta-1b | | | Risk Ratio | Risk Ratio |
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.1.1 At 24 Months							
REGARD 2008	132	378	126	386	100.0%	1.07 [0.88, 1.30]	
Subtotal (95% CI)		378		386	100.0%	**1.07 [0.88, 1.30]**	
Total events	132		126				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.67 (P = 0.51)							
3.1.2 At 36 Months							
CombiRx 2013	53	259	65	250	100.0%	0.79 [0.57, 1.08]	
Subtotal (95% CI)		259		250	100.0%	**0.79 [0.57, 1.08]**	
Total events	53		65				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.47 (P = 0.14)							

Test for subgroup differences: Chi² = 2.57, df = 1 (P = 0.11), I² = 61.1%

Figure 11. Glatiramer Acetate vs. Interferon Beta-1a. Relapse.

The impact of treatment on ARRs varied across the 3 RCTs:

- In the trial by Calabrese et al., the ARR was 0.5 (standard deviation [SD], 0.4) in the glatiramer acetate group compared with 0.4 (SD, 0.6) in the subcutaneous and 0.5 (SD, 0.6) in the intramuscular interferon beta-1a groups at 24 months.[80] No *P* value was reported.[80]
- In the REGARD trial, participants in the glatiramer acetate group had a similar ARR to participants in the interferon beta-1a group at 24 months (0.29 vs. 0.30; *P* = .83).[72]
- In the CombiRx trial, participants in the glatiramer acetate group had a lower ARR at 36 months than participants in the interferon beta-1a group (0.11 vs. 0.16; *P* = .03).[75] ARR was also assessed at 24 months and was reported as being very similar to the 36-month results, but data were not reported.[75]

Functional Outcomes

In the CombiRx trial, patients experienced similar improvements in function (MSFC) in the 3 treatment groups (0.2 glatiramer acetate, vs. 0.1 interferon beta-1a, vs. 0.1 combination; *P* > .05).[75] Similar results were also seen for the individual tasks of the timed 25-foot walk, the 9-hole peg test, and the PASAT.[75]

Persistence

Overall, more patients in the glatiramer acetate groups tended to complete the trial compared with patients in the interferon beta-1a groups at 24 months, in both the REGARD trial and the trial by Calabrese et al.,[80] and at 36 months in the CombiRx trial (Figure 12).[72,75,80]
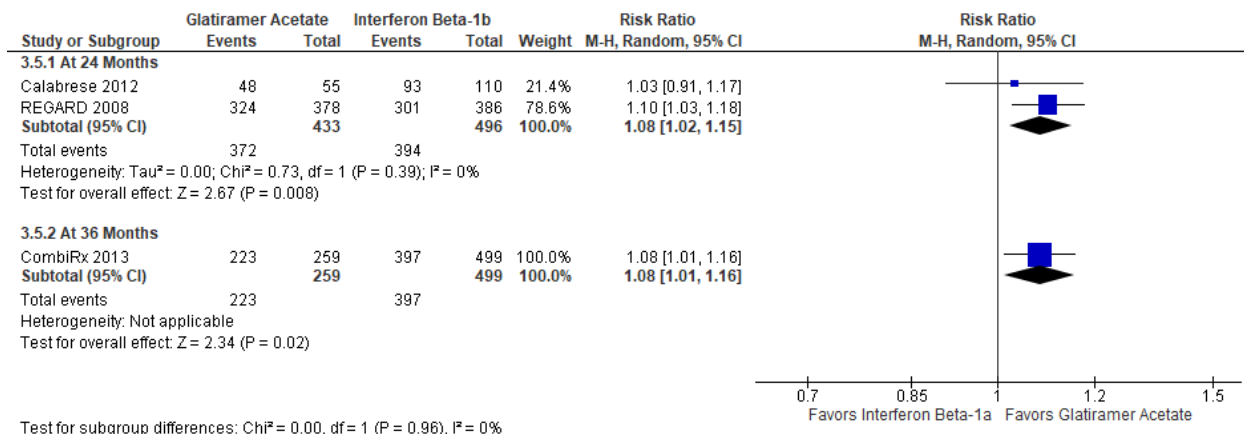
Figure 12. Glatiramer Acetate vs. Interferon Beta-1a. Completed Study.

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the 3 eligible trials.[72,75,80]

Effectiveness by Subgroup

The presence of neutralizing antibodies to interferon beta-1a did not appear to have a significant effect on clinical efficacy (relapse rate or time to relapse) in the REGARD trial.[72]

Adverse Events

There was no clear pattern of withdrawals because of adverse events between the glatiramer acetate and interferon beta-1a groups:

- At 24 and 36 months, 5% and 2.3% respectively of the glatiramer acetate group and 6% and 1.6%, respectively, of the interferon beta-1a group had withdrawn because of adverse events in the REGARD trial.[72]

However, the rates of serious adverse events were similar between the glatiramer acetate and interferon beta-1a groups (Figure 13).[72,75]

Figure 13. Glatiramer Acetate vs. Interferon Beta-1a. Serious Adverse Events.

Overall, 4 deaths were reported in 2 of the 3 eligible trials:

- In the CombiRx trial, 1 patient died from suicide about 3 months after taking the last dose of study drug in the interferon beta-1a group[75]
- In the REGARD trial, 3 patients died (1 due to seizure activity secondary to MS in the interferon beta-1a group; 1 due to pulmonary embolism in the interferon beta-1a group; and 1 due to large-cell lymphoma of the central nervous system in the glatiramer acetate group[72]

- Deaths were not reported in the trial by Calabrese et al.[80]

In the REGARD trial,[72] more participants in the interferon beta-1a group than in the glatiramer acetate group experienced influenza-like illness (31% vs. 1%; *P* < .001), headache (19% vs. 9%; *P* < .001).[72] More participants in the glatiramer acetate group than in the interferon beta-1a group experienced injection-site itching (20% vs. 2%; *P* < .001) and swelling (11% vs. 1%; *P* < .001).[72] In the interferon beta-1a group, 38% were positive for binding antibodies; overall, 34% of patients were positive for neutralizing antibodies at any time during REGARD.[72] Binding antibodies to glatiramer acetate were present in 28% of patients in the glatiramer acetate group at baseline and in 94% at the final assessment.[72]

In the CombiRx trial,[75] the most commonly reported adverse events in the glatiramer acetate group were categorized as nervous system disorders (e.g., extremity pain, soreness or stiffness; 1.9%), psychiatric disorders (e.g., depression; 1.9%), and surgical and medical procedures (details of the specific adverse events were not reported; 1.9%).[75] The most commonly reported adverse events in the interferon beta-1a group were categorized as nervous system disorders (e.g., extremity pain, soreness or stiffness; 4.4%), neoplasms (details of the specific neoplasms were not reported; 2.0%), and surgical and medical procedures (details of the specific adverse events were not reported; 2.0%).[75]

More participants in the interferon beta-1a group than in the glatiramer acetate group experienced raised alanine aminotransferase levels (6% vs. 1%; *P* = .002).[72]

Harms by Subgroup
We did not identify any evidence of harms by subgroup in the 3 eligible trials.[72,75,80]

Interferon Beta-1b vs. Interferon Beta-1a
Study Characteristics
We identified 5 eligible RCTs comparing interferon beta-b and interferon beta-1a in people with MS, including people with RRMS and people with a CIS (Table 33).[76,77,81,83,84]
- The INCOMIN trial[76] randomized 188 participants with RRMS to subcutaneous injections of interferon beta-1b 250 µg every other day or intramuscular interferon beta-1a 30 µg once a week for 24 months. We assessed the INCOMIN trial as of fair methodological quality because of concerns about the lack of blinding.
- The Danish MS Group trial[84] randomized 301 participants with RRMS to subcutaneous injections of interferon beta-1b 250 µg every other day or subcutaneous injections of interferon beta-1a 22 µg 3 times a week for 24 months. We assessed the Danish MS Group trial as of poor methodological quality because of a lack of blinding and the method of analysis (per-protocol rather than intention to treat).
- The trial by Etemadifar et al.[83] randomized 90 participants with RRMS to subcutaneous injections of interferon beta-1b 250 µg every other day, subcutaneous injections of interferon beta-1a 44 µg 3 times a week, or intramuscular interferon beta-1a 30 µg once a week for 24 months. We assessed the trial by Etemadifar et al.[83] as of poor methodological quality because of concerns about a lack of details around randomization, a lack of reporting of author conflicts of interest and funding, and patients were not blinded.

- The trial by Mazdeh et al.[81] randomized 90 participants with MS (including some participants with CIS) to subcutaneous injections of interferon beta-1b 250 µg every other day, subcutaneous injections of interferon beta-1a 44 µg 3 times a week, or intramuscular interferon beta-1a 30 µg once a week for 24 months. We assessed the trial by Mazdeh et al.[81] as of poor methodological quality because of concerns about the lack of details around key study components (e.g., randomization and concealment) and patient characteristics.
- The trial by Mokhber et al.[77] randomized 69 participants with newly diagnosed MS to subcutaneous injections of interferon beta-1b 250 µg every other day, subcutaneous injections of interferon beta-1a 44 µg 3 times a week, or intramuscular interferon beta-1a 30 µg once a week for 12 months. We assessed the trial by Mokhber et al.[77] as of poor methodological quality because of concerns about the lack of details around study components (e.g., randomization) and patients not being blind to treatment.

Table 33. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Interferon Beta-1b vs. Interferon Beta-1a				
Durelli et al., 2002[76] 15 sites in Italy Not reported INCOMIN	• Adults with RRMS • Total N = 188 randomized; n = 96, interferon beta-1b; n = 92, interferon beta-1a	Interferon beta-1b 250 µg SC, every other day	Interferon beta-1a 30 µg IM, once a week	24 months
Etemadifar et al., 2006[83] 2 sites in Iran Not reported Not reported	• Adults with RRMS • Total N = 90 randomized; n = 30, interferon beta-1b; n = 30, interferon beta-1a SC; n = 30, interferon beta-1a IM	Interferon beta-1b 250 µg SC, every other day	Interferon beta-1a 44 µg SC, 3 times a week; interferon beta-1a 30 µg IM, once a week	24 months
Koch-Henriksen et al., 2006[84] 15 sites in Denmark Not reported Danish MS Group	• Adults with RRMS • Total N = 301 randomized; n = 158, interferon beta-1b; n = 143, interferon beta-1a	Interferon beta-1b 250 µg SC, every other day	Interferon beta-1a 22 µg SC, 3 times a week	24 months
Mazdeh et al., 2010[81] Single site in Iran Not reported Not reported	• Adults with MS • Total N = 90 randomized; n = 30, interferon beta-1b; n = 30, interferon beta-1a SC, n = 30, interferon beta-1a IM	Interferon beta-1b 250 µg SC, every other day	Interferon beta-1a 44 µg SC, 3 times a week; interferon beta-1a 30 µg IM, once a week	12 months
Mokhber et al., 2014[77] Single site in Iran Not reported	• Adults with MS • Total N = 69 randomized; n = 23, interferon beta-1b; n = 23 interferon beta-1a SC; n = 23 interferon beta-1a IM	Interferon beta-1b 250 µg SC, every other day	Interferon beta-1a 44 µg SC, 3 times a week; interferon beta-	12 months

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Not reported			1a 30 µg IM, once a week	

Abbreviations. µg: microgram; IM: intramuscular; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous.

Disability

Participants in the interferon beta-1b and interferon beta-1a groups had similar rates of disability progression at 24 months (Figure 14).[76,84]

Figure 14. Interferon Beta-1b vs. Interferon Beta-1a. Confirmed Disability Progression.

In the INCOMIN trial,[76] the time to sustained and confirmed disability progression was significantly longer in the interferon beta-1b group than in the interferon beta-1a group (reported graphically; *P* < .01).

There was also no difference in the levels of disability (EDSS) between groups at 12 months in the trial by Mokhber et al.[77] or at 24 months in the trials by Etemadifar et al.,[83] Mazdeh et al.,[81] and the INCOMIN trial[76] (Figure 15).
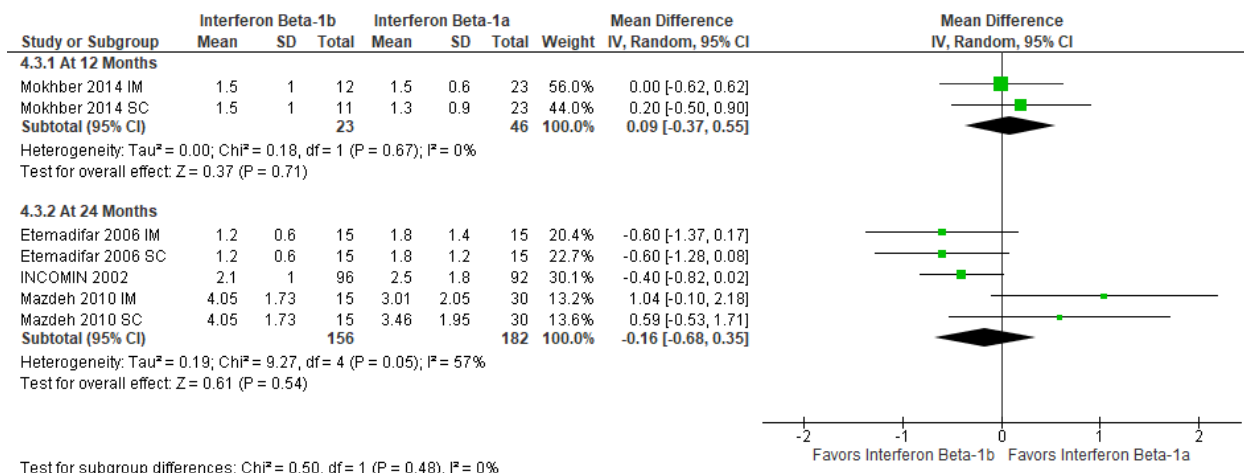

Figure 15. Interferon Beta-1b vs. Interferon Beta-1a. Disability (EDSS).

Clinical Exacerbation or Relapse

Participants in the interferon beta-1b and interferon beta-1a groups had similar rates of relapse at 24 months (Figure 16).[76,83]
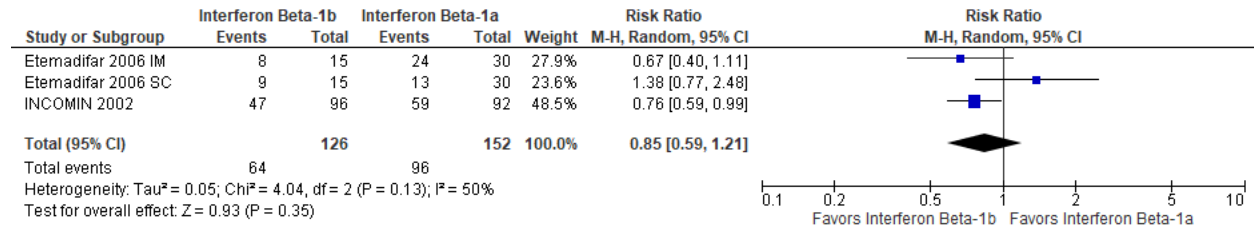

Study or Subgroup	Interferon Beta-1b Events	Total	Interferon Beta-1a Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Etemadifar 2006 IM	8	15	24	30	27.9%	0.67 [0.40, 1.11]
Etemadifar 2006 SC	9	15	13	30	23.6%	1.38 [0.77, 2.48]
INCOMIN 2002	47	96	59	92	48.5%	0.76 [0.59, 0.99]
Total (95% CI)		**126**		**152**	**100.0%**	**0.85 [0.59, 1.21]**
Total events	64		96			

Heterogeneity: Tau² = 0.05; Chi² = 4.04, df = 2 (P = 0.13); I² = 50%
Test for overall effect: Z = 0.93 (P = 0.35)

Figure 16. Interferon Beta-1b vs. Interferon Beta-1a. Relapse.

In the INCOMIN trial,[76] participants in the interferon beta-1b group had a lower ARR than participants in the interferon beta-1a group (0.5 vs. 0.7; *P* = .03).

In the Danish MS Group trial,[84] both groups had similar risks of relapse over the study period (HR, 0.98; 95% CI, 0.72 to 1.32). In the trial by Mazdeh et al.,[81] participants had a similar interval between relapses (mean 0.80 interferon beta-1b, vs. 0.80 interferon beta-1a SC, vs. 1.1 interferon beta-1a IM; the unit was not reported, but is assumed to be years).

Functional Outcomes

Only the trial by Mokhber et al. reported functional outcomes.[77] Participants in the interferon beta-1a groups had higher scores on the PASAT-Easy than at baseline, but participants in the interferon beta-1b group did not show any significant improvement from baseline.[77]

Persistence

At 24 months, similar numbers of participants in the interferon beta-1b and interferon beta-1a groups remained in the trial (Figure 17).

Study or Subgroup	Interferon Beta-1b Events	Total	Interferon Beta-1a Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 At 12 Months						
Mokhber 2014 IM	11	12	20	23	24.2%	1.05 [0.84, 1.33]
Mokhber 2014 SC	11	11	23	23	75.8%	1.00 [0.88, 1.14]
Subtotal (95% CI)		**23**		**46**	**100.0%**	**1.01 [0.90, 1.14]**
Total events	22		43			

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)

Study or Subgroup	Interferon Beta-1b Events	Total	Interferon Beta-1a Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.5.2 At 24 Months						
DMSG 2006	114	158	110	143	11.0%	0.94 [0.82, 1.07]
Etemadifar 2006 IM	15	15	30	30	18.6%	1.00 [0.91, 1.10]
Etemadifar 2006 SC	15	15	30	30	18.6%	1.00 [0.91, 1.10]
INCOMIN 2002	94	96	88	92	51.7%	1.02 [0.97, 1.08]
Subtotal (95% CI)		**284**		**295**	**100.0%**	**1.01 [0.96, 1.05]**
Total events	238		258			

Heterogeneity: Tau² = 0.00; Chi² = 3.45, df = 3 (P = 0.33); I² = 13%
Test for overall effect: Z = 0.22 (P = 0.83)

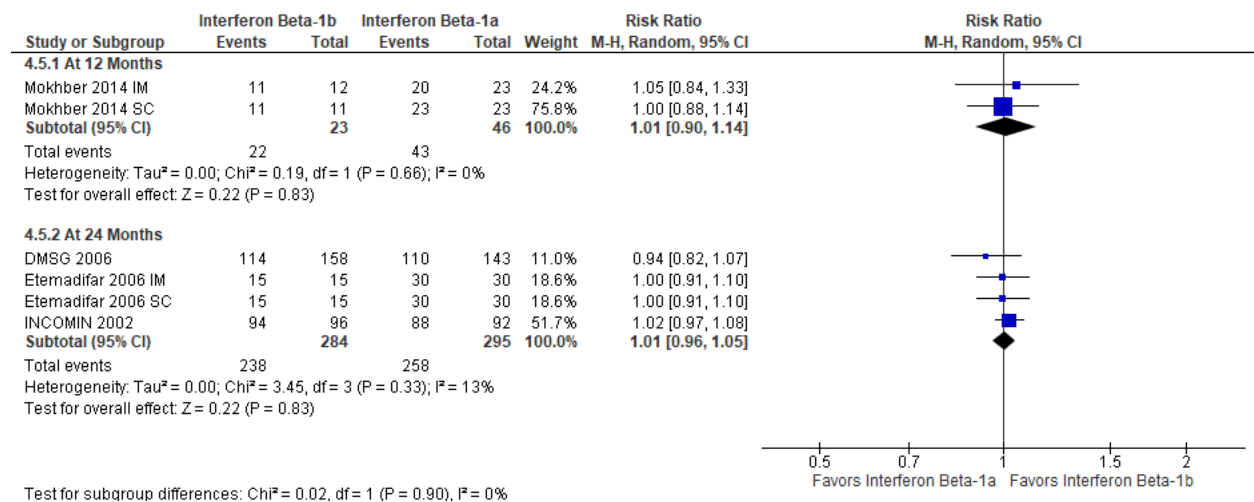Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%

Figure 17. Interferon Beta-1b vs. Interferon Beta-1a. Completed Study.

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the eligible trials.[76,77,81,83,84]

Effectiveness by Subgroup

In the Danish MS Group trial, the presence of neutralizing antibodies at 12 months increased the relapse rate in both groups, but the rates of relapse between interferon beta-1b and interferon beta-1a remained similar.[84]

Adverse Events

In the INCOMIN trial, more patients discontinued because of adverse events or laboratory abnormalities in the interferon beta-1b group (compared with the interferon beta-1a group (5.2% vs 1.1%; *P* = .02).[76] Serious adverse events and deaths were not reported in any of the eligible trials.[76,77,81,83,84]

In general, the RCTs did not report adverse events comprehensively.
- In the INCOMIN trial,[76] the most commonly reported adverse events in both groups were flu-like symptoms (76% to 77%), fever (72% to 73%), and fatigue (48% to 59%). However, participants in the interferon beta-1b group had more injection-site reactions (37% vs. 8%; *P* < .001).[76]
- In the Danish MS Group trial,[84] participants experienced side effects known to be associated with interferon beta-1b and interferon beta-1a (flu-like symptoms, 9.5%; fever, 4.8%; skin reactions, 5.1%; depressive symptoms, 4.0%).
- In the trial by Mazdeh et al.,[81] participants experienced dermal reactions at the site of injection, numbness, flu-like illness, and irregular menses (no further details reported).

Similarly, serious adverse events were not reported well in the included trials. Mazdeh et al.[81] reported that 2 patients in the interferon beta-1b group developed severe necrotizing vasculitis and were excluded from the study. No other trials reported serious adverse events, including deaths.[76,77,83,84] In the INCOMIN trial.[76] more patients in the interferon beta-1b group developed neutralizing antibodies compared to patients in the interferon beta-1a group (30% vs. 7% at 12 months; *P* < .001; 22% vs. 6 % at 24 months; *P* = .01).[76]

Harms by Subgroup

The frequency of neutralizing antibodies in INCOMIN did not differ significantly between patients who relapsed and those who did not relapse during the study.[76]

Ocrelizumab vs. Interferon Beta-1a
Study Characteristics

We identified 3 RCTs comparing ocrelizumab and interferon beta-1a in adults with RRMS and relapsing MS (Table 34).[60,73] In the trial by Kappos et al.,[73] 11 participants were randomized to intravenous infusions of ocrelizumab 600 mg or intramuscular injections of interferon beta-1a 30 µg once a week.[73] A further 109 participants were randomized to intravenous infusions of ocrelizumab 2,000 mg (a non-FDA-approved dose) or placebo.[73] In the OPERA trials, 821 participants in OPERA I and 835 participants in OPERA II were randomized to intravenous infusions of ocrelizumab 600 mg, or subcutaneous injections of interferon beta-1a 44 µg 3 times a week.[60] We assessed the trial by Kappos et al.[73] as of poor methodological quality due to

concerns about lack of blinding, the shorter length of follow-up, author conflict of interests, and funding by industry. We assessed the two OPERA trials as of fair methodological quality because of concerns about author conflict of interests and funding by industry.

Table 34. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Ocrelizumab vs. Interferon Beta-1a				
Hauser et al., 2017[60] 141 sites in 32 countries, including 41 sites in the U.S. NCT01247324 OPERA I	• Adults with relapsing MS • Total N = 821 randomized, n = 410, ocrelizumab; n = 411, interferon beta-1a	Ocrelizumab; 600 mg IV infusion every 24 weeks, administered as 2 300 mg infusions on days 1 and 15 for the first dose and as a single 600 mg infusion thereafter; also received a matching SC placebo injection	Interferon beta-1a 44 µg SC injection, 3 times a week; also received a matching IV placebo infusion	96 weeks
Hauser et al., 2017[60] 166 sites in 24 countries, including 48 sites in the U.S. NCT01412333 OPERA II	• Adults with relapsing MS • Total N = 835 randomized; n = 417, ocrelizumab; n = 418, interferon beta-1a • Mean number of lesions on T_2-weighted MRI (SD): 49.26 (38.59), ocrelizumab; 51.0016 (35.69), interferon beta-1a	Ocrelizumab; 600 mg IV infusion every 24 weeks, administered as 2 300 mg infusions on days 1 and 15 for the first dose and as a single 600 mg infusion thereafter; also received a matching SC placebo injection	Interferon beta-1a 44 µg SC injection, 3 times a week; also received a matching IV placebo infusion	96 weeks
Kappos et al., 2011[73] 79 sites in 20 countries, including the U.S. NCT00676715 Not reported	• Adults with RRMS • Total N = 220 randomized, with 56 in the ocrelizumab 600 mg group, 55 in the ocrelizumab 2,000 mg group, 55 in the interferon beta-1a group, and 54 in the placebo group	Ocrelizumab 600 mg IV, over 2 days in 2 cycles; ocrelizumab 2,000 mg IV, over 2 days in 2 cycles	Interferon beta-1a 30 µg IM, once a week; also placebo	24 weeks

Abbreviations. µg: microgram; IM: intramuscular; IV: intravenous; mg: milligram; MRI: magnetic resonance imaging; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous; SD: standard deviation. T_2: transverse relaxation time.

Disability

Participants in both OPERA trials had lower rates of disability progression in the ocrelizumab groups compared with the interferon beta-1a groups.[60]

- OPERA I: 7.6% vs. 12.2% (HR, 0.57; 95% CI, 0.37 to 0.90)
- OPERA II: 10.6% vs. 15.1% (HR, 0.63; 95% CI, 0.42 to 0.92)

The effectiveness of ocrelizumab on disability progression was also seen when the OPERA I and OPERA II trial results were combined in a preplanned pooled analysis, giving a summary estimate of disability progression in the ocrelizumab groups of 9.1%, vs. 13.6% in the interferon beta-1a groups (HR, 0.60; 95% CI, 0.45 to 0.81).[60] The trial by Kappos et al.[73] did not report any disability-related outcomes.

Clinical Exacerbation or Relapse

Overall, participants in the ocrelizumab 600 mg groups experienced lower rates of relapse than participants in the interferon beta-1a groups:

- ARR of 0.13 in the ocrelizumab group vs. 0.36 in the interferon beta-1a group (P = .03) in the trial by Kappos et al.[73]
- ARR of 0.16 in the ocrelizumab group vs. 0.29 in the interferon beta-1a group in the two OPERA trials (P < .001)[60]

In a pooled analysis of the two OPERA trials, the ARR remained lower in the ocrelizumab group than in the interferon beta-1a groups at all time periods (weeks 8, 12, 24, 48, and 96).[137]

In the trial by Kappos et al.,[73] ocrelizumab 2,000 mg resulted in lower relapse rates than placebo (ARR, 0.17 vs. 0.64; P < .001), but not interferon beta-1a (ARR, 0.17 vs. 0.36; P = .09).

Functional Outcomes

Overall, participants in the two OPERA trials experienced significantly greater improvements in function (MSFC) in the ocrelizumab groups compared with participants in the interferon beta-1a groups (Figure 18).[60] However, the changes are small and the clinical importance is not known. The trial by Kappos et al.[73] did not report any functional outcomes.

Study or Subgroup	Ocrelizumab Mean	SD	Total	Interferon Beta-1a Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
OPERA I 2017	0.21	0.618	410	0.17	0.6188	411	50.0%	0.04 [-0.04, 0.12]
OPERA II 2017	0.28	0.6233	417	0.17	0.6241	418	50.0%	0.11 [0.03, 0.19]
Total (95% CI)			827			829	100.0%	0.07 [0.02, 0.13]

Heterogeneity: Chi² = 1.31, df = 1 (P = 0.25); I² = 24%
Test for overall effect: Z = 2.46 (P = 0.01)

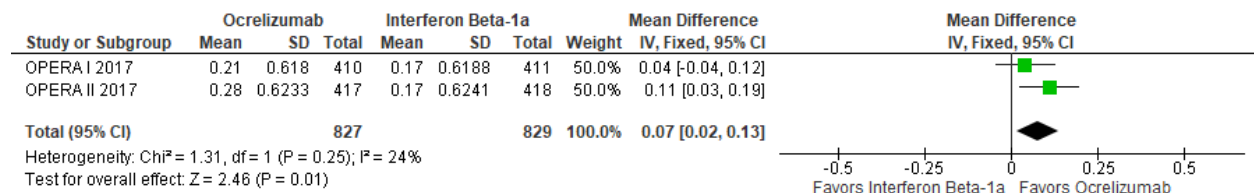Figure 18. Ocrelizumab vs. Interferon Beta-1a. Functional Capacity (MSFC).

Persistence

In the trial by Kappos et al.,[73] at 6 months there was no difference between the ocrelizumab and interferon beta-1a groups in terms of study completion.[73] In the OPERA trials, at 24 months the proportion of people who remained in the trial was significantly higher in the ocrelizumab group (Figure 19).[60]

Study or Subgroup	Ocrelizumab Events	Total	Interferon Beta-1a Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 At 6 Months						
Kappos 2011	51	56	51	55	100.0%	0.98 [0.88, 1.10]
Subtotal (95% CI)		56		55	100.0%	0.98 [0.88, 1.10]
Total events	51		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
5.5.2 At 24 Months						
OPERA I 2017	366	410	340	411	57.8%	1.08 [1.02, 1.14]
OPERA II 2017	360	417	320	418	42.2%	1.13 [1.06, 1.20]
Subtotal (95% CI)		827		829	100.0%	1.10 [1.05, 1.15]
Total events	726		660			
Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 1 (P = 0.31); I² = 3%						
Test for overall effect: Z = 4.31 (P < 0.0001)						

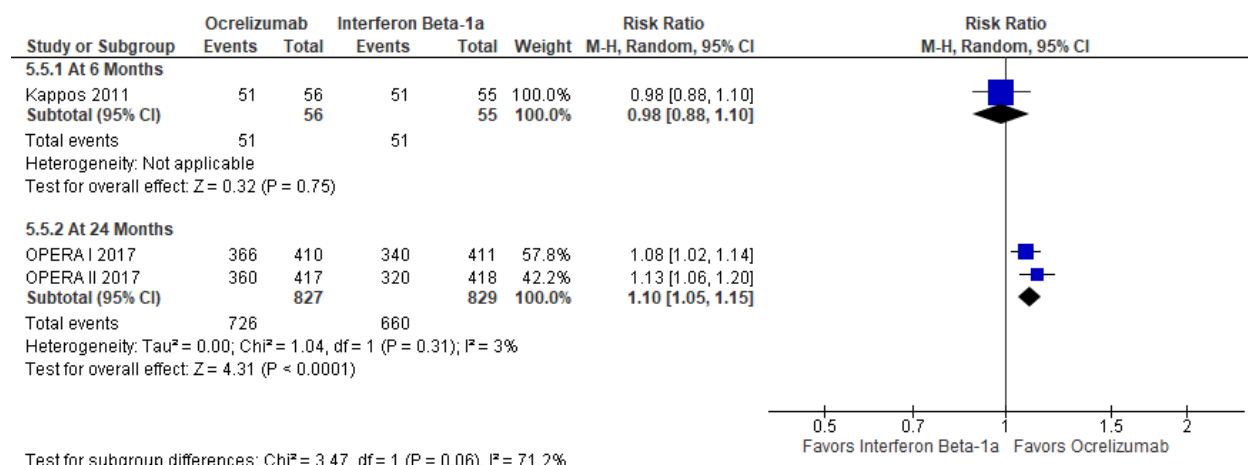Test for subgroup differences: Chi² = 3.47, df = 1 (P = 0.06), I² = 71.2%

Figure 19. Ocrelizumab vs. Interferon Beta-1a. Completed Study.

Other Outcomes of Effectiveness

In OPERA I, participants in both groups had similar changes in their QoL, as measured by the 36-Item Short Form Health Survey ([SF-36]; mean difference [MD], 0.69; 95% CI, -0.41 to 1.80).[60] However, in OPERA II, participants in the ocrelizumab group had greater improvements in their QoL as measured by the SF-36 (MD, 1.16; 95% CI, 0.05 to 2.27).[60]

Effectiveness by Subgroup

In 2019, Turner et al.[163] conducted subgroup analyses of the main endpoints from the pooled OPERA I and OPERA II populations. Overall, ocrelizumab was more effective compared with interferon beta-1a for most subgroups:

- Patients in the ocrelizumab group had lower ARRs in all subgroups (i.e., study, region, sex, age under 40, body mass index [BMI], normalized brain volume, prior disease-modifying therapy in the past 2 years, number of prior relapse, EDSS score, number of T1 gadolinium-enhancing lesions) compared with interferon beta-1a.[163]
  - Older patients (aged 40 and over) had similar ARRs in the ocrelizumab and interferon beta-1a groups (rate ratio, 0.76; 95% CI, 0.56 to 1.03).[163]
- Patients in the ocrelizumab group had lower rates of disease progression in all subgroups (i.e., study, rest of the world, sex, age under 40, normal or low BMI, normalized brain volume, no prior disease-modifying therapy in the past 2 years, 1 or fewer prior relapses, EDSS score of 2.5 or greater, presence of T1 gadolinium-enhancing lesions) compared with interferon beta-1a.[163]
  - Patients in the U.S. had similar rates of disability progression in the ocrelizumab and interferon beta-1a groups (HR, 0.77; 95% CI, 0.47 to 1.26).[163]
  - Patients with a BMI of 25 or more had similar rates of disability progression in the ocrelizumab and interferon beta-1a groups (HR, 0.81; 95% CI, 0.55 to 1.18).[163]
  - Patients who had previous disease-modifying therapy in the last 2 years had similar rates of disability progression in the ocrelizumab and interferon beta-1a groups (HR, 0.61; 95% CI, 0.35 to 1.06).[163]
  - Patients who had 2 or more prior relapses had similar rates of disability progression in the ocrelizumab and interferon beta-1a groups (HR, 0.67; 95% CI, 0.39 to 1.16).[163]

- o Patients who had an EDSS score below 2.5 had similar rates of disability progression in the ocrelizumab and interferon beta-1a groups (HR, 0.82; 95% CI, 0.53 to 1.27).[163]

Adverse Events

In the two OPERA trials, fewer participants in the ocrelizumab groups discontinued because of adverse events, compared to participants in the interferon beta-1a groups.[60] However, more participants in the ocrelizumab groups discontinued because of adverse events, compared to participants in the interferon beta-1a groups in the trial by Kappos et al.[73]

- 3.2% vs. 6.4% in OPERA I[60]
- 3.8% vs. 6.0% in OPERA II[60]
- 4% vs. 2% in the trial by Kappos et al.[60,73]

Participants in the ocrelizumab groups and interferon beta-1a groups experienced similar levels of serious adverse events (Figure 20).[60,73]

Study or Subgroup	Ocrelizumab Events	Total	Interferon Beta-1a Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kappos 2011	1	55	2	54	1.9%	0.49 [0.05, 5.26]
OPERA I 2017	28	408	32	409	45.9%	0.88 [0.54, 1.43]
OPERA II 2017	29	417	40	417	52.1%	0.72 [0.46, 1.15]
Total (95% CI)		880		880	100.0%	0.79 [0.56, 1.09]
Total events	58		74			

Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.43 (P = 0.15)

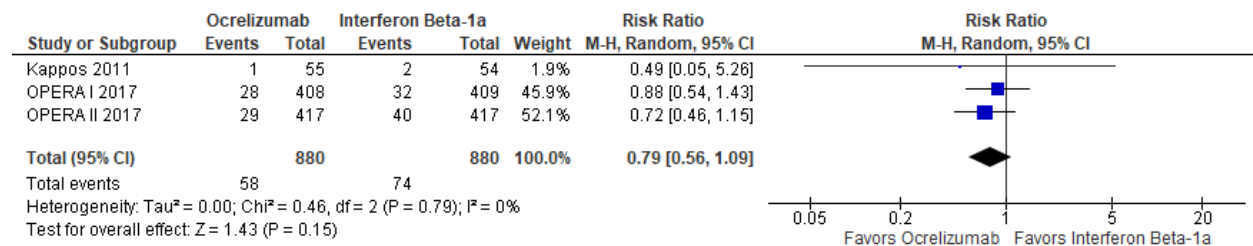Risk Ratio M-H, Random, 95% CI — 0.05 0.2 1 5 20 — Favors Ocrelizumab Favors Interferon Beta-1a

Figure 20. Ocrelizumab vs. Interferon Beta-1a. Serious Adverse Events.

Across the 3 RCTs, 4 participants died[60,73]:
- In OPERA I, 1 participant died by suicide in the interferon beta-1a group.
- In OPERA II, 1 participant died by suicide in the ocrelizumab group and 1 participant died from mechanical ileus in the interferon beta-1a group.
- In the RCT by Kappos et al.,[73] no patients died in the ocrelizumab 600 mg or interferon beta-1a groups. However, 1 patient died of systemic inflammatory response syndrome of undetermined origin in the ocrelizumab 2,000 mg group.[73]

Across OPERA I and II, the most common infections were upper respiratory tract infections (15.2%), nasopharyngitis (14.8%), and urinary tract infections (11.6%).[60] Rates of upper respiratory tract infection and nasopharyngitis were numerically higher with ocrelizumab compared with interferon beta-1a, but rates of urinary tract infections were numerically higher in the interferon beta-1a group.[60] Antidrug-binding antibodies developed in 0.4% of participants who received ocrelizumab in OPERA I and OPERA II and neutralizing antibodies developed in 1 patient in the OPERA II trial.[60] Across OPERA I and OPERA II, neutralizing anti‑interferon beta-1a antibodies were detected in 21.3% of patients.[60]

In the trial by Kappos et al.,[73] participants in the ocrelizumab group experienced urinary tract infections and upper respiratory tract infections more commonly, whereas participants in the interferon beta-1a experienced influenza-like illness and headache more commonly. In the ocrelizumab group, 1 patient had positive human antihuman antibody results at baseline, week 24, and on study day 91.[73]

In OPERA I, 1 patient had a life-threatening episode of bronchospasm during the first infusion of dose 1 and 1 patient was hospitalized for a severe genital herpes simplex infection, which resolved with treatment.[60] Both participants were in the ocrelizumab group.[60] Across the OPERA I and II trials, 6 patients were diagnosed with cancer (2 ductal breast carcinomas, 1 renal cancer, and 1 malignant melanoma in the ocrelizumab groups; 1 mantle-cell lymphoma and 1 squamous cell carcinoma in the interferon beta-1a groups).[60]

A pooled analysis of the two OPERA trials[160] assessed the frequency and severity of infusion-related reactions with ocrelizumab and interferon beta-1a:

- 34.3% of patients in the ocrelizumab group vs. 9.7% in the interferon beta-1a group had an infusion-related reaction
- 92.6% of reactions in the ocrelizumab group vs. 98.8% in the interferon beta-1a group were mild to moderate, and most reactions occurred with the first infusion
- 2.4% of reactions in the ocrelizumab group vs. 0.1% in the interferon beta-1a group were severe.

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the 3 eligible trials.[60,73]

Ozanimod vs. Interferon Beta-1a

Study Characteristics

We identified 2 eligible RCTs comparing ozanimod with interferon beta-1a in adults with relapsing MS (Table 35).[66,67] In the 2 RCTs, 1,320 participants in the RADIANCE Phase 3 trial[66] and 1,346 participants in the SUNBEAM trial[67] were randomized to oral ozanimod 0.5 mg, oral ozanimod 1 mg (both once daily), or intramuscular injections of interferon beta-1a 30 μg once a week. The SUNBEAM trial followed participants for at least 12 months (median duration of follow-up of 13.6 months in the ozanimod groups and 13.5 months in the interferon beta-1a group).[67] The RADIANCE Phase 3 trial assessed participants over a 24-month study period.[66] Ozanimod is not currently FDA-approved, so it is not clear which dose of ozanimod would be the recommended regimen. We assessed the RADIANCE Phase 3 and SUNBEAM RCTs as of fair methodological quality because of concerns about author conflict of interests and funding by industry.

Table 35. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Ozanimod vs. Interferon Beta-1a				
Cohen et al., 2019[66] 147 sites in 21 countries, including the U.S. NCT02047734	• Adults with relapsing MS • Total N = 1,320 randomized; n = 443, interferon beta-1a; n = 443, ozanimod 0.5 mg; n = 434, ozanimod 1 mg	Ozanimod 0.5 mg oral, once daily; ozanimod 1 mg oral, once day; both also received a	Interferon beta-1a 30 μg IM injection, once a week; also received matching	24 months

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
RADIANCE Phase 3		matching IM placebo injection	placebo capsules	
Comi et al., 2019[67] 152 sites in 20 countries, including the U.S. NCT02294058 SUNBEAM	• Adults with relapsing MS • Total N = 1,346 randomized; n = 448, interferon beta-1a; n = 451, ozanimod 0.5 mg; n = 447, ozanimod 1 mg	Ozanimod 0.5 mg oral, once daily; ozanimod 1 mg oral, once daily; both also received a matching IM placebo injection	Interferon beta-1a 30 µg IM injection, once a week; also received matching placebo capsules	Minimum of 12 months

Abbreviations. µg: microgram; IM: intramuscular; mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial.

Disability

In the RADIANCE Phase 3 trial, at 24 months participants in each of the 3 treatment groups had similar rates of disability progression (9.3% ozanimod 0.5 mg, vs. 12.5% vs. ozanimod 1 mg, vs. 11.3% interferon beta-1a; *P* > .05).[66] The SUNBEAM trial did not report disability outcomes.[67] However, a preplanned pooled analysis of the RADIANCE Phase 3 and SUNBEAM trials showed no differences between groups in disability progression (6.5% ozanimod 0.5 mg, vs. 7.6% vs. ozanimod 1 mg, vs. 7.8% interferon beta-1a; *P* > .05).[66]

Clinical Exacerbation or Relapse

In the SUNBEAM trial,[67] patients in the 2 ozanimod groups had a lower relapse rate after treatment for at least 12 months (ARR, 0.24 ozanimod 0.5 mg, 0.18 ozanimod 1 mg) than patients in the interferon beta-1a group (ARR, 0.35 interferon beta-1a; rate ratio, ozanimod 0.5 mg vs. interferon beta-1a, 0.69; 95% CI, 0.55 to 0.86; rate ratio, ozanimod 1 mg vs. interferon beta-1a, 0.52; 95% CI, 0.41 to 0.66.[67]

The RADIANCE Phase 3 trial[66] showed a similar pattern of results at 24 months, with patients in both ozanimod groups having a lower relapse rate (ARR, 0.22 ozanimod 0.5 mg, 0.17 ozanimod 1 mg) than patients in the interferon beta-1a group (ARR, 0.28 interferon beta-1a; RR, ozanimod 0.5 mg vs. interferon beta-1a, 0.79; 95% CI, 0.65 to 0.96; RR, ozanimod 1 mg vs. interferon beta-1a, 0.62; 95% CI, 0.51 to 0.77).[66]

Functional Outcomes

After a minimum of 12 months of treatment, participants in the SUNBEAM trial had similar levels of function, as measured by the MSFC (mean difference, 0.02 for ozanimod 0.5 mg vs. interferon beta-1a; 95% CI, -0.03 to 0.07; mean difference, 0.04 for ozanimod 1 mg vs. interferon beta-1a; 95% CI, -0.01 to 0.09).[67] In the RADIANCE Phase 3 trial, participants had a greater improvement in function, as measured by the MSFC, in the ozanimod 0.5 mg group (mean difference vs. interferon beta-1a, 0.10; 95% CI, 0.01 to 0.19), but not in the ozanimod 1 mg group (mean difference vs. interferon beta-1a, 0.06; 95% CI, -0.03 to 0.15).[66] However, these results are

considered nominal only, because of the preplanned hierarchical statistical testing, and should not be considered as definitive differences between treatment groups.[66,67]

Persistence

Overall, there were no meaningful differences in persistence between the different dosages of ozanimod (0.5 mg and 1 mg) and interferon beta-1a groups at 6 months in the SUNBEAM trial, or at 12 months in the RADIANCE Phase 3 trial (Figure 21).[66,67]
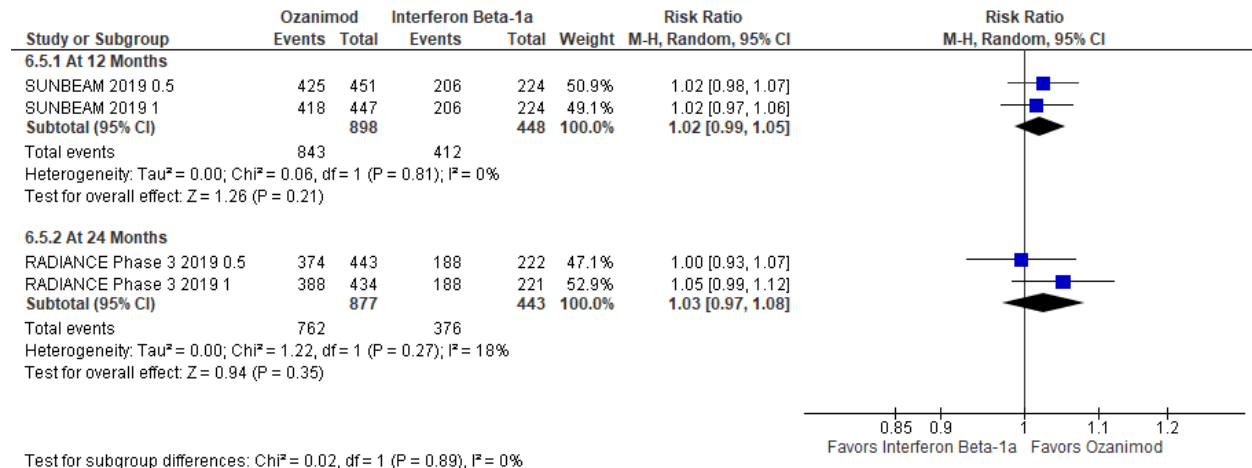

Figure 21. Ozanimod vs. Interferon Beta-1a. Completed Study.

Other Outcomes of Effectiveness

The SUNBEAM and the RADIANCE Phase 3 trials reported measures of QoL.[66,67] There were no differences between groups for QoL (physical or mental) other than an improvement in the physical health-related QoL at 12 months in the ozanimod 1 mg group (P = .04[67] and at 24 months in the ozanimod 0.5 mg group (P = .02).[66] However, these results are considered exploratory only, like other outcomes and should not be considered as definitive differences between treatment groups.[66,67]

Effectiveness by Subgroup

In the RADIANCE Phase 3 trial,[66] when analyzed by subgroups:

- Ozanimod 1 mg remained more effective in reducing the ARR than interferon beta-1a when analyzed by subgroup for sex, body weight, number of prior relapses, baseline EDSS, and prior treatment. There were some differences by age and location, where ozanimod 1 mg remained more effective in reducing the ARR than interferon beta-1a:
  - In younger people, aged 40 and under, (rate ratio, 0.61; 95% CI, 0.48 to 0.77) but not in older people
  - In people in Eastern Europe (rate ratio, 0.63; 95% CI, 0.50 to 0.77) but not people in the rest of the world
- Ozanimod 0.5 mg remained more effective in reducing the ARR than interferon beta-1a:
  - In women (rate ratio, 0.68; 95% CI, 0.53 to 0.86) but not in men
  - In younger people, aged 40 and under, (rate ratio, 0.78; 95% CI, 0.63 to 0.98) but not in older people

- In people with a lower body mass, under 68 kilograms (kgs), (rate ratio, 0.73; 95% CI, 0.52 to 0.96) but not in people with a higher body mass
- In people in Eastern Europe (rate ratio, 0.76; 95% CI, 0.62 to 0.93) but not in people in the rest of the world
- In people with fewer relapses (fewer than 2) in the past year, (rate ratio, 0.75; 95% CI, 0.58 to 0.97) but not in people with more relapses
- In people with a lower baseline EDSS score, 3.5 or less, (rate ratio, 0.77; 95% CI, 0.61 to 0.97) but not in people with a higher baseline EDSS score
- In people with previous disease-modifying therapy (rate ratio, 0.54; 95% CI, 0.37 to 0.77) but not in people with no previous disease-modifying therapy

In the SUNBEAM trial,[67] when analyzed by subgroups:
- Ozanimod 1 mg remained more effective in reducing the ARR than interferon beta-1a when analyzed by subgroup for sex, body weight, location, number of prior relapses, and prior treatment. There were some differences by age and baseline EDSS, where ozanimod 1 mg remained more effective in reducing the ARR than interferon beta-1a:
  - In younger people, aged 40 and under, (rate ratio, 0.47; 95% CI, 0.35 to 0.63) but not in older people
  - In people with a lower baseline EDSS score, 3.5 or less, (rate ratio, 0.46; 95% CI, 0.34 to 0.62) but not in people with a higher baseline EDSS score
- Ozanimod 0.5 mg remained more effective in reducing the ARR than interferon beta-1a when analyzed by subgroup for body weight and the number of prior relapses. There were some differences by sex, age, location, baseline EDSS, and prior treatment where ozanimod 0.5 mg remained more effective in reducing the ARR than interferon beta-1a:
  - In women (rate ratio, 0.63; 95% CI, 0.48 to 0.85) but not in men
  - In younger people, aged 40 and under, (rate ratio, 0.62; 95% CI, 0.47 to 0.82) but not in older people
  - In people in Eastern Europe (rate ratio, 0.67; 95% CI, 0.53 to 0.85) but not in people in the rest of the world
  - In people with a lower baseline EDSS score, 3.5 or less, (rate ratio, 0.58; 95% CI, 0.44 to 0.76) but not in people with a higher baseline EDSS score
  - In people with no previous disease-modifying therapy (rate ratio, 0.52; 95% CI, 0.46 to 0.84) but not in people with previous disease-modifying therapies

Adverse Events

After a minimum of 12 months of treatment in the SUNBEAM trial, 1.5% of participants in the ozanimod 0.5 mg group, 2.9% in the ozanimod 1 mg group, and 3.6% in the interferon beta-1a group withdrew because of adverse events.[67] The most frequent treatment-emergent adverse events leading to discontinuation were influenza-like illness, back pain, headache, and alanine aminotransferase increase.[67] The rates of serious treatment-emergent adverse events were 3.5% for ozanimod 0.5 mg, 2.9% for ozanimod 1 mg, and 2.5% for interferon beta-1a (Figure 22).[67] No deaths were observed during the study period.[67]
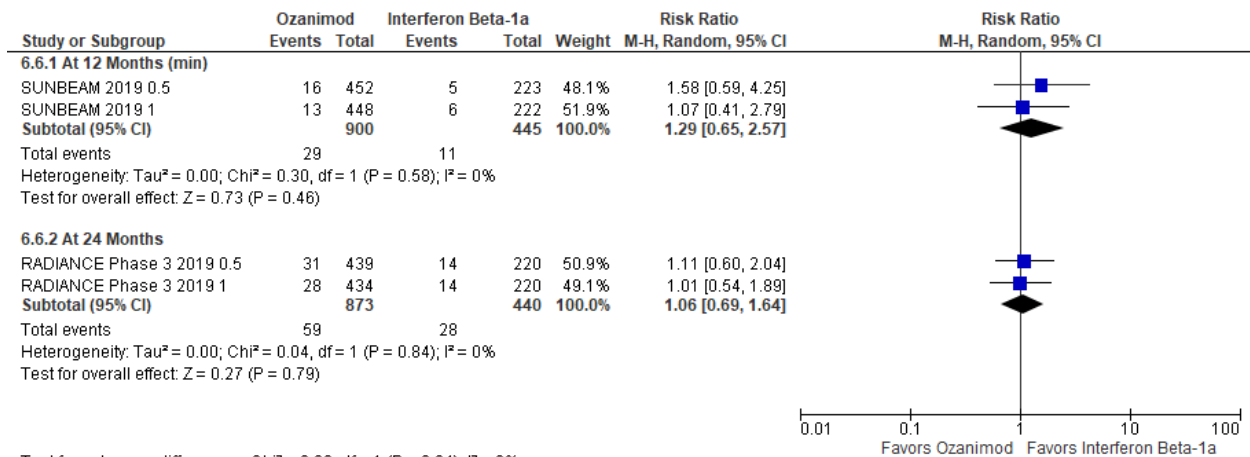
Figure 22. Ozanimod vs. Interferon Beta-1a. Serious Adverse Events.

In the SUNBEAM trial, patients reported nasopharyngitis (7% to 10%), headache (6% to 8%), and upper respiratory tract infections (4% to 7%) as the most common adverse events across all 3 groups.[67]

Participants treated with ozanimod in the SUNBEAM trial did not contract any serious infections, and 1 patient in the interferon beta-1a group contracted a moderate case of herpes zoster.[67] Participants in each group experienced raised alanine aminotransferase levels of at least 3 times the upper normal level (1.8% ozanimod 0.5 mg, vs. 4.3% ozanimod 1 mg, vs. 2.2% interferon beta-1a).[67] Also, 0.2% of participants in the ozanimod 0.5 mg group, 0.9% of participants in the ozanimod 1 mg group, and 0.2% of participants in the interferon beta-1a group had hepatobiliary dysfunction or related investigations that led to discontinuation.[67]

In the SUNBEAM trial, at 24 months, 3.2% of participants in the ozanimod 0.5 mg group, 3.0% in the ozanimod 1 mg group, and 4.1% in the interferon beta-1a group withdrew because of adverse events.[66] The most frequent treatment-emergent adverse events leading to discontinuation were influenza-like illness, alanine aminotransferase increase, aspartate aminotransferase increase, and macular edema in the interferon beta-1a group, and alanine aminotransferase increase, hives, and γ-glutamyltransferase increase in the combined ozanimod groups (rates were not reported).[66] The rates of serious treatment-emergent adverse events were 7.1% in the ozanimod 0.5 mg group, 6.5% in the ozanimod 1 mg group, and 6.4% in the interferon beta-1a group (Figure 22).[66] No deaths were observed during the study period.[66]

In the SUNBEAM trial, serious events that occurred in more than 1 participant in any treatment group were appendicitis (1 in the ozanimod 0.5 mg group, 2 in the ozanimod 1 mg group, and 2 in the interferon beta-1a group), ovarian cysts (2 in the ozanimod 1 mg group), and sinus tachycardia (2 in the ozanimod 0.5 mg group).[66]

The most frequently reported adverse events in the RADIANCE Phase 3 trial were nasopharyngitis (13% to 16%), alanine aminotransferase increase (6% to 7%), hypertension 5% to 6%), γ-glutamyltransferase increase (4% to 6%), pharyngitis (4% to 6%), and urinary tract infection in the ozanimod groups (4% to 5%).[66] The most frequent adverse events in the interferon beta-1a group were influenza-like illness (incidence not reported), headache

(incidence not reported), nasopharyngitis (11%), upper respiratory tract infection (incidence not reported), fever (incidence not reported), and orthostatic hypotension (incidence not reported).[66]

In the RADIANCE Phase 3 trial, the incidence of infection-related adverse events was similar across treatment groups.[66] Serious infections were infrequent, and no serious opportunistic infections occurred.[66] Participants in each group experienced raised alanine aminotransferase levels of at least 3 times the upper normal level (5.9% ozanimod 0.5 mg vs. 6.7% ozanimod 1 mg vs. 3.9% interferon beta-1a).[66] Also, 0.7% of participants in the ozanimod 0.5 mg group, 1.6% of participants in the ozanimod 1 mg group, and 1.4% of participants in the interferon beta-1a group had hepatobiliary dysfunction or related investigations that led to discontinuation.[66]

Harms by Subgroup

We did not identify any evidence of harms by subgroup for the SUNBEAM and RADIANCE Phase 3 trials.[66,67]

Teriflunomide vs. Interferon Beta-1a

We identified 1 eligible RCT comparing teriflunomide with interferon beta-1a in adults with relapsing MS (Table 36).[99] In the TENERE trial,[99] 324 participants were randomized to oral teriflunomide 7 mg or 14 mg once daily, or subcutaneous injections of interferon beta-1a 44 μg 3 times a week for up to 48 weeks. We assessed the TENERE trial as of fair methodological quality because of concerns about high and differential loss to follow-up, author conflicts of interest, and funding by industry.

Table 36. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Teriflunomide vs. Interferon Beta-1a				
Vermersch et al., 2014[99] 54 sites in 13 countries, no sites in the U.S. NCT00883337 TENERE	• Adults with relapsing MS • Total N = 324 randomized; n = 109, teriflunomide 7 mg; n = 111, teriflunomide 14 mg; n = 104, interferon beta-1a	Teriflunomide 7 mg oral, daily; teriflunomide 14 mg oral, daily	Interferon beta-1a 44 μg SC, 3 times a week	Minimum of 48 weeks

Abbreviations. μg: microgram; mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; SC: subcutaneous.

Disability

No disability outcomes were reported in the TENERE trial.[99]

Clinical Exacerbation or Relapse

Patients in the teriflunomide 7 mg group had lower rates of relapse than patients in the interferon beta-1a group (ARR, 0.41 vs. 0.22; *P* = .03) but patients in the teriflunomide 14 mg

group had similar rates of relapse compared with the interferon beta-1a group (ARR, 0.26 vs. 0.22; *P* = .59).[99]

Patients in the teriflunomide groups and the interferon beta-1a groups had similar rates of treatment failure (defined as a first occurrence of confirmed relapse or permanent treatment discontinuation for any cause, 48.6% teriflunomide 7 mg, vs. 37.8% teriflunomide 14 mg, vs. 42.3%, interferon beta-1a; *P* > .05 for each group vs. placebo).[99] The time to treatment failure was also similar between teriflunomide and interferon beta-1a (HR, teriflunomide 7 mg 1.12; 95% CI, 0.75 to 1.67; HR, 0.86 teriflunomide 14 mg; 95% CI, 0.56 to 1.31).[99] Fewer patients in the teriflunomide groups discontinued treatment compared with the interferon beta-1a group (6.4% vs. 13.5% vs. 24.0%; *P* value not reported), but patients in the teriflunomide groups had higher rates of relapse (42.2% vs. 23.4% vs. 15.4%; *P* value not reported).[99]

Functional Outcomes

Patients in the teriflunomide 7 mg group had greater improvements in fatigue compared with patients in the interferon beta-1a group, as measured by the Fatigue Impact Scale (a difference of -8.13 vs. interferon beta-1a; *P* = .03).[99] Patients in the teriflunomide 14 mg group did not experience as great an improvement in fatigue when compared with interferon beta-1a (a difference of -5.00 vs. interferon beta-1a; *P* = .18).[99]

Persistence

Overall, 81.7% (89 of 109) of participants in the teriflunomide 7 mg group, 80.2% (89 of 111) of participants in the teriflunomide 14 mg group and 68.3% (71 of 104) of participants in the interferon beta-1a group completed the 48-week trial, with significantly higher persistence with teriflunomide 7 mg and marginally higher persistence with teriflunomide 14 mg compared with placebo.[99] Fewer patients in the teriflunomide groups permanently discontinued treatment compared with the interferon beta-1a group (6.4% vs. 13.5% vs. 24.0%; *P* value not reported).[99]

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the TENERE trial.[99]

Effectiveness by Subgroup

The effectiveness of teriflunomide did not appear to differ for people in whom previous treatment with interferon beta had failed.[99]

Adverse Events

Fewer participants in the teriflunomide groups discontinued treatment because of adverse events (3.7% and 9.9%) compared with participants in the interferon beta-1a group (18.3%; *P* value not reported).[99] Also, patients in the teriflunomide 7 mg group experienced higher rates of serious adverse events (10.9%) than patients in the teriflunomide 14 mg group (5.5%) or patients in the interferon beta-1a group (6.9%; *P* value not reported).[99] No deaths were observed during the study.[99]

Patients in the teriflunomide groups reported higher rates of nasopharyngitis than did patients in the interferon beta-1a group (20% to 26%, vs. 18%), as well as higher rates of diarrhea (21% to 23%, vs. 8%), hair thinning (6% to 20%, vs. 1%), paresthesia (10% to 13% vs. 8.0%), and back pain

(10% vs. 8%).[99] Patients in the interferon beta-1a group reported influenza-like symptoms (54%, vs. 3% to 4%), alanine aminotransferase increases (31%, vs. 10% to 11%), and headache (26%, vs. 16% to 21%) more frequently than patients in the teriflunomide groups.[99]

Serious adverse events included tuberculosis and uterine leiomyosarcoma, but most serious adverse events only occurred once, other than 3 reports of increased alanine aminotransferase in the teriflunomide 7 mg group.[99] Increased alanine aminotransferase was the most frequent cause of treatment discontinuation, and reported more frequently with interferon beta-1a than with teriflunomide.[99] Most patients with elevated alanine aminotransferase experienced the increase within the first few months of treatment, and levels generally normalized with continued treatment or following treatment withdrawal.[99]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the TENERE trial.[99]

Cladribine vs. Placebo

Study Characteristics

We identified 1 eligible RCT comparing cladribine and placebo in adults with RRMS (Table 37).[65] In the CLARITY trial, 1,326 participants were randomized to 3.5 mg/kg of cladribine, 5.25 mg/kg of cladribine, or placebo for 96 weeks.[65] We assessed the CLARITY trial as of poor methodological quality because of concerns about baseline differences between treatment groups and funding by industry. The FDA-approved cladribine dosage is 3.5 mg/kg.

Participants in the CLARITY trial were eligible to continue in a 2-year extension study.[148] In this extension, patients in the CLARITY placebo group received cladribine 3.5 mg/kg and patients in the CLARITY cladribine group were re-randomized to cladribine 3.5 mg/kg or placebo, with blinding maintained.[148]

Table 37. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Cladribine vs. Placebo				

Giovannoni et al., 2010[65]
155 sites in 32 countries, including sites in the U.S.
NCT00213135
CLARITY
	• Adults with RRMS
	• Total N = 1,326 randomized;
	n = 456, cladribine 5.25 mg/kg;
	n = 433, cladribine 3.5 mg/kg;
	n = 437, placebo
		Cladribine 5.25 mg/kg, cumulative oral doses; cladribine 3.5 mg/kg, cumulative oral doses	Placebo	96 weeks

Abbreviations. kg: kilogram; mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis.

Disability

During the 96-week study period, participants in the cladribine 3.5 mg/kg group had lower rates of disability progression when compared to participants in the placebo group (HR, 0.67; 95% CI, 0.48 to 0.93).[65] Participants in the cladribine 3.5 mg/kg group were also more likely to have no progression in disability when compared to placebo (odds ratio [OR], 1.55; 95% CI 1.09 to 2.22).[65] The time to disease progression was longer in the cladribine 3/5 mg/kg group compared with placebo (13.6 months vs. 10.8 months; *P* = .02).[65] Similar results were seen in the non-FDA-approved dose group of 5.25 mg/kg.[65]

In the CLARITY extension study,[148] the rates of no disability progression ranged from 72.4% in the cladribine 3.5 mg/kg group to 78.3% in the cladribine 5.25 mg/kg group, with no differences between the treatment groups.[148]

Clinical Exacerbation or Relapse

Participants in the cladribine 3.5 mg/kg group had lower rates of relapse compared to those in the placebo group (ARR, 0.14 vs. 0.33; *P* < .001).[65] A higher proportion of participants in the cladribine 3.5 mg/kg group remained relapse-free compared to placebo (79.7% vs. 60.9%; *P* < .001).[65] The time to first relapse was also significantly longer among participants in the cladribine 3.5 mg/kg group compared to placebo (13.4 months vs. 4.6 months; HR, 0.44; 95% CI, 0.34 to 0.58).[65] Similar results were seen in the non-FDA-approved dose group of 5.25 mg/kg.[65]

In the CLARITY extension study,[148] patients in the initial CLARITY placebo group who then received cladribine had a significant reduction in ARR (0.26 to 0.10; *P* <.0001). This difference in ARR was comparable to that seen between the cladribine and placebo groups in the initial RCT.[148] In addition, the lower risk of relapse with cladribine was maintained in patients who were in the initial CLARITY group who were then allocated to placebo, with approximately 75% of patients remaining relapse-free.[148]

Functional Outcomes

No functional outcomes were reported in the CLARITY trial.[65]

Persistence

Overall, 91.9% (398 of 433) of participants in the cladribine 3.5 mg/kg group completed the 96-week study compared to 87.0% (380 of 437) in the placebo group, and the majority of participants in the both groups completed the treatment schedule (91.2% vs. 86.3%).[65] Persistence was significantly higher in the cladribine group compared with placebo. In the non-FDA approved dose group, 89.0% of participants in the 5.25 mg/kg completed the 96-week study and 86.2% completed the scheduled treatment.[65]

Other Outcomes of Effectiveness

At 2 years, participants in the cladribine groups reported significantly improved QoL as measured by a generic QoL tool, compared with placebo.[131] Patients in the cladribine groups also reported improved QoL as measured by an MS-specific QoL tool, compared with placebo, but the differences were not significant.[131]

Effectiveness by Subgroup

In CLARITY, 2 subgroups of patients with high disease activity were defined[149]:

- High relapse activity (HRA), defined as patients with 2 or more relapses during the year prior to study entry, whether on disease-modifying treatment or not
- HRA plus disease activity on treatment (DAT), defined as patients with 1 or more relapse during the year prior to study entry while on therapy and 1 or more T1 gadolinium-enhancing lesion or 9 or more T2 lesions

Patients in the HRA and HRA plus DAT subgroups had higher reductions in the risk of disability progression than patients in the non-HRA and non-HRA plus DAT subgroups (risk reduction of 82% and 82% for cladribine vs. 19% and 18% for placebo).[149] Rate ratios of ARR were lower in the HRA and HRA plus DAT subgroups compared with the non-HRA and non-HRA plus DAT subgroups, but the differences were not statistically significant.[149]

When CLARITY was reanalyzed to assess the effectiveness of cladribine in people with a first clinical demyelinating attack fulfilling the newer McDonald criteria (McDonald 2010[173]) for MS and CIS, Freedman et al.[147] found that:

- Cladribine reduced the risk of next attack or confirmed disability compared with placebo in patients meeting the newer criteria for MS at baseline ($P < .001$).[147]
- In patients who still have CIS under the newer criteria, cladribine also reduced the risk of conversion to clinically definite MS ($P < .001$).[147]

Adverse Events

More participants in the cladribine 3.5 mg/kg group withdrew because of adverse event compared to placebo (3.5% vs. 2.1%; P value not reported).[65] More participants in the cladribine 3.5 mg/kg group also experienced serious adverse events compared to placebo (8.4% vs. 6.5%, P value not reported).[65] In the CLARITY trial, 4 participants total died (1 death by suicide and 1 due to hemorrhagic stroke in the placebo group; 1 death by drowning and 1 due to cardiopulmonary arrest in the 5.25 mg/kg group), with 2 further deaths occurring after patients withdrew from the trial (1 because of acute myocardial infarction and 1 because of metastatic pancreatic carcinoma in the 3.5 mg/kg group).[65]

The most common adverse events reported by participants were headache (17% to 24%), lymphocytopenia (22% to 32% in the cladribine groups, vs. 2% in the placebo group), nasopharyngitis (13% to 14%), upper respiratory tract infection (10% to 13%), and nausea (9% to 11%).[65] In addition, 2.3% of participants in the cladribine 3.5 mg/kg group reported infections and infestations compared to 1.6% of those on placebo.[65] Neoplasms (benign, malignant, and unspecified) were diagnosed in 1.4% of participants in the cladribine 3.5 mg/kg group. No neoplasms were reported in the placebo group.[65] There were 3 cases of cancer in the cladribine 3.5 mg/kg group (1 melanoma, 1 pancreatic cancer, and 1 ovarian cancer).[65] In addition, 20 patients in the cladribine groups (8, 3.5 mg/kg vs. 12, 5.25 mg/kg) developed herpes zoster infections.[65]

In the CLARITY extension study, the rates of adverse event rates were generally similar between groups.[148] However, patients in the cladribine group had higher rates of lymphopenia (grade 3 or higher) than patients in the placebo group.[148]

In 2019, Cook et al.[143] conducted an integrated safety analysis of 3 RCTs trials and extended follow-up in patients with MS. Overall, the incidence rates of treatment-emergent adverse events were 103.3 adjusted adverse events per 100 person-years with cladribine vs. 94.26 for placebo:

- Lymphopenia was more common in people treated with cladribine compared with placebo (7.94 vs. 1.06 adjusted adverse events per 100 person-years)
- Decreased lymphocyte was more common in people treated with cladribine compared with placebo (0.78 vs. 0.10 adjusted adverse events per 100 person-years)
- Herpes zoster was more common in people treated with cladribine compared with placebo (0.83 vs. 0.20 adjusted adverse events per 100 person-years)

The malignancies observed in the cladribine groups were typical of those seen in the general population, and there was no increase in the incidence of malignancies over time in patients treated with cladribine.

Harms by Subgroup

Patients in the HRA and HRA plus DAT subgroups experienced similar rates of adverse events compared with patients in the non-HRA and non-HRA plus DA subgroups.[149]

Cladribine Plus Continued Interferon Beta vs. Placebo Plus Continued Interferon Beta

Study Characteristics

We identified 1 eligible RCT (ONWARD) comparing cladribine (3.5 mg/kg) plus existing interferon-beta therapy to existing interferon-beta therapy plus a placebo in adults with relapsing MS over a 96-week study period (Table 38).[70] The trial was designed to evaluate a 5.25 mg/kg dosage of cladribine, but was discontinued because of an association with lymphopenia.[70] We assessed ONWARD as of poor methodological quality because of concerns about high and differential loss to follow-up, author conflicts of interest, and funding by industry.[70]

Table 38. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Cladribine + Interferon Beta vs. Placebo + Interferon Beta				
Montalban et al., 2018[70] 50 sites in 4 countries, including the U.S. NCT00436826 ONWARD	• Adults with RRMS or SPMS with relapses • Total N = 172 randomized; n = 124, cladribine; n = 48, placebo	Cladribine 3.5 mg/kg with interferon-beta, oral; switching from 1 interferon beta therapy to another was permitted in the 48 weeks preceding screening if the patient had been on a stable regimen of the current interferon beta ≥ 3 months before screening	Placebo with interferon-beta, oral; switching from 1 interferon beta therapy to another was permitted in the 48 weeks preceding screening if the patient had been on a stable regimen of the current interferon beta ≥ 3 months before screening	96 weeks

Abbreviations. kg: kilogram; mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Disability

Participants in the combination therapy group and the interferon beta group had similar rates of disability progression (15.3% vs. 12.5%; *P* value not reported).[70]

Clinical Exacerbation or Relapse

Patients in the combination therapy group had lower rates of relapse than those in the interferon beta group (ARR, 0.12 vs. 0.32; RR of relapse, 0.37; 95% CI, 0.22 to 0.63).[70] Similarly, the proportion of patients who experienced a first qualifying relapse was lower in the combination therapy group compared to those in the interferon beta group (18.5% vs. 33.3%).[70] However, the survival curves crossed, and *P* values were not reported for this comparison.[70]

Functional Outcomes

No functional outcomes were reported in the ONWARD trial[70].

Persistence

Overall, 64.5% (80 of 124) of participants in the combination therapy group completed the 96-week trial compared with 81.3% (39 of 48) of participants in the interferon beta group, with persistence being significantly lower in the combination group.[70]

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the ONWARD trial[70].

Effectiveness by Subgroup

Cladribine in combination with interferon beta was significantly more effective in reducing relapses than placebo with interferon beta, both in subgroups of patients with RRMS (RR, 0.50; 95% CI, 0.30 to 0.84) and patients with SPMS (RR, 0.11; 95% CI, 0.01 to 0.94).[70]

Adverse Events

Significantly more participants in the cladribine plus interferon-beta group discontinued the study due to adverse events than those in the placebo plus interferon beta group (29.8% vs. 8.3%).[70] However, occurrence of serious adverse events was not significantly different between groups in the ONWARD trial.[70] No deaths were observed in the ONWARD trial.[70]

The most commonly reported adverse events in the cladribine plus interferon beta group were lymphopenia (40%), headache (25%), and nasopharyngitis (23%).[70] In the placebo plus interferon beta group, patients commonly reported headache (21%), nasopharyngitis (17%), and upper respiratory tract infection (17%).[70] In the cladribine plus interferon beta group, 3.2% had serious infections or infestations, compared with no participants in the placebo plus interferon beta group.[70] Participants in the cladribine plus interferon beta group also had higher rates of neoplasms, including 1 report of squamous cell carcinoma, than participants in the placebo plus interferon beta group (4.0% vs. 0).[70] Raised levels of alanine transaminase and aspartate transaminase were seen in 2 participants in the cladribine plus interferon beta group and 1 patient in the placebo plus interferon beta group (1.6% vs. 2.1%).[70]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the ONWARD trial.[70]

Diroximel Fumarate vs. Placebo

We did not identify any eligible RCTs comparing diroximel fumarate with placebo. The FDA approval of diroximel fumarate in 2019 was based on bioavailability studies comparing oral dimethyl fumarate delayed-release capsules to diroximel fumarate delayed-release capsules and 2 placebo-controlled trials of dimethyl fumarate.[24] Since FDA approval, we found 1 ongoing study and 1 published RCT evaluating the efficacy and safety of diroximel fumarate:

- EVOLVE-MS-1 is an ongoing, open-label, 96-week study in adults with RRMS.[174] The study is due to complete in May 2021.[174] A published interim analysis of EVOLVE-MS-1 found the rate of relapse in the 696 participants was low, with an ARR of 0.16 (95% CI, 0.13 to 0.20) at 48 weeks.[175] Similar rates of relapse were seen in the overall cohort and in people who were newly diagnosed (14.0% vs. 13.1%).[175] Overall, 30.9% of participants had gastrointestinal treatment-emergent adverse events.[176] Most of the gastrointestinal adverse events (96%) were mild or moderate, and occurred early in treatment.[176] Over 14.9% of participants discontinued treatment (6.3% because of adverse events and < 1% because of gastrointestinal adverse events).[175,176]
- EVOLVE-MS-2 is a RCT comparing diroximel fumarate and dimethyl fumarate in 506 adults with RRMS.[177] The duration of the trial was 5 weeks and assessed gastrointestinal tolerability and other adverse events.[177] No relevant effectiveness outcomes were reported.[177] Participants in the diroximel fumarate group had significantly less severe gastrointestinal events and fewer days of self-assessed gastrointestinal symptoms (rate ratio, 0.54; 95% CI, 0.39 to 0.75), fewer gastrointestinal adverse events (34.8% vs. 49.0%), and lower discontinuation rates because of gastrointestinal adverse events (0.8% vs. 4.8%).[177]

These studies are not eligible for this review, and have not been formally quality assessed; however, we briefly report on them because of the dearth of other evidence for this drug.

Ozanimod vs. Placebo

Study Characteristics

We identified 1 eligible RCT comparing ozanimod with placebo in adults with relapsing MS (Table 39).[62] In the RADIANCE Phase 2 trial, participants were randomized to ozanimod 0.5 mg, ozanimod 1 mg or placebo for 24 weeks.[62] Ozanimod is not currently FDA-approved, so it is not clear which dose of ozanimod would be the recommended regimen. We assessed RADIANCE Phase 2 as of poor methodological quality because of concerns about baseline differences, the short duration of follow-up, author conflict of interest, and funding by industry.[62]

At the end of the 24-week RADIANCE Phase 2 trial, participants were eligible to continue in a 2 year, dose-blinded extension study.[139] Participants in the ozanimod groups continued their allocated dose and participants in the placebo group were rerandomized to ozanimod 0.5 mg or ozanimod 1 mg.[139]

Table 39. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Ozanimod vs. Placebo				
Cohen et al., 2016[62] 55 sites in 13 countries, including the U.S. NCT01628393 RADIANCE Phase 2	• Adults with relapsing MS • Total N = 258 randomized; n = 87, ozanimod 0.5 mg; n = 83, ozanimod 1 mg; n = 88, placebo	Ozanimod 0.5 mg oral, once daily; ozanimod 1 mg oral, once daily	Placebo	24 weeks

Abbreviations. mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial.

Disability

No disability-related findings were reported in the RADIANCE Phase 2 trial.[62]

Clinical Exacerbation or Relapse

Participants in both ozanimod groups experienced similar rates of relapse to participants in the placebo group (ARR, 0.35 0.5 mg, vs. 0.50 placebo; OR, 0.69; 95% CI, 0.36 to 1.34; ARR, 0.24 1 mg, vs. 0.50 placebo; OR, 0.47; 95% CI, 0.22 to 1.01).[62] Participants in both ozanimod groups were more likely to be relapse-free at 24 weeks than participants in the placebo group, but this difference was not formally statistically tested (83% ozanimod 0.5 mg, vs. 89% ozanimod 1 mg, vs. 77% placebo; *P* value not reported).[62]

The ARR in the continued ozanimod 0.5 m group was 0.32, compared with 0.18 in the continued ozanimod 1 mg group.[139] In the placebo-ozanimod 0.5 mg group the ARR was 0.30, and in the placebo-ozanimod 1 mg, 0.18.[139]

Functional Outcomes

No functional outcomes were reported in the RADIANCE Phase 2 trial.[62]

Persistence

Overall, 98% of participants completed the 24-week trial, comprising 97.7% (85 of 87) of participants in the ozanimod 0.5 mg group, 98.8% (82 of 83) of participants in the ozanimod 1 mg group, and 96.6% (85 of 88) of participants in the placebo group, with no significant differences between groups.[62]

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the RADIANCE Phase 2 trial.[62]

Effectiveness by Subgroup

We did not identify any evidence on the effectiveness by subgroup in the RADIANCE Phase 2 trial.[62]

Adverse Events

No participants withdrew because of adverse events in any of the 3 treatment groups.[62] Overall, 3 participants experienced a serious adverse event, all of whom were in the ozanimod 0.5 mg group and were assessed as being unrelated to treatment (3%).[62] Deaths were not reported.[62]

The most commonly reported adverse events in the ozanimod groups were nasopharyngitis (6% to 13%), headache (4% to 6%), and urinary tract infection (2% to 7%).[62] Participants in the placebo groups also experienced these adverse events, with the proportions of headache (9%) and nasopharyngitis (14%) numerically higher in the placebo group compared with the ozanimod groups.[62] In the ozanimod 0.5 mg group, 3 serious treatment-emergent adverse events occurred (3%) and were assessed as being unrelated to treatment (optic neuritis, somatoform autonomic dysfunction, and uterine cervical squamous metaplasia).[62] Increased alanine aminotransferase greater than 3 times the upper limit of normal occurred in 3 participants in the ozanimod groups.[62] All cases resolved despite continuing treatment.[62]

In the extension study,[139] 78.6% of patients in the ozanimod 0.5 mg group and 75.6% in the ozanimod 1 mg group had an adverse event over the 2-year study period. No patients died during the extension period.[139]

Harms by Subgroup

We did not identify any evidence on the harms by subgroup in the RADIANCE Phase 2 trial.[62]

Peginterferon Beta-1a vs. Placebo
Study Characteristics

We identified 1 eligible RCT comparing peginterferon beta-1a and placebo in adults with RRMS (Table 40).[98] In the ADVANCE trial,[98] 1,012 participants were randomized to subcutaneous injections of peginterferon beta-1a 125 µg every 2 weeks or placebo, for 48 weeks. A further 500 participants were randomized to peginterferon beta-1a 125 µg every 4 weeks, and the results for the different dosing schedules are presented later in the report (Different Dosing Schedule for Peginterferon Beta-1a).[98] The recommended dose for MS is 125 µg of peginterferon beta-1a every 2 weeks. We assessed the ADVANCE trial as of fair methodological quality because of concerns about differential loss to follow-up, author conflicts of interest, and funding by industry.

Table 40. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Peginterferon Beta-1a vs. Placebo				
Calabresi et al., 2014[98] 183 sites in 26 countries, including the U.S. NCT00906399	• Adults with RRMS • Total N = 1,512 randomized; n = 512, peginterferon beta-1a every 2 weeks; n = 500,	Peginterferon beta-1a 125 µg SC, every 2 weeks; peginterferon beta-1a 125 µg SC every 4 weeks; placebo injections were given alternately every 2 weeks for the 4-week dosing group	Placebo	48 weeks

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
ADVANCE	peginterferon beta-1a every 4 weeks; n = 500, placebo			

Abbreviations. µg: microgram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous.

Disability

Fewer participants in the peginterferon beta-1a every 2 weeks group had disability progression at 48 weeks than did participants in the placebo group (7% vs. 10%; HR, 0.62; 95% CI, 0.40 to 0.97).[98] Similar results were seen for peginterferon beta-1a every 4 weeks.[98]

Clinical Exacerbation or Relapse

Participants taking peginterferon beta-1a at 2 and 4 weeks had fewer relapses when compared to those in the placebo group (ARR, 0.26 vs. 0.40; rate ratio, 0.64; 95% CI 0.50 to 0.83).[98] Fewer participants in the peginterferon beta-1a every 2 weeks group experienced relapse compared to those in the placebo group (19% vs. 29%; HR, 0.61; 95% CI, 0.47 to 0.80).[98] Similar results were seen for peginterferon beta-1a every 4 weeks.[98]

After the initial double-blind trial period, participants in the peginterferon beta-1a groups continued with active treatment and participants in the placebo group transitioned to active treatment, defined as a delayed treatment group.[132] At 2 years, more participants in the continuous peginterferon beta-1a every 2 weeks group met the clinical criteria for no evidence of disease activity, defined as no relapse or no confirmed disability progression, compared with the delayed treatment group (71% vs 57%; OR, 1.90; *P* < .001).[132]

Functional Outcomes

No functional outcomes were reported in the ADVANCE trial.[98]

Persistence

Overall, 85.5% (438 of 512) of participants in the peginterferon beta-1a every 2 weeks group completed the 48-week trial compared with 91.2% (456 of 500) of participants in the placebo group, with significantly lower persistence in the peginterferon group.[98]

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the ADVANCE trial.[98]

Effectiveness by Subgroup

At year 1, patients treated with peginterferon beta1a every 2 weeks or every 4 weeks had a lower ARR than patients in the placebo, regardless of antibody status.[165]

Adverse Events

More participants in the peginterferon beta-1a every 2 weeks group withdrew because of adverse events than participants in the placebo group (5% vs. 1%; P < .05).[98] The rate of serious

adverse events was similar at 11% in the peginterferon beta-1a every 2 weeks group and 15% in the placebo group.[98] When relapses were excluded, rates of serious adverse events were the same in the peginterferon beta-1a every 2 weeks and placebo groups (5% vs. 5%).[98] In total, 3 patients died in the peginterferon beta-1a every 2 weeks and placebo groups during the 48-week study.[98] None of the deaths were deemed due to treatment.[98]

The most commonly reported adverse events in the peginterferon beta-1a every 2 weeks group were injection site erythema (62%), influenza-like illness (47%), fever (45%), and headache (44%).[98] In the placebo group, the most commonly reported adverse events were headache (33%) and relapse (32%).[98] Relapse was reported as a serious adverse event in both groups (7% vs. 11%) with rates of other serious adverse events (including infections) being low in both groups (< 1% vs. < 1%).[98] Raised alanine aminotransferase greater than 5-times the upper limit of normal occurred in 12 (2%) patients in the peginterferon beta-1a every 2 weeks group and 5 (1%) in the placebo group.[98] Raised aspartate aminotransferase levels occurred in 1% of patients in the peginterferon beta-1a every 2 weeks group and 1% in the placebo group.[98] The development of neutralizing antibodies to interferon beta-1a was low and generally transient, patients in each treatment group developing neutralizing antibodies (< 1% peginterferon beta-1a every 2 weeks vs. < 1% placebo.[98]

Peginterferon immunogenicity was evaluated in the ADVANCE trial by White et al.[165] Overall, 6% of patients in the peginterferon beta-1a groups had treatment-emergent anti-interferon binding antibodies, and less than 1% developed neutralizing antidrug antibodies.[165]

Harms by Subgroup

For patients in the peginterferon beta-1a group, antibody status did not appear to have any effect on the incidence of adverse events, including serious adverse events and injection-site reactions.[165]

Siponimod vs. Placebo
Study Characteristics

We identified 2 eligible trials comparing siponimod to placebo (Table 41).[61,71] In the EXPAND trial,[61] 1,651 adults with SPMS were randomized to oral siponimod 2 mg once daily or placebo for up to 3 years. In the BOLD trial,[71] 2 cohorts of patients with RRMS were randomized.[71] In cohort 1, 188 patients were randomized to 1 of 4 groups; siponimod 10 mg, siponimod 2 mg, siponimod 0.5 mg, or placebo once daily for 6 months.[71] Patients in cohort 2 were randomized to 1 of 3 groups; siponimod 1.25 mg, siponimod 0.25 mg, or placebo once daily for 3 months.[71] The recommended maintenance dose for siponimod is 2 mg for adults with MS and 1 mg for adults with a CYP2C9*1/*3 or *2/*3 genotype. We assessed the EXPAND and BOLD trials as of fair methodological quality because of concerns about author conflict of interest and funding by industry.

Patients in the BOLD trial could continue in an extension study for up to 24 months, with patients continuing on the initial dose of siponimod and patients in the placebo group being re-randomized to 1 of the 5 siponimod doses.[155]

Table 41. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Siponimod vs. Placebo				
Kappos et al., 2018[61] 292 sites in 31 countries, including the U.S. NCT01665144 EXPAND	• Adults with SPMS • Total N = 1,651 randomized; n = 1,105, siponimod; n = 546, placebo	Siponimod 2 mg oral, once daily	Placebo	Up to 3 years
Selmaj et al., 2013[71] 73 sites in 12 countries, including the U.S. NCT00879658 BOLD	• Adults with RRMS • Total N = 188 randomized in cohort 1; n = 50, siponimod 10 mg; n = 49, siponimod 2 mg; n = 43, siponimod 0.5 mg; n = 45, placebo group • Cohort 2 did not use FDA-approved doses	Siponimod 10 mg, 2 mg, or 0.25 mg oral, once daily,	Placebo	6 months

Abbreviations. mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Disability

Participants with SPMS in the siponimod 2 mg group experienced lower rates of disability progression confirmed at 3 months than participants with SPMS in the placebo group (26% vs. 32%; HR, 0.79; 95% CI, 0.65 to 0.95).[61] No disability outcomes were reported in the BOLD trial.[71]

Clinical Exacerbation or Relapse

Participants in the siponimod group experienced significantly lower rates of relapse than participants in the placebo group:
- In adults with SPMS, the ARR was 0.07 for siponimod 2 mg vs. 0.16 for placebo (rate ratio, 0.45; 95% CI, 0.34 to 0.59)[61]
- In adults with RRMS, the ARR was 0.20 for siponimod 2 mg vs. 0.58 for placebo (P = .04)[71]

In the BOLD trial,[71] participants in the siponimod 2 mg group were more likely to be relapse-free than participants in the placebo group (90% vs. 73%; P value not reported). In the extension period of the BOLD trial, patients who continued on siponimod 2 mg or who were randomized to siponimod 2 mg after the placebo phase had lower relapse rates in the siponimod 2 mg group at up to 24 months (ARR, 0.20; 95% CI, 0.10 to 0.38).[155]

Functional Outcomes

Patients with SPMS in the siponimod 2 mg and placebo groups had similar levels of functioning, specifically walking function, at 12 months (*P* = .08) and 24 months (*P* = .37); they also had similar rates of worsening in walking, as measured by the timed 25-foot walk (*P* = .44).[61] No disability outcomes were reported in the BOLD trial.[71]

Persistence

In the EXPAND trial,[61] 81.7% of participants with SPMS in the siponimod 2 mg group completed the trial compared with 77.7% in the placebo group, with a maximum trial duration of 3.5 years. This finding was marginally significantly different (Figure 23; *P* = .06).

In the BOLD trial,[71] 89.8% of participants with RRMS in the siponimod 2 mg group completed the 6-month trial compared with 95.1% in the placebo group.

	Siponimod		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
7.5.1 RRMS							
BOLD 2013	44	49	58	61	100.0%	0.94 [0.85, 1.05]	
Subtotal (95% CI)		49		61	100.0%	0.94 [0.85, 1.05]	
Total events	44		58				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
7.5.2 SPMS							
EXPAND 2018	903	1105	424	546	100.0%	1.05 [1.00, 1.11]	
Subtotal (95% CI)		1105		546	100.0%	1.05 [1.00, 1.11]	
Total events	903		424				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.89 (P = 0.06)							

Test for subgroup differences: Chi² = 3.00, df = 1 (P = 0.08), I² = 66.7%

0.85 0.9   1   1.1   1.2
Favors Placebo   Favors Siponimod

Figure 23. Siponimod 2 mg vs. Placebo. Completed Study.

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the EXPAND and BOLD trials.[61,71]

Effectiveness by Subgroup

In the EXPAND trial,[61] siponimod remained more effective in reducing the risk of disability progression than placebo:
- In people with superimposed relapses in the 2 years before enrollment (HR, 0.67; 95% CI, 0.49 to 0.91), but not people without superimposed relapses in the 2 years before enrollment
- In people with rapid progression of disease (HR, 0.46; 95% CI, 0.65 to 0.91), but not people without superimposed relapses in the 2 years before enrollment
- In people with greater severity of disease (HR, 0.65; 95% CI, 0.80 to 0.99), but not people with less severe disease

Adverse Events

More participants in the combined siponimod groups than in the placebo groups withdrew because of adverse events:

- 7.6% vs. 5.1% over a maximum of 3 years in the EXPAND trial[61]
- 12% vs. 4% over 6 months in the BOLD trial[71]

The rates of serious adverse events were similar for siponimod 2 mg and placebo for adults with SPMS and adults with RRMS (Figure 24).[61,71]
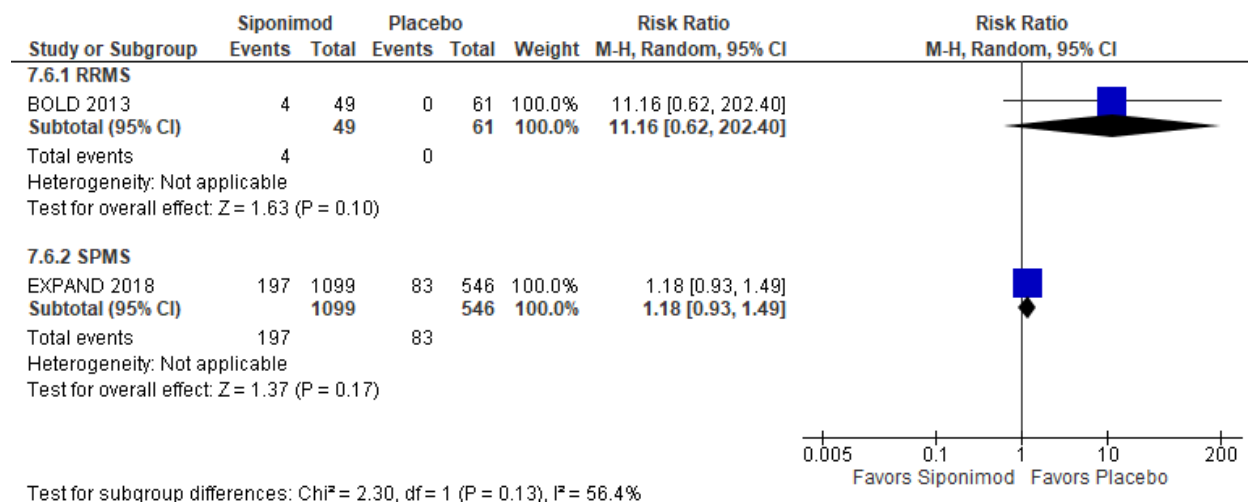

Figure 24. Siponimod 2 mg vs. Placebo. Serious Adverse Events.

In the EXPAND trial, 8 participants in the siponimod 2 mg and placebo groups died[61]:
- In the siponimod group, 4 participants died (1 metastatic gastrointestinal melanoma, 1 septic shock, 1 by suicide, and 1 unspecified)
- In the placebo group, 4 participants died (1 hemorrhagic stroke, 1 lung cancer, 1 gastric cancer, 1 unspecified)

In the BOLD trial, no patients died in the siponimod 2 mg group.[71]

In the siponimod 2 mg groups, the most commonly reported adverse events were headache (31%), nasopharyngitis (12%), vertigo (12%), infections and infestations (49%), and hypertension (12%).[61,71] In the placebo groups, the most commonly reported adverse events were infections and infestations (49%), dizziness (9% to 13%), nasopharyngitis (11% to 19%), and upper respiratory tract infections (0% to 16%).[61,71] Serious adverse events in the siponimod groups included second-degree atrioventricular block (6%), intentional overdose (2%), and urinary tract infection (1%).[61,71] Serious adverse events in the placebo groups included urinary tract infection (1%), suicide attempt (1%), gait disturbance (1%), and paraparesis (i.e., partial paralysis of the legs; 1%).[61,71] Overall, 2 patients (1 in the siponimod group and 1 in the placebo group) were diagnosed with a basal cell carcinoma.[61] Participants in the siponimod groups and in the placebo groups had raised alanine aminotransferase levels (1% vs. < 1% in EXPAND; 8% vs. 0 in BOLD) and raised aspartate aminotransferase levels (< 1% vs. < 1% in BOLD).[61,71]

During the extension period of up to 24 months, the proportion of overall adverse events was 89.7% and the proportion of serious adverse events was 10.3% in the siponimod 2 mg group.[155]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the EXPAND and BOLD trials.[71,155]

Different Dosing Schedule for Dimethyl Fumarate

Study Characteristics

We identified 3 eligible RCTs comparing different dosing schedules of dimethyl fumarate in adults with RRMS (Table 42).[79,92,96]

- In the DEFINE trial,[92] 827 participants were randomized to dimethyl fumarate 240 mg twice a day or dimethyl fumarate 240 mg 3 times a day for 24 months. A further 410 participants were randomized to placebo; however, the comparison of dimethyl fumarate and placebo is not a relevant one for this report, so no results for this comparison are reported.[92]
- In the CONFIRM trial,[79] 707 participants were randomized to dimethyl fumarate 240 mg twice a day or dimethyl fumarate 240 mg 3 times a day for 24 months. A further 723 participants were randomized to glatiramer acetate or placebo.[79] The comparisons of glatiramer acetate or dimethyl fumarate with placebo is not relevant for this report, so no results for these comparisons are reported. The results from the comparison of dimethyl fumarate and glatiramer acetate are presented earlier in the report (Dimethyl Fumarate vs. Glatiramer Acetate).
- In the BG-12 Phase 2b trial,[96] 257 participants were randomized to dimethyl fumarate 120 mg once a day, dimethyl fumarate 120 mg 3 times a day, dimethyl fumarate 240 mg 3 times a day, or placebo. The FDA-approved dose of dimethyl fumarate is 240 mg twice a day. The BG-12 Phase 2b trial [96] did not include an evaluation of the FDA-approved dose so we do not refer to this trial any further in this report; however, detailed study characteristics and study findings are reported in the Appendix (Appendix B).

The CONFIRM and DEFINE trials were not designed to compare different dosing schedules of dimethyl fumarate and did not report any formal statistical testing comparing the different dosing schedules.[79,92] We therefore did not combine the results of these RCTs in a meta-analysis. We assessed the DEFINE and CONFIRM trials as of poor methodological quality because of concerns about author conflicts of interest, funding by industry, and the potential for unblinding in the dimethyl fumarate groups (a flushing reaction is known to be an adverse effect associated with dimethyl fumarate).

Participants in the DEFINE and CONFIRM trials were able to continue with dimethyl treatment, with patients who were originally randomized to placebo or glatiramer acetate rerandomized to dimethyl fumarate 240 mg twice a day or 3 times a day, for a minimum of 3 years in the ENDORSE trial.[150] In March 2014, a protocol amendment was approved to switch all participants receiving dimethyl fumarate 240 mg 3 times a day to 2 times a day at the end of the 5 year period.[150]

Table 42. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Dimethyl Fumarate				
Fox et al., 2012[79] 200 sites in 28 countries, including the U.S. NCT00451451 CONFIRM	See characteristics reported in the head-to-head comparison section (Table 27)			
Gold et al., 2012[92] 198 sites in 28 countries, including the U.S. NCT00420212 DEFINE	• Adults with RRMS • Total N = 1,237 randomized; n = 411, dimethyl fumarate 2 times daily; n = 416, dimethyl fumarate 3 times daily; n = 410, placebo	Dimethyl fumarate 240 mg oral, 2 times daily	Dimethyl fumarate 240 mg oral, 3 times daily; placebo	24 months
Kappos et al., 2008[96] 43 sites in 10 countries, no sites in the U.S. NCT00168701 BG-12 Phase 2b	• Adults with RRMS • Total N = 257 randomized; n = 64, dimethyl fumarate 120 mg 1 time daily; n = 64, dimethyl fumarate 120 mg 3 times daily; n = 64, dimethyl fumarate 240 mg 3 times daily; n = 65, placebo • Mean age (SD): 34.8 years (10.2) dimethyl fumarate 120 mg 1 time daily; 36.3 years (9.5) dimethyl fumarate 120 mg 3 times daily; 37.3 years (9.1) dimethyl fumarate 240 mg 3 times daily; 35.6 years (8.2) placebo	Dimethyl fumarate 120 mg oral, 1 time daily; dimethyl fumarate 120 mg oral, 3 times daily	Dimethyl fumarate 240 mg oral, 3 times daily; placebo	24 weeks

Abbreviations. mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation.

Disability

In the CONFIRM trial, participants in the dimethyl fumarate 240 mg 2 times a day group had a similar rate of disability progression to the dimethyl fumarate 240 mg 3 times a day group (13% vs. 13%; *P* value not reported).[79]

In the DEFINE trial, participants in the dimethyl fumarate 240 mg 2 times a day group had similar rate of disability progression to the dimethyl fumarate 240 mg 3 times a day group (16% vs 18%; *P* value not reported).[92]

In the ENDORSE trial, at 5 years, the estimated rate of disability progression was between 18.5% and 25.7%, with highest rate in the patients who switched from glatiramer acetate to dimethyl fumarate.[150]

Clinical Exacerbation or Relapse

In the CONFIRM trial, participants in the dimethyl fumarate 240 mg 2 times a day group had similar ARRs to the 240 mg 3 times a day group (0.22 vs. 0.20; *P* value not reported).[79] The proportion of patients who relapsed at 2 years was 29% in the dimethyl fumarate 240 mg 2 times a day group and 24% in the 240 mg 3 times a day group (*P* value not reported).[79]

In the DEFINE trial, participants in the dimethyl fumarate 240 mg 2 times a day group had similar ARRs to the 240 mg 3 times a day group (0.17 vs. 0.19; *P* value not reported).[79] The proportion of patients who relapsed at 2 years was 27% in the dimethyl fumarate 240 mg 2 times a day group and 26% in the 240 mg 3 times a day group (*P* value not reported).[79]

In the ENDORSE trial,[150] at 5 years:
- The cumulative ARR ranged from 0.16 to 0.24, with the highest rate in the patients who switched from placebo to dimethyl fumarate
- The proportion of patients who relapsed ranged from 40.1% to 51.5%, with the highest proportion in the patients who switched from placebo to dimethyl fumarate

Functional Outcomes

No functional outcomes were reported in the CONFIRM or DEFINE RCTs.[79,92]

Persistence

In the CONFIRM and DEFINE trials, similar number of participants in both dimethyl fumarate dosing groups completed the 24-month trials (284 of 362 [78.5%] vs. 273 of 345 [79.1%] in CONFIRM; 315 of 411 [76.6%] vs. 320 of 416 [76.9%] in DEFINE).[79,92]

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the CONFIRM or DEFINE RCTs.[79,92]

Effectiveness by Subgroup

At 6 years, the proportion of newly-diagnosed patients with confirmed disability progression was[151]:
- 15.7% (95% CI, 10.3% to 23.7%) in patients who continued with dimethyl fumarate 240 mg 2 times a day
- 24.3% (95% CI, 15.9% to 36.2%) in patients who switched from placebo to dimethyl fumarate 240 mg 2 times a day

Patients in the continued dimethyl fumarate group had a lower disability-progression rate over 6 years than patients in the placebo switch group (HR, 0.51; 95% CI, 0.27 to 0.97).[151]

At 6 years, ARRs in the subgroup of newly-diagnosed MS were[151]:
- 0.14 (95% CI, 0.10 to 0.19) in patients who continued with dimethyl fumarate 240 mg 2 times a day

- 0.17 (95% CI, 0.11 to 0.25) in patients who switched from placebo to dimethyl fumarate 240 mg 2 times a day

The cumulative ARRs over the 6 years were not significantly different between the groups (0.14 vs. 0.17; rate ratio, 0.81; 95% CI, 0.51 to 1.31).[151] However, patients who switched from placebo to dimethyl fumarate 240 mg 2 times a day had significant improvements in ARR after switching (ARR, 0.26; 95% CI, 0.18 to 0.37 for years 0 to 2 in initial trials; vs. ARR, 0.10; 95% CI, 0.06 to 0.16 for years 3 to 6 in the extension study; *P* < .001).[151]

Adverse Events

Adverse events from the CONFIRM trial[79] are reported in the head-to-head comparison findings above.

In the DEFINE trial, participants in the dimethyl fumarate 240 mg 2 times a day group had similar rate of withdrawals because of adverse events to the 240 mg 3 times a day group (16% vs 16%).[92] The rates of serious adverse events were also similar between the 2 groups (18% vs. 16%).[92] Overall, 2 patients died in traffic accidents in the DEFINE trial, but this is unlikely to be related to the study treatment.[92]

The most commonly reported adverse events in the dimethyl fumarate groups were flushing (32% to 38%), relapse (27%), and diarrhea (15% to 19%), with the most commonly reported serious adverse events being relapse (27%).[92] Across both treatment groups, 18 patients experienced serious infections (2% vs. 2%) and a further 4 patients were diagnosed with cancer (2 participants in each dimethyl fumarate group).[92] Alanine aminotransferase levels that were 3 or more times the upper limit of the normal range were seen in in 6% of the patients in each dimethyl fumarate group.[92] No participants had hepatic failure.[92]

In the ENDORSE trial, the rates of adverse events were 91% in the continued dimethyl fumarate 2 times a day group, 95% in the placebo-dimethyl group, and 88% in the glatiramer acetate-dimethyl group over 5 years.[150] Rates of serious adverse events were 22% in the continued dimethyl fumarate 2 times a day group, 24% in the placebo-dimethyl group, and 16% in the glatiramer acetate-dimethyl group.[150] Progressive multifocal leukoencephalopathy, in the setting of severe, prolonged lymphopenia, was diagnosed in 1 patient.[150]

Harms by Subgroup

In patients with newly diagnosed MS, 9% of patients who continued with dimethyl fumarate 240 mg 2 times a day and 18% of patients who switched from placebo to dimethyl fumarate 240 mg 2 times a day discontinued study treatment because of adverse events.[151]

Different Dosing Schedule for Glatiramer Acetate

Study Characteristics

We identified 2 eligible RCTs comparing different dosing schedules of glatiramer acetate in adults with RRMS (Table 43).[68,93] Investigators randomized 861 participants in the CONFIDENCE trial[68] and 209 participants in the GLACIER trial[68] to subcutaneous injections of glatiramer acetate 40 mg 3 times a week or 20 mg once a day. We assessed the CONFIDENCE and GLACIER trials as of poor methodological quality because of concerns about randomization, blinding, author conflicts of interest, and funding by industry.

Patients in the CONFIDENCE trial were eligible to continue in a 6-month, single-arm extension study.[145] The aims were to determine whether benefits observed in the core trial were sustained during the extension study, to ascertain if switching from glatiramer acetate 20 mg to glatiramer acetate 40 mg resulted in patient-reported changes, and to assess safety outcomes.[145]

Table 43. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Glatiramer Acetate				
Cutter et al., 2019[68] 88 sites in 14 countries, including sites in the U.S. NCT02499900 CONFIDENCE	• Adults with RRMS • Total N = 861 randomized; n = 431, glatiramer acetate 40 mg 3 times a week; n = 430, glatiramer acetate 20 mg once a day	Glatiramer acetate 40 mg SC injection, 3 times a week	Glatiramer acetate 20 mg SC injection, once daily	6 months
Wolinsky et al., 2015[93] 31 sites, all in the U.S. NCT01874145 GLACIER	• Adults with RRMS • Total N = 209 randomized; n = 108, glatiramer acetate 40 mg 3 times a week; n = 101, glatiramer acetate 20 mg once a day	Glatiramer acetate 40 mg SC injection, 3 times a week	Glatiramer acetate 20 mg SC injection, once daily	4 months

Abbreviations. mg: milligram; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous.

Disability

Disability outcomes were not reported in the CONFIDENCE and GLACIER trials.[68,93]

Clinical Exacerbation or Relapse

Relapse-related outcomes were not reported in the CONFIDENCE and GLACIER trials.[68,93]

Functional Outcomes

Patients in the glatiramer acetate 40 mg group reported greater reductions in fatigue compared with the 20 mg group (a reduction in the Modified Fatigue Impact Scale of -3.6 vs. -2.8), but the difference was not significant ($P = .21$).[68] In the longer-term extension study, patients in the glatiramer acetate 40 mg group continued to report greater reductions in fatigue compared with the 20 mg group, but the difference remained non-significant.[145]

Persistence

At 4 and 6 months, 93.5% (GLACIER) and 92.6% (CONFIDENCE) of participants in the glatiramer 40 mg group remained in the studies, respectively, compared with 97.0% and 91.9%, respectively, in the glatiramer acetate 20 mg group (Figure 25).[93]
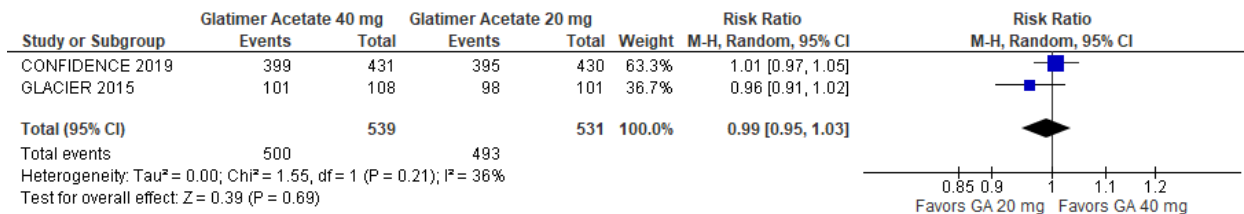
Study or Subgroup	Glatimer Acetate 40 mg		Glatimer Acetate 20 mg			Risk Ratio	Risk Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CONFIDENCE 2019	399	431	395	430	63.3%	1.01 [0.97, 1.05]	
GLACIER 2015	101	108	98	101	36.7%	0.96 [0.91, 1.02]	
Total (95% CI)		539		531	100.0%	0.99 [0.95, 1.03]	
Total events	500		493				

Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.39 (P = 0.69)

Favors GA 20 mg   Favors GA 40 mg

Figure 25. Glatiramer Acetate 40 mg vs. 20 mg. Completed Study.

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the CONFIDENCE and GLACIER trials.[68,93]

Effectiveness by Subgroup

We did not identify any evidence of effectiveness by subgroup in the CONFIDENCE and GLACIER trials.[68,93]

Adverse Events

In the CONFIDENCE trial,[68] 3.0% of participants in the glatiramer acetate 40 mg group withdrew because of adverse events compared with 4.2% in the 20 mg group. The rates of serious adverse events were 3.0% in the glatiramer acetate 40 mg group compared with 1.9% in the 20 mg group.[68] During the study period, 1 patient died in the glatiramer acetate 40 mg group due to intracranial hemorrhage, but this was not considered to be related to the study drug.[68]

The most common adverse events in the glatiramer acetate 40 mg group were injection-site pain (20%) and erythema (14%).[68] In the glatiramer acetate 20 mg group, the most commonly reported adverse events were injection-site pain (20%), erythema (17%), and itching (14%).[68] More people in the glatiramer acetate 20 mg group experienced itching than in the 40 mg group (13.6% vs. 8.6%; P = .02).[68]

In the GLACIER trial,[93] only 1 participant in the glatiramer acetate 40 mg group withdrew because of injection-site necrosis. The rate of moderate or severe injection-related adverse events as lower in the glatiramer acetate 40 mg group compared with the 20 mg group (9.1% vs. 18.8%; RR, 0.40; 95% CI, 0.34 to 0.74).[93]

The most common adverse events in both glatiramer acetate groups were injection-site pain (25% to 55%) and erythema (22% to 44%).[93] The GLACIER trial did not report on mortality.[93]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the CONFIDENCE and GLACIER trials.[68,93]

Different Dosing Schedule for Interferon Beta-1a

Study Characteristics

We identified 5 eligible RCTs comparing different dosing schedules of interferon beta-1a in people with relapsing MS or CIS (Table 44).[77,80,81,83,88] The trial by Etemadifar et al.[83] compared subcutaneous injections of interferon beta-1a 44 µg once a week with intramuscular injections

of interferon beta-1a 30 µg once a week. Once a week interferon beta-1a 44 µg is not an FDA-approved dosage, and we do not refer to this trial again for this comparison.

- In the trial by Calabrese et al.,[80] 165 participants were randomized to subcutaneous injections of glatiramer acetate 20 mg once a day, subcutaneous interferon beta-1a 44 µg 3 times a week, and intramuscular interferon beta-1a 30 µg once a week. We assessed the trial by Calabrese at al.[80] as of fair methodological quality because of concerns about randomization and blinding, author conflicts of interest, and funding by industry.
- The EVIDENCE trial[88] randomized 677 participants with RRMS to subcutaneous interferon beta-1a 44 µg 3 times a week, or intramuscular interferon beta-1a 30 µg once a week for 48 weeks. We assessed the EVIDENCE trial as of poor methodological quality because of concerns about the use of odds ratios (i.e., overestimates risk), not reporting conflicts of interest, and funding by industry.[88]
- The trial by Mazdeh et al.[81] randomized 90 participants with MS (including some participants with CIS) to subcutaneous injections of interferon beta-1b 250 µg every other day, subcutaneous injections of interferon beta-1a 44 µg 3 times a week, or intramuscular interferon beta-1a 30 µg once a week for 24 months. We assessed the trial by Mazdeh et al.[81] as of poor methodological quality because of concerns about the lack of details around key study components (e.g., randomization).
- The trial by Mokhber et al.[77] randomized 69 participants with newly diagnosed MS to subcutaneous injections of interferon beta-1b 250 µg every other day, subcutaneous injections of interferon beta-1a 44 µg 3 times a week, or intramuscular interferon beta-1a 30 µg once a week for 12 months. We assessed the trial by Mokhber et al.[77] as of poor methodological quality because of concerns about the lack of details around key study components (e.g., randomization) and patients not being blind to treatment.

Table 44. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Interferon Beta-1a				
Calabrese et al., 2012[80] Single site in Italy Not reported Not reported	See characteristics reported in the head-to-head section (Table 32)			
Etemadifar et al., 2006[83] 2 sites in Iran Not reported Not reported	See characteristics reported in the head-to-head section (Table 33)			
Mazdeh et al., 2010[81] Single site in Iran Not reported Not reported	See characteristics reported in the head-to-head section (Table 33)			

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Mokhber et al., 2014[77] Single site in Iran Not reported Not reported	See characteristics reported in the head-to-head section (Table 33)			
Panitch et al., 2002[88] 56 sites in Europe, Canada, and the U.S. Not reported EVIDENCE	• Adults with RRMS • Total N = 677 randomized; n = 339, interferon beta-1a 3 times a week; n = 338, interferon beta-1a once a week	Interferon beta-1a 44 µg SC injection, 3 times a week	Interferon beta-1a 30 µg IM injection, once a week	48 weeks

Abbreviations. µg: microgram; IM: intramuscular; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous.

Disability

Patients in the subcutaneous interferon beta-1a 44 µg 3 times a week and intramuscular interferon beta-1a 30 µg once a week groups had similar levels of disability (EDSS) at 12 months in the trial by Mokhber et al.[77] and at 24 months in the trial by Mazdeh et al.[81] (Figure 26).
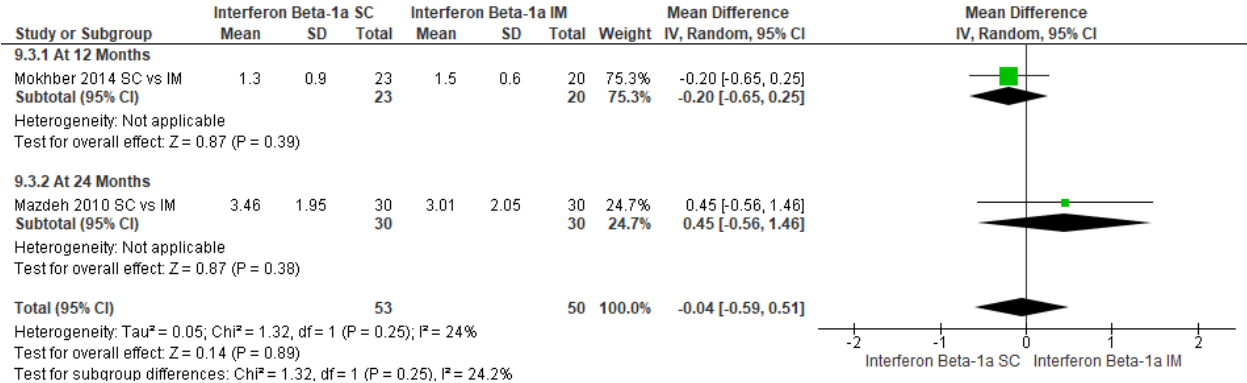
Figure 26. Interferon Beta-1a SC vs. Interferon Beta-1a IM. Mean Disability Score (EDSS).

Patients in the subcutaneous interferon beta-1a 44 µg 3 times a week and intramuscular interferon beta-1a 30 µg once a week groups also had similar rates of disability progression (HR, 0.87; 95% CI, 0.58 to 1.31; *P* = .51[88]

Clinical Exacerbation or Relapse

In the trial by Calabrese et al., patients in the subcutaneous interferon beta-1a 44 µg 3 times a week and intramuscular interferon beta-1a 30 µg once a week groups had similar rates of relapse (ARR, 0.4 vs. 0.5; *P* value not reported[80]

In the EVIDENCE trial, patients in the subcutaneous interferon beta-1a 44 µg 3 times a week were more likely to remain relapse-free than patients in the intramuscular interferon beta-1a 30 µg once a week group[88]:

- At 24 weeks (OR, 1.9; 95% CI, 1.3 to 2.6; *P* < .001)[88]
- At 48 weeks (OR, 1.5; 95% CI, 1.1 to 2.1; *P* = .009)[88]

In the trial by Panitch et al., The time to relapse was also longer with interferon beta-1a 44 µg 3 times a week compared with intramuscular interferon beta-1a 30 µg once a week (HR, 0.70; 95% CI, 0.55 to 0.88; *P* = .003).[88] The relapse rate was also lower with interferon beta-1a 44 µg 3 times a week compared with intramuscular interferon beta-1a 30 µg once a week at 24 weeks (0.29 vs. 0.40; *P* = .02), but not at 48 weeks (0.54 vs. 0.64; *P* = .09).[88]

In the trial by Mazdeh et al.,[81] no differences were seen between the 2 treatment groups for mean relapse interval or the change in relapse rate.

Functional Outcomes
No functional outcomes were reported in the eligible trials.[77,80,81,88]

Persistence
There was no difference in the completion rates between the subcutaneous interferon beta-1a 44 µg 3 times a week and intramuscular interferon beta-1a 30 µg once a week groups at 12 months in the trial by Mokhber et al.[77] and the EVIDENCE trial[88] or at 24 months in the trial by Calabrese et al (Figure 27).[80]
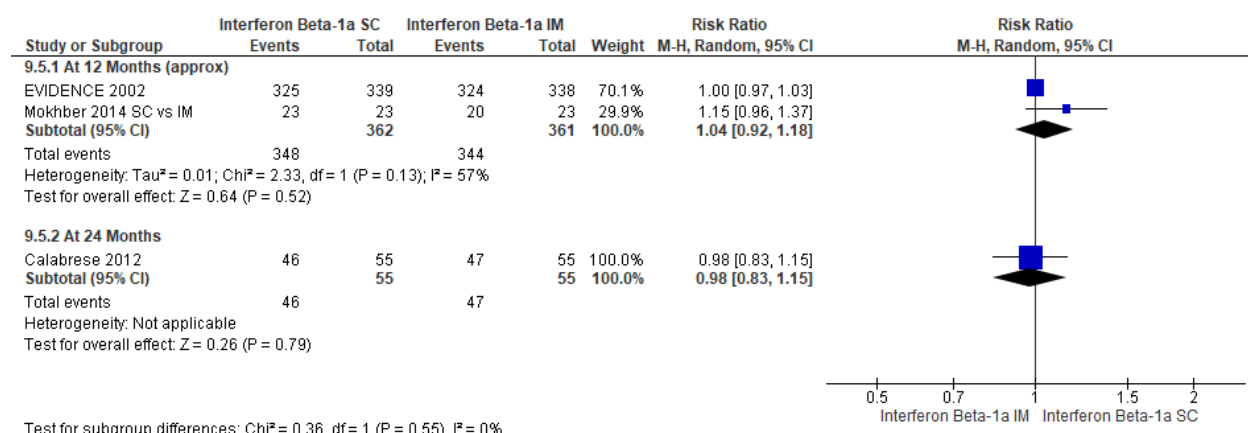
Figure 27. Interferon Beta-1a SC vs. Interferon Beta-1a IM. Completed Study.

Other Outcomes of Effectiveness
No other relevant outcomes were reported in the eligible trials.[77,80,81,88]

Effectiveness by Subgroup
The presence of neutralizing antibodies did not have any impact on the clinical outcomes.[88]

Adverse Events
In the EVIDENCE trial,[88] patients in both groups withdrew because of adverse events (4.7% vs. 4.2%) and patients in both groups experienced serious adverse events (6% vs. 5%). Rates of withdrawals, serious adverse events, or deaths related to treatment were not reported in any of the other eligible trials.[77,81,88]

In general, the RCTs did not report adverse events comprehensively:

- In the EVIDENCE trial,[88] more patients in the subcutaneous interferon beta-1a 44 µg 3 times a week group had specific adverse events than patients in the intramuscular interferon beta-1a 30 µg once a week group
  - Injection-site reactions, 83% vs. 28% ($P < .001$)
  - Liver function abnormality, 18% vs. 9% ($P = .002$)
  - Raised alanine transferase, 12% vs. 5% ($P = .002$)
- In the trial by Mazdeh et al.,[81] participants experienced dermal reactions at the site of injection, numbness, flu-like illness and irregular menses (incidence rates were not reported).

Similarly, serious adverse events were not reported well in the other included trials:

- In the EVIDENCE trial, 9 serious adverse events were considered by the investigators to be related to the study drug (1 case each of lymphopenia, spontaneous abortion, depression, and suicidal ideation for the 44 µg 3 times a week group; 2 cases of depression, 1 MS relapse, 1 episode of diplopia (not considered a relapse), and 1 of chest pain for the 30 µg once a week group)
- Mazdeh et al.[81] reported that 2 patients in the interferon beta-1b group developed severe necrotizing vasculitis and were excluded from the trial.

Harms by Subgroup

We did not identify any evidence on the harms by subgroup in the eligible trials.[77,80,81,88]

Different Dosing Schedule for Peginterferon Beta-1a

Study Characteristics

We identified 1 eligible RCT comparing different dosing schedules of peginterferon beta-1a in adults with RRMS (Table 45).[98] In the ADVANCE trial,[98] 1,012 participants were randomized to subcutaneous injections of peginterferon beta-1a 125 µg every 2 weeks or every 4 weeks, for 48 weeks. The recommended dose for MS is 125 µg of peginterferon beta-1a every 2 weeks. A further 500 participants were randomized to placebo, and the results are presented earlier in the report (Peginterferon Beta-1a vs. Placebo).[98] We assessed the ADVANCE trial as of fair methodological quality because of concerns about differential loss to follow-up, author conflicts of interest, and funding by industry.

Patients in the ADVANCE trial were eligible to continue in the ATTAIN 2-year extension study.[133] Patients in the peginterferon groups continued their allocated doses and patients in the placebo groups were rerandomized to peginterferon beta-1a 125 µg every 2 weeks or every 4 weeks, for 48 weeks.[133]

Table 45. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Peginterferon Beta-1a				
Calabresi et al., 2014[98] 183 sites in 26 countries, including the U.S. NCT00906399 ADVANCE	See characteristics reported in the head-to-head section (Table 40)			

Abbreviations. MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial.

Disability

Patients in both peginterferon beta-1a groups had similar rates of disability progression (6.8% in each group; a direct comparison was not made).[98]

Clinical Exacerbation or Relapse

Patients in both peginterferon beta-1a groups had similar rates of relapse (19% in the every 2 weeks group vs. 29% in the every 4 weeks group; a direct comparison was not made).[98] The ARRs were also similar between the 2 different dosing schedule (0.26 vs. 0.29; a direct comparison was not made).[98]

In the ATTAIN extension study, the absence of clinical disease activity was defined as no relapses and no disease progression.[133] More patients in the peginterferon beta-1a every 2 weeks groups than in the every 4 weeks groups had no clinical disease activity (60.6% vs. 50.6%; P = .006).[133]

Functional Outcomes

No functional outcomes were reported in the ADVANCE trial.[98]

Persistence

Overall, 85.5% (438 of 512) of participants in the peginterferon beta-1a every 2 weeks group completed the 48-week trial compared with 87.6% (438 of 500) of participants in the peginterferon beta-1a every 4 weeks group.[98]

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the ADVANCE trial.[98]

Effectiveness by Subgroup

We did not identify any evidence of effectiveness by subgroup in the ADVANCE trial.[98]

Adverse Events

Similar numbers of participants in the peginterferon beta-1a every 2 weeks group withdrew because of adverse events compared to the every 4 weeks group (5% vs. 5%).[98] The rate of serious adverse events was similar at 11% in the every 2 weeks group and 14% in the every 4

weeks group.[98] When relapses were excluded, rates of serious adverse events were the same in both groups (5% vs. 5%).[98] In total, 2 patients died during the 48 week study; in the peginterferon beta-1a every 2 weeks group, 1 patient died from an unknown cause, and in the every 4 weeks group, 1 patient died from septic shock.[98] Neither of the deaths were deemed due to treatment.[98]

The most commonly reported adverse events in the peginterferon beta-1a every 2 weeks group were injection site erythema (62%), influenza-like illness (47%), fever (45%), and headache (44%).[98] The same adverse events were reported in the every 4 weeks group (41% to 56%).[98] Relapse was reported as a serious adverse events in both groups (7% vs. 9%) with rates of other serious adverse events (including infections) being low in both groups (< 1% vs. < 1%).[98] Raised alanine aminotransferase greater than 5-times the upper limit of normal occurred in 12 patients (2%) in the every 2 weeks group and 9 patients (2%) in the every 4 weeks group.[98] Raised aspartate aminotransferase levels occurred in 1% of patients in the every 2 weeks group and 1% in the every 4 weeks group.[98]

Harms by Subgroup
We did not identify any evidence of harms by subgroup in the ADVANCE trial.[98]

Combination of Glatiramer Acetate Plus Interferon Beta-1a
Study Characteristics
We identified 1 eligible RCT comparing the combination of glatiramer acetate and interferon beta-1a with glatiramer acetate and interferon beta-1a alone in adults with RRMS (Table 46).[75] In the CombiRx trial,[75] 1,008 participants were randomized to subcutaneous injections of glatiramer acetate 20 mg daily, intramuscular injections of interferon beta-1a 30 μg once a week, or both for 36 months. We assessed the CombiRx trial as fair-methodological quality because of concerns about high loss to follow-up and author conflicts of interest.

In the CombiRx trial, all participants were followed on protocol until the last participant enrolled completed 3 years, meaning that some patients were followed for up to 7 years.[159]

Table 46. Summary Table of Included RCTs for MS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Glatiramer Acetate Plus Interferon Beta-1a				
Lublin et al., 2013[75] 68 sites in the U.S. and Canada NCT00211887 CombiRx	See characteristics reported in the head-to-head section (Table 32)			

Abbreviations. MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial.

Disability

Patients experienced similar rates of disability progression in each of the treatment groups (24.8% glatiramer acetate vs. 21.6% interferon beta-1a vs. 23.9% combination; *P* > .05).[75] In the longer term, in each of the treatment groups continued to have similar rates of disability progression.[159]

Clinical Exacerbation or Relapse

Patients in the combination group had a lower ARR compared with interferon beta-1a alone (0.12 vs. 0.16; *P* = .02) but a similar ARR to those in the glatiramer acetate alone group (0.12 vs. 0.11; *P* = .30).[75] The time to relapse was no different between groups.[75] Patients in the combination group also had a similar risk of relapse when compared to glatiramer acetate alone (HR, 1.10; 95% CI, 0.82 to 1.46).[75]

Over the longer term, patients in the combination group had a similar risk of relapse to patients in the glatiramer acetate group.[159] Patients in the combination group and patients in the glatiramer acetate group had a lower risk of relapse than patients in the interferon beta-1a group.[159]

Functional Outcomes

Patients experienced similar improvements in function (MSFC) in the 3 treatment groups (0.2 glatiramer acetate vs. 0.1 interferon beta-1a vs. 0.1 combination; *P* > .05).[75] Similar results were also seen for the timed 25-foot walk, the 9-hole peg test, and the PASAT.[75] In the longer term, in each of the treatment groups continued to have similar levels of function (MSFC).[159]

Persistence

The completion rates at 36 months for each treatment group were 79.6% (397 of 499) in the combination group, 86.1% (223 of 259) in the glatiramer acetate group, and 77.6% (194 of 250) in the interferon beta-1a group.[75] Persistence was significantly lower in the combination group compared to the glatiramer acetate group, but not compared to the interferon beta-1a group.

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the CombiRx trial.[75]

Effectiveness by Subgroup

We did not identify any evidence of effectiveness by subgroup in the CombiRx trial.[75]

Adverse Events

In the combination group, 8 of 499 (1.6%) people withdrew for adverse events compared with 6 of 259 (2.3%) in the glatiramer acetate group and 4 of 250 (1.6%) in the interferon beta-1a group.[75] The rates of serious adverse events were lowest in the glatiramer acetate group (11.6%) and highest in the interferon beta-1a group (15.2%).[75] The CombiRx trial did not report any further information on the specific serious adverse events experienced by the participants.[75] Overall, 3 patients died (1 because of seizure activity secondary to MS in the interferon beta-1a group, 1 because of pulmonary embolism in the interferon beta-1a group, and 1 of large-cell lymphoma of the central nervous system [present at study entry] in the glatiramer acetate group).[75]

The most commonly reported adverse events in the combination group were nervous system disorders (3.2%), including extremity pain, soreness or stiffness, headache, and general neuropathic symptoms.[75] Patients in the glatiramer acetate group and the interferon beta-1a group also reported adverse events related to the nervous system (1.9% for glatiramer acetate and 4.4% for interferon beta-1a).[75] The most commonly reported adverse events in the glatiramer acetate group were categorized as nervous system disorders (e.g., extremity pain, soreness or stiffness; 1.9%), psychiatric disorders (e.g., depression; 1.9%), and surgical and medical procedures (details of the specific adverse events were not reported; 1.9%).[75] The most commonly reported adverse events in the interferon beta-1a group were categorized as nervous system disorders (e.g., extremity pain, soreness or stiffness; 4.4%), neoplasms (details of the specific neoplasms were not reported; 2.0%), and surgical and medical procedures (details of the specific adverse events were not reported; 2.0%).[75]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the CombiRx trial.[75]

Summary of Findings from Randomized Controlled Trials for CIS

Cladribine 3.5 mg/kg vs. Placebo

- Cladribine significantly reduced conversion to MS (HR, 0.33; 95% CI, 0.21 to 0.51; moderate QoE; 1 RCT; Table 47)
- Cladribine significantly reduced persistence (RR, 0.90; 95% CI, 0.82 to 0.99; low QoE; 1 RCT; Table 47)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 47)
- Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated

Glatiramer Acetate 20 mg vs. Placebo

- Glatiramer acetate reduced conversion to MS (HR, 0.55; 95% CI, 0.40 to 0.77; Table 48; moderate QoE; 1 RCT; Table 48)
- No significant difference in persistence (low QoE; 1 RCT; Table 48)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 48)
- Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated

Interferon Beta-1b 250 µg vs. Placebo

- Interferon beta-1b significantly reduced conversion to MS (HR, 0.50; 95% CI, 0.36 to 0.70; moderate QoE; 1 RCT; Table 49)
- No significant difference in persistence (low QoE; 1 RCT; Table 49)
- No significant difference in serious adverse events (very low QoE; 1 RCT; Table 49)
- Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated

Interferon Beta-1a (various doses) vs. Placebo

- Interferon beta-1a significantly reduced conversion to MS at 2 years (RR, 0.80; 95% CI, 0.68 to 0.95) and at 3 years (RR, 0.62; 95% CI, 0.505o to 0.78; low QoE; meta-analysis of 4 RCTs; Table 50)
- No significant difference in disability, as measured by the EDSS (low QoE; 1 RCT; Table 50)
- No significant difference in persistence (moderate QoE; 2 RCTs; Table 50)
- No significant difference in serious adverse events (very low QoE; meta-analysis of 4 RCTs; Table 50)
- Disability progression and change in function (MSFC) were not evaluated

Teriflunomide 7 mg and 14 mg vs. Placebo

- Teriflunomide significantly reduced conversion to MS (HR, 0.63; 95% CI, 0.42 to 0.95 for teriflunomide 7 mg; HR, 0.57; 95% CI, 0.38 to 0.87 for teriflunomide 14 mg; low QoE; 1 RCT; Table 51)
- No significant difference in disability progression (very low QoE; 1 RCT; Table 51)
- Teriflunomide significantly improved disability, as measured by the EDSS (HR, 0.98; 95% CI, 0.52 to 1.83 for teriflunomide 7 mg; HR, 0.70; 95% CI, 0.36 to 1.37 for teriflunomide 14 mg; low QoE; 1 RCT; Table 51)
- No significant difference in function, as measured by the MSFC (low QoE; 1 RCT; Table 51)
- No significant difference in persistence (low QoE; 1 RCT; Table 51)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 51)

Different Dosing Schedule for Interferon Beta-1a

- No significant difference in conversion to MS with interferon beta-1a 44 µg 3 times a week (very low QoE; 1 RCT; Table 52)
- No significant difference in persistence (moderate QoE; 1 RCT; Table 52)
- No significant difference in serious adverse events (low QoE; 1 RCT; Table 52)
- Disability progression and changes in disability (EDSS) and function (MSFC) were not evaluated

GRADE Summary of Findings for Clinically Isolated Syndrome

Cladribine 3.5 mg/kg vs. Placebo

Table 47. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Conversion to MS (1 RCT with 412 participants[63])	⊕⊕⊕◯ MODERATE	Lower with cladribine compared with placebo	Downgraded 1 level for risk of bias
Disability Progression (No RCTs)	Not reported		
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		

Outcome	Quality of the Evidence	Relationship	Rationale
Function **(as measured by the MSFC)** (No RCTs)	Not reported		
Persistence (1 RCT with 412 participants[63])	⊕⊕◯◯ LOW	Lower with cladribine compared with placebo	Downgraded 1 level for risk of bias and imprecision
Serious Adverse Events (1 RCT with 412 participants[63])	⊕⊕◯◯ LOW	No difference between cladribine and placebo	Downgraded 1 level for risk of bias and imprecision[a]

Note. [a] Imprecision was not assessable. Inconsistency was not assessable as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MS: multiple sclerosis; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Glatiramer Acetate 20 mg vs. Placebo

Table 48. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Conversion to MS (1 RCT with 481 participants[91])	⊕⊕⊕◯ MODERATE	Lower with glatiramer acetate compared with placebo	Downgraded 1 level for risk of bias
Disability Progression (No RCTs)	Not reported		
Change in Disability **(as measured by the EDSS)** (No RCTs)	Not reported		
Function **(as measured by the MSFC)** (No RCTs)	Not reported		
Persistence (1 RCT with 481 participants[91])	⊕⊕◯◯ LOW	No difference between glatiramer acetate and placebo	Downgraded 1 level for risk of bias and 2 levels for imprecision
Serious Adverse Events (1 RCT with 481 participants[91])	⊕⊕◯◯ LOW	No difference between glatiramer acetate and placebo	Downgraded 1 level for risk of bias and imprecision[a]

Note. [a] Imprecision was not assessable. Inconsistency was not assessable as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MS: multiple sclerosis; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Interferon Beta-1b 250 µg vs. Placebo

Table 49. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Conversion to MS (1 RCT with 468 participants[89])	⊕⊕⊕◯ MODERATE	Lower with interferon beta-1b compared with placebo	Downgraded 1 level for risk of bias
Disability Progression (No RCTs)	Not reported		
Change in Disability **(as measured by the EDSS)** (No RCTs)	Not reported		
Function **(as measured by the MSFC)** (No RCTs)	Not reported		
Persistence (1 RCT with 487 participants[89])	⊕⊕◯◯ LOW	No difference between interferon beta-1b and placebo	Downgraded 1 level each for risk of bias and imprecision
Serious Adverse Events (1 RCT with 468 participants[89])	⊕◯◯◯ VERY LOW	No difference between interferon beta-1b and placebo	Downgraded 1 level for risk of bias and 2 levels for imprecision

Note. Inconsistency was not assessable as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MS: multiple sclerosis; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Interferon Beta-1a (various doses) vs. Placebo

Table 50. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Conversion to MS (4 RCTs with 1,411 total participants[64,87,90,97])	⊕⊕◯◯ LOW	Lower with interferon beta-1a compared with placebo	Downgraded 1 level each for risk of bias and imprecision
Disability Progression (No RCTs)	Not reported		
Change in Disability **(as measured by the EDSS)** (1 RCT with 308 participants[97])	⊕⊕◯◯ LOW	No difference between interferon beta-1a and placebo	Downgraded 1 level each for risk of bias and imprecision[a]
Function **(as measured by the MSFC)** (No RCTs)	Not reported		
Persistence (2 RCTs with 826 total participants[64,97])	⊕⊕⊕◯ MODERATE	No difference between interferon beta-1a and placebo	Downgraded 1 level for risk of bias
Serious Adverse Events (4 RCTs with 1,325 total participants[64,87,90,97])	⊕◯◯◯ VERY LOW	No difference between interferon beta-1a and placebo	Downgraded 1 level for risk of bias and 2 levels for imprecision

Note. [a] Imprecision was not assessable. If there is only 1 trial for an outcome, Inconsistency was not assessable. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MS: multiple sclerosis; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Teriflunomide 7 mg and 14 mg vs. Placebo

Table 51. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Conversion to MS (1 RCT with 614 participants[94])	⊕⊕○○ LOW	Lower with teriflunomide 7 mg and teriflunomide 14 mg compared with placebo	Downgraded 1 level each for risk of bias and imprecision
Disability Progression (1 RCT with 614 participants[94])	⊕○○○ VERY LOW	No difference between teriflunomide 7 mg or teriflunomide 14 mg and placebo	Downgraded 1 level for risk of bias and 2 levels for imprecision
Change in Disability (as measured by the EDSS) (1 RCT with 614 participants[94])	⊕⊕○○ LOW	Greater improvements with teriflunomide 7 mg and teriflunomide 14 mg compared with placebo; differences were small and may not be clinically important	Downgraded 1 level each for risk of bias and imprecision[a]
Function (as measured by the MSFC) (1 RCT with 614 participants[94])	⊕⊕○○ LOW	No difference between teriflunomide 7 mg or teriflunomide 14 mg and placebo	Downgraded 1 level each for risk of bias and imprecision[a]
Persistence (1 RCT with 618 participants[94])	⊕⊕○○ LOW	No difference between teriflunomide 7 mg or teriflunomide 14 mg and placebo	Downgraded 1 level each for risk of bias and imprecision
Serious Adverse Events (1 RCT with 614 participants[94])	⊕⊕○○ LOW	No difference between teriflunomide 7 mg or teriflunomide 14 mg and placebo	Downgraded 1 level each for risk of bias and imprecision[a]

Note. [a] Imprecision was not assessable. Inconsistency was not assessable as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MS: multiple sclerosis; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Different Dosing Schedule for Interferon Beta-1a

Table 52. Summary of Findings (GRADE)

Outcome	Quality of the Evidence	Relationship	Rationale
Conversion to MS (1 RCT with 346 participants[64])	⊕○○○ VERY LOW	No difference between interferon beta-1a 44 μg 3 times a week and interferon beta-1a 44 μg once a week	Downgraded 1 level for risk of bias and 2 levels for imprecision
Disability Progression (No RCTs	Not reported		

Outcome	Quality of the Evidence	Relationship	Rationale
Change in Disability (as measured by the EDSS) (No RCTs)	Not reported		
Function (as measured by the MSFC) (No RCTs)	Not reported		
Persistence (1 RCT with 346 participants[64])	⊕⊕⊕◯ MODERATE	No difference between interferon beta-1a 44 µg 3 times a week and interferon beta-1a 44 µg once a week	Downgraded 1 level for risk of bias
Serious Adverse Events (1 RCT with 344 participants[64])	⊕⊕◯◯ LOW	No difference between interferon beta-1a 44 µg 3 times a week and interferon beta-1a 44 µg once a week	Downgraded 1 level each for risk of bias and imprecision[a]

Note. [a] Imprecision was not assessable. Inconsistency was not assessable as only 1 eligible study. Abbreviations. EDSS: Expanded Disability Status Scale; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation approach; MS: multiple sclerosis; MSFC: Multiple Sclerosis Functional Composite; RCT: randomized controlled trial.

Effectiveness and Harms of Disease-modifying Treatments for CIS

Cladribine vs. Placebo

Study Characteristics

We identified 1 eligible RCT comparing cladribine and placebo in people with a first clinical demyelinating event (Table 53).[63] In the ORACLE MS trial,[63] 412 participants were randomized to cladribine 3.5 mg/kg or placebo for 96 weeks.[63] A further 205 participants were randomized to cladribine 5.25 mg/kg; this dose is not FDA-approved for the treatment of any condition.[63] The ORACLE MS trial[63] was terminated early because the sponsor suspended the development of cladribine. We assessed the ORACLE MS trial as of poor methodological quality because of concerns about high and differential loss to follow-up, early termination, author conflict of interest, and funding by industry. Cladribine is not FDA-approved for use in people with CIS because of concerns about safety.[10]

Table 53. Summary Table of Included RCTs for CIS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Cladribine vs. Placebo				
Leist et al., 2014[63] 160 sites in 34 countries, including the U.S. NCT00725985	• Adults with a first clinical demyelinating event • Total N = 617 randomized; n = 205, cladribine 5.25 mg/kg; n = 206, cladribine	Cladribine 5.25 mg/kg; cladribine 3.5 mg/kg; cumulative oral doses	Placebo	96 weeks

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
ORACLE MS	3.5 mg/kg; n = 206, placebo			

Abbreviations. CIS: clinically isolated syndrome; kg: kilogram; mg: milligram; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial.

Progression to a Diagnosis of MS

Participants in the cladribine 3.5 mg/kg group were followed-up for a mean duration of 79.2 weeks (SD, 25.1) and participants in the placebo group were followed-up for a mean duration of 66.0 weeks (SD, 31.4). Over this period, patients in the cladribine 3.5 mg/kg group had lower rates of conversion to clinically definite MS than patients in the placebo group (HR, 0.33; 95% CI, 0.21 to 0.51).[63] The cumulative probability of progressing to clinically definite MS over the period of the trial was 14.0% in the cladribine 3.5 mg/kg group and 38.0% in the placebo group.[63] Patients in the cladribine 3.5 mg/kg group also had a longer time of progression to MS based on the McDonald criteria[173] than patients in the placebo group (338 days vs. 120 days; *P* value not reported).[63] Similar results to the cladribine 3.5 mg/kg group were seen in the cladribine 5.25 mg/kg group.[63]

Disability

No disability-related outcomes were reported in the ORACLE MS trial.[63]

Functional Outcomes

No functional outcomes were reported in the ORACLE MS trial.[63]

Persistence

At study termination, 76.7% (158 of 206) of participants in the cladribine 3.5 mg/kg remained in ORACLE MS, compared to 65.9% (135 of 205) in the cladribine 5.25 mg/kg group and 84.9% (175 of 206) in the placebo group.[63] Overall, persistence was lower in the cladribine groups compared with the placebo group.

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the ORACLE MS trial.[63]

Effectiveness by Subgroup

We did not identify any evidence of effectiveness by subgroup in the ORACLE MS trial.[63]

Adverse Events

In the cladribine 3.5 mg/kg group, 5% of participants withdrew because of adverse events and 11% experienced a serious adverse event.[63] In the placebo group, 2% of participants withdrew because of adverse events and 10% experienced a serious adverse event.[63] No deaths were observed during the study period.[63]

The most commonly reported adverse events in the cladribine 3.5 mg/kg and placebo groups were headache (31% vs. 28%) and nasopharyngitis (17% vs. 18%).[63] Participants in the cladribine

3.5 mg/kg group contracted herpes virus infections at a higher rate than participants in the placebo group (8% vs. 1%).[63] Overall, 3 patients in the cladribine 3.5 mg/kg group and 6 patients in the placebo group were diagnosed with neoplasms.[63] Of these, 2 patients in the cladribine 3.5 mg/kg group were diagnosed with cancer; 1 with papillary thyroid cancer and 1 with squamous cell carcinoma.[63]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the ORACLE MS trial.[63]

Glatiramer Acetate vs. Placebo

Study Characteristics

We identified 1 eligible RCT comparing glatiramer acetate to placebo in people with clinically isolated syndrome (Table 54).[91] In the PreCISe trial,[91] 481 participants were randomized to subcutaneous injections of glatiramer acetate 20 mg once daily or placebo for up to 36 months.[91] We assessed the PreCISe trial as fair-methodological quality because of concerns about early termination of the study, author conflict of interest, and funding by industry.

Table 54. Summary Table of Included RCTs for CIS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Glatiramer Acetate vs. Placebo				
Comi et al., 2009[91] 80 sites in 16 countries (U.S., Europe, Argentina, Australia, New Zealand) NCT00666224 PreCISe	• Adults with a unifocal neurological event • Total N = 481 randomized; n = 243, glatiramer acetate; n = 238, placebo	Glatiramer acetate 20 mg SC injection, once daily	Placebo	Up to 36 months

Abbreviations. CIS: clinically isolated syndrome; mg: milligram; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; SC: subcutaneous.

Progression to a Diagnosis of MS

Patients in the glatiramer acetate group had a lower risk of conversion to clinically definite MS than patients in the placebo group (HR, 0.55; 95% CI, 0.40 to 0.77).[91] Patients in the glatiramer acetate group also had a lower risk of a second attack (24.7% vs. 42.9%; OR, 0.41; 95% CI, 0.28 to 0.62).[91] The time to conversion to MS was also longer in the glatiramer acetate group compared with the placebo group (722 days vs. 336 days; *P* = .004).[91]

Disability

No disability-related outcomes were reported in the PreCISe trial.[91]

Functional Outcomes

No functional outcomes were reported in the PreCISe trial.[91]

Persistence

In the glatiramer acetate group, 84.8% (206 of 243) of participants completed the trial or were still in the double-blind period at study termination, compared with 91.2% (217 of 238) in the placebo group.[91] Persistence was not significantly different between groups.

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the PreCISe trial.[91]

Effectiveness by Subgroup

In the PreCISe trial,[91] glatiramer acetate remained more effective in reducing the risk of conversion to clinically definite MS than placebo when analyzed by subgroups:
- In women (HR, 0.52; 95% CI, 0.34 to 0.81) but not men
- In younger people, aged 30 and under, (HR, 0.47; 95% CI, 0.27 to 0.80) but not older people

Adverse Events

More participants in the glatiramer acetate group than in the placebo group withdrew because of adverse events (5.8% vs. 1.7%; $P = .02$).[91] The rates of serious adverse events in the glatiramer acetate group were 8%, compared to 5% in the placebo group.[91] In the placebo group, 1 patient died by suicide.[91]

The most commonly reported adverse events in the glatiramer acetate group were lymphadenopathy (5%) and vomiting (6%).[91] In the placebo group, the most commonly reported adverse events were vomiting (2%), itching (1%), erythema (1%), and rash (1%); each of these were reported less than in the glatiramer acetate group (no formal statistical testing was conducted).[91] Participants in the glatiramer acetate group also reported more injection-site reactions (56% vs. 24%) and immediate post-injection reactions (19% vs. 5%) than in the placebo group.[91] In the glatiramer acetate group, 2 patients had injection-site necrosis and 10 patients had injection-site atrophy or lipotrophy.[91] Overall, 1 patient in each group terminated the study prematurely because of elevated liver enzymes.[91]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the PreCISe trial.[91]

Interferon Beta-1b vs. Placebo

Study Characteristics

We identified 1 eligible RCT comparing interferon beta-1b and placebo in adults with a first clinical demyelinating event (Table 55).[89] In the BENEFIT trial,[89] 487 participants were randomized to subcutaneous injections of interferon beta-1b 250 µg every other day or placebo for 24 months.[89] We assessed the BENEFIT trial as of fair methodological quality because of concerns about author conflict of interest and funding by industry.

After conversion to clinically definite MS or 2 years in the BENEFIT trial, patients on placebo could switch to interferon beta-1b or another treatment (delayed treatment) and continue for up to 11 years.[154]

Table 55. Summary Table of Included RCTs for CIS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Interferon Beta-1b vs. Placebo				
Kappos et al., 2006[89] 98 sites in Israel, Canada, and 18 European countries Not reported BENEFIT	• Adults with CIS • Total N = 487 randomized; n = 305, interferon beta-1b; n = 182, placebo	Interferon beta-1b 250 µg SC, every other day	Placebo	24 months

Abbreviations. µg: microgram; CIS: clinically isolated syndrome; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; SC: subcutaneous.

Progression to a Diagnosis of MS

Patients in the interferon beta-1b group had a lower probability of conversion to clinically definite MS than patients in the placebo group (28% vs. 45% placebo; HR, 0.50; 95% CI, 0.36 to 0.70).[89] Similar results were see for progression to MS based on the McDonald criteria[178] (69% vs. 85%; HR, 0.54; 95% CI, 0.43 to 0.67).[89] Patients in the interferon beta-1b group also had a longer time to clinically definite MS, 618 days compared to 255 days in the placebo group.[89]

After 11 years, participants in the early treatment group had a lower risk of conversion to clinically definite MS than participants in the delayed treatment group (HR, 0.67; 95% CI, 0.53 to 0.85), a longer time to first relapse (median, 1,888 days vs. 931 days), and lower overall ARR (0.21 vs 0.26; $P < .001$).[154]

Disability

No disability-related outcomes were reported in the BENEFIT trial.[89]

Over the 11 years of follow-up, participants in the early and delayed treatments groups had similar levels of disability (median EDSS change of 0.5; interquartile range [IQR], -0.50 to 1.50).[154]

Functional Outcomes

No functional outcomes were reported in the BENEFIT trial.[89]

After 11 years, participants in the early group had higher function, as measures on the PASAT-3 ($P = .007$).[154] Overall, employment rates were high (73.4%), with 64.4% of people being employed for 20 hours or more a week.[154]

Persistence

Overall, 78.7% (240 of 305) of participants in the interferon beta-1b group, and 84.6% (154 of 182) of the placebo group completed the 24-month trial.[89] Persistence was not significantly different between groups.

Other Outcomes of Effectiveness

QoL did not change in either group over the study period, and there were no differences between the groups (*P* value not reported).[89]

Effectiveness by Subgroup

In the BENEFIT trial, the effectiveness of interferon beta-1b in reducing the rate of conversion to clinically definite MS did not vary by the type of initial event (monofocal or multifocal).[89]

Adverse Events

More patients in the interferon beta-1b group withdrew because of adverse events than patients in the placebo group (7.9% vs. 0.5%; *P* value not reported).[89] The rates of serious adverse events were similar in both groups (6.8%).[89] No deaths occurred during the course of the study.[89]

The most commonly reported adverse events in the interferon beta-1b group were injection-site reactions (48%), flu-like syndrome (44%), headache (27%), and asthenia (i.e., loss of strength; 22%).[89] In the placebo group, the most commonly reported adverse events were flu-like syndrome (18%), headache (17%), and asthenia (17%).[89] However, patients in the placebo group reported these in fewer numbers than did patients in the interferon beta-1b group.[89] Patients in the interferon beta-1b group had higher rates of raised alanine aminotransferase levels (17.8% vs. 4.5%) and aspartate aminotransferase levels (6.2% vs. 0.6%) than in the placebo group.[89]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the BENEFIT trial.[89]

Interferon Beta-1a vs. Placebo

Study Characteristics

We identified 4 eligible RCTs comparing interferon beta-1a and placebo in people with a first episode suggestive of MS, including a first clinical demyelinating event (Table 56).[64,87,90,97]

- In the ETOMS trial,[97] 309 participants were randomized to subcutaneous injections of interferon beta-1a 22 μg once a week and placebo, for 24 months. We assessed the ETOMS trial as of fair methodological quality because of concerns about the lack of reporting on randomization, author conflict of interest, and funding by industry.
- In the REFLEX trial,[64] 517 participants were randomized to subcutaneous injections of interferon beta-1a 44 μg 3 times a week, subcutaneous interferon beta-1a 44 μg once a week, and placebo, for 24 months. We assessed the REFLEX trial as of fair methodological quality because of concerns about author conflict of interest and funding by industry.
- In the CHAMPS trial,[87] 383 participants were randomized to intramuscular injections of interferon beta-1a 30 μg once a week and placebo, for 3 years.[87] We assessed the CHAMPS trial as of fair methodological quality because of concerns about author conflict of interest and funding by industry.
- In the RCT by Pakdaman et al.,[90] 217 participants were randomized to intramuscular injections of interferon beta-1a 30 μg once a week and placebo, for 3 years. We assessed the trial by Pakdaman et al.[90] as of poor methodological quality because of concerns about the lack of reporting on key study components (including randomization and blinding), intent-to-treat analysis not being conducted, and no information on author conflicts of interest or study funding.

After the completion of CHAMPS, all patients were offered active treatment for an additional 2 years to complete 5 years in the CHAMPIONS extension study.[158] In the second extension phase, all patients were offered an additional 5 years of active treatment to complete a 10-year follow-up.[153] Patients who received placebo in CHAMPS were classified as the delayed treatment group, and patients who received interferon beta-1a in CHAMPS were classified as the immediate treatment group.[153,158]

Table 56. Summary Table of Included RCTs for CIS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Interferon Beta-1a vs. Placebo				
Comi et al., 2001[97] 57 centers in 14 European countries Not reported ETOMS	• Adults with a first presentation of a neurological event and at high risk of conversion to clinically definite MS • Total N = 309 randomized; n = 154, interferon beta-1a; n = 155, placebo	Interferon beta-1a 22 µg SC, once a week	Placebo	24 months
Comi et al., 2012[64] 80 sites in 28 countries, no sites in the U.S. NCT00404352 REFLEX	• Adults with a first clinical demyelinating event • Total N = 517 randomized; n = 171, interferon beta-1a 3 times a week; n = 175, interferon beta-1a once a week; n = 171,placebo group	Interferon beta-1a 44 µg SC, 3 times a week; interferon beta-1a 44 µg SC, once a week, plus 2 placebo injections twice a week	3 placebo SC injections per week	24 months
Jacobs et al., 2000[87] 50 sites in the U.S. and Canada Not reported CHAMPS	• Adults with a first clinical demyelinating event • Total N = 383 randomized; n = 193, interferon beta-1a; n = 190, placebo	Interferon beta-1a 30 µg IM, once a week	Placebo	3 years
Pakdaman et al., 2007[90] 4 sites in Iran Not reported Not reported	• Adults with a first neurological event consistent with demyelination • Total N = 217; numbers by group not reported	Interferon beta-1a 30 µg IM, once a week	Placebo	3 years

Abbreviations. µg: microgram; CIS: clinically isolated syndrome; IM: intramuscular; MS: multiple sclerosis; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; SC: subcutaneous.

Progression to a Diagnosis of MS

Participants in the interferon beta-1a groups had significantly lower rates of progression at 2 years in the ETOMS and REFLEX trials (subcutaneous interferon beta-1a 22 µg or 44 µg) and at 3 years in the CHAMPS trial (intramuscular interferon beta-1a 30 µg; Figure 28).[64,87,90,97]
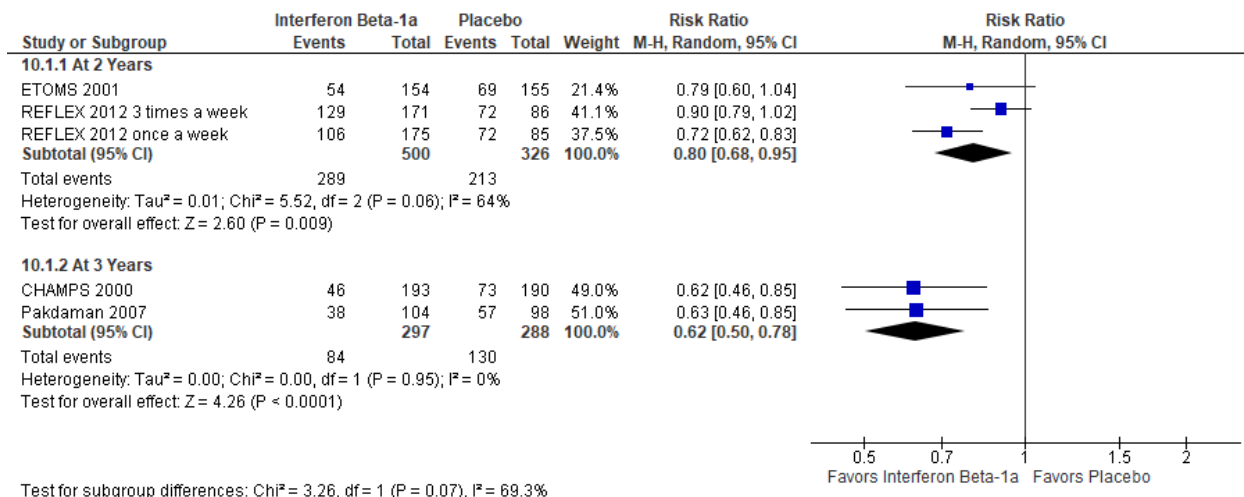
Study or Subgroup	Interferon Beta-1a Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
10.1.1 At 2 Years						
ETOMS 2001	54	154	69	155	21.4%	0.79 [0.60, 1.04]
REFLEX 2012 3 times a week	129	171	72	86	41.1%	0.90 [0.79, 1.02]
REFLEX 2012 once a week	106	175	72	85	37.5%	0.72 [0.62, 0.83]
Subtotal (95% CI)		500		326	100.0%	0.80 [0.68, 0.95]
Total events	289		213			
Heterogeneity: Tau² = 0.01; Chi² = 5.52, df = 2 (P = 0.06); I² = 64%						
Test for overall effect: Z = 2.60 (P = 0.009)						
10.1.2 At 3 Years						
CHAMPS 2000	46	193	73	190	49.0%	0.62 [0.46, 0.85]
Pakdaman 2007	38	104	57	98	51.0%	0.63 [0.46, 0.85]
Subtotal (95% CI)		297		288	100.0%	0.62 [0.50, 0.78]
Total events	84		130			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 4.26 (P < 0.0001)						

Risk Ratio M-H, Random, 95% CI — scale: 0.5 0.7 1 1.5 2 — Favors Interferon Beta-1a Favors Placebo

Test for subgroup differences: Chi² = 3.26, df = 1 (P = 0.07), I² = 69.3%

Figure 28. Interferon Beta-1a vs. Placebo. Progression to MS.

In ETOMS,[97] patients in the interferon beta-1a group also had lower relapse rates (ARR, 0.33 vs. 0.43; *P* = .045) and a longer time to conversion to a diagnosis of MS compared with placebo (549 days vs. 252 days; *P* = .03).[97] Similarly, patients in the trial by Pakdaman et al.[90] had lower relapse rates in the interferon beta-1a group compared with the placebo group (ARR, 0.13 vs. 0.22; *P* value not reported).[90]

In the CHAMPIONS extension study, participants in the immediate treatment group had significantly lower rates of conversion to clinically definite MS compared with participants in the delayed treatment group at 5 years (HR, 0.65; 95% CI, 0.43 to 0.97).[158]

Disability

No disability progression outcomes were reported in the 4 included trials.[64,87,90,97] In the ETOMS trial, patients in both groups experienced no change in disability as measured by the EDSS (*P* = .75 for differences between groups).[97]

In the CHAMPIONS extension study at 5 years, participants in the immediate treatment group and participants in the delayed treatment group had similar levels of disability, as measured by the EDSS.[158]

In the CHAMPIONS extension study at 10 years, good recovery from the initial relapse was defined as either[153]:

- When the peak deficit at enrollment within the 28 days of symptom onset was the EDSS score of 0, and the EDSS score of 0 is maintained through the 6th-month visit, the patient was assumed to have already recovered fully at enrollment; or,
- When the peak deficit at enrollment within the 28 days of symptom onset was an EDSS score greater than 0, the patient was assumed to have good recovery if the EDSS score improvement from peak deficit to 6th-month visit, was equal to, or better than the median of the group

Patients with good recovery and immediate initiation of therapy after their first relapse had approximately a 65% chance of remaining at a minimal disability level by age 45 years.[153]

Patients with poor recovery and delayed therapy initiation had an approximately 20% chance of remaining at a minimal disability level by age 45 years.[153] Patients with poor recovery but immediate therapy initiation, or patients with good recovery but delayed therapy initiation similarly had an approximately 50% chance of remaining at a minimal disability by age 45 years.[153]

Functional Outcomes
No functional outcomes were reported in the 4 included trials.[64,87,90,97]

Persistence
At 2 years, similar numbers of participants in the interferon beta-1a groups and placebo groups completed the trials (Figure 29).[64,97]
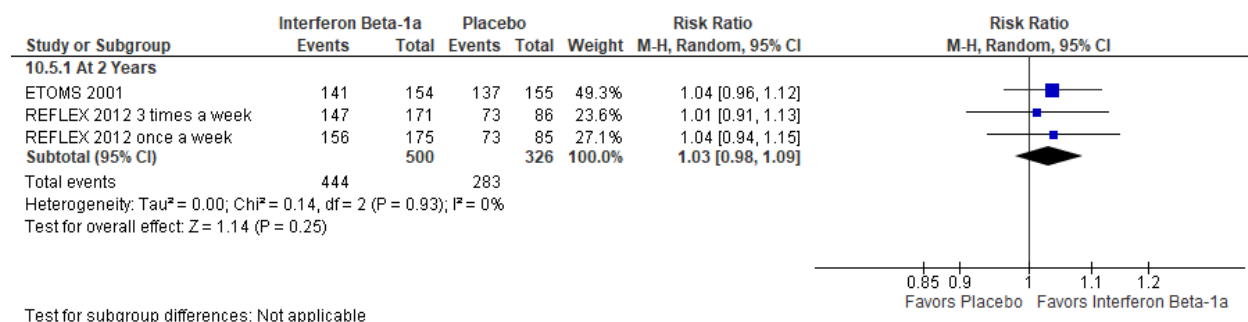
Figure 29. Interferon Beta-1a vs. Placebo. Completed Study.

In the CHAMPS trial,[87] 16% of patients in the interferon beta-1a group and 14% in the placebo group discontinued the study for reasons other than conversion to MS. In the trial by Pakdaman et al.,[90] 93.1% of all participants completed the study.

Other Outcomes of Effectiveness
No other relevant outcomes were reported in the 4 included trials.[64,87,90,97]

Effectiveness by Subgroup
In the CHAMPS trial, the effectiveness of interferon beta-1a on reducing the time to clinically definite MS did not vary by the type of initial event (optic neuritis, spinal cord syndrome, or brainstem or cerebellar syndrome).[87]

In a sub group analysis of the REFLEX trial, time to conversion to clinically definite MS[146]:
- Was lower in the interferon beta-1a groups compared to placebo regardless of age
- Was similar in the interferon beta-1a groups compared to placebo for men, but was lower in the interferon beta-1a groups for women
- Was lower in the interferon beta-1a groups compared to placebo for people who had steroid treatment for the first demyelinating event, lower in the interferon beta-1a 3 times a week group for people who had no steroid treatment for the first demyelinating event, but similar for interferon beta-1a in people who had no steroid treatment for the first demyelinating event
- Was lower in the interferon beta-1a groups compared to placebo regardless of the type of the first demyelinating event (monofocal or multifocal[146]

However, in the primary publication,[64] time to progression to clinically definite MS was no different between interferon beta-1a once a week and placebo for patients with a monofocal presentation. In addition, patients with a multifocal presentation had a lower risk of progression in the interferon beta-1a 3 times a week group compared with patients in the interferon beta-1a once a week group (P = .02).[64]

Adverse Events

Patients in the interferon beta-1a groups tended to have similar or lower rates of withdrawal because of adverse events, compared with placebo:
- 24% of patients in the interferon beta-1a 3 times a week group, vs. 27% in the interferon beta-1a once a week group, vs. 30% in the placebo, in the REFLEX trial[64]
- < 1% in the interferon beta-1a group, vs. 4% in the placebo group, in the CHAMPS trial[64]

Rates of serious adverse events were similar in the interferon beta-1a and placebo groups (Figure 30).[64,87,90,97] Overall, 3 deaths were reported in 2 of the 4 eligible trials:
- 2 patients died in the placebo group in the REFLEX trial[64]
- 1 patient died in the interferon beta-1a group (car accident) in the CHAMPS trial[87]

	Interferon Beta-1a		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CHAMPS 2000	12	193	9	104	28.6%	0.72 [0.31, 1.65]	
ETOMS 2001	6	154	5	155	14.5%	1.21 [0.38, 3.87]	
Pakdaman 2007	9	104	7	98	21.9%	1.21 [0.47, 3.13]	
REFLEX 2012 3 times a week	6	171	6	86	16.3%	0.50 [0.17, 1.51]	
REFLEX 2012 once a week	8	175	6	85	18.7%	0.65 [0.23, 1.81]	
Total (95% CI)		797		528	100.0%	0.80 [0.52, 1.25]	
Total events	41		33				
Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 4 (P = 0.71); I² = 0%							
Test for overall effect: Z = 0.96 (P = 0.34)							

0.01 0.1 1 10 100
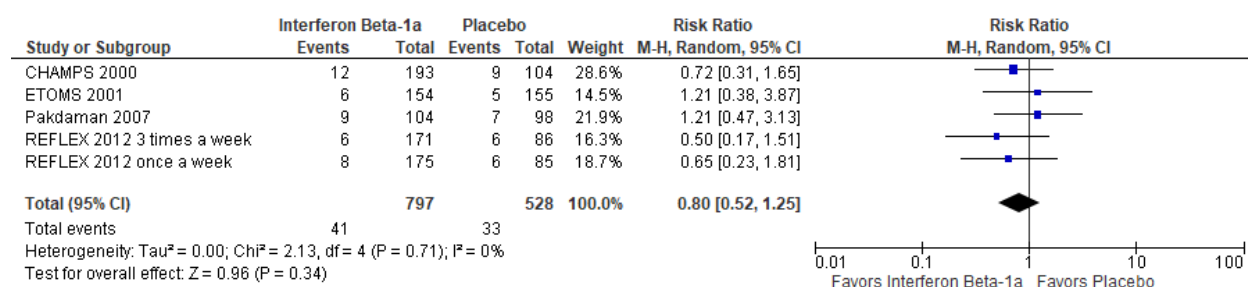Favors Interferon Beta-1a   Favors Placebo

Figure 30. Interferon Beta-1a vs. Placebo. Serious Adverse Events.

Over the 5 years of the CHAMPIONS extension study, 13 serious adverse events occurred in 12 patients on or within a month of discontinuation of interferon beta-1a treatment, including hospitalizations for MS relapses, deep vein thrombosis, infection/sepsis, atrial fibrillation, supraventricular tachycardia, and a suicide attempt by overdose.[158] The serious adverse events were assessed as being likely unrelated or unrelated to the study drug.[158] Overall, no new safety concerns with interferon beta-1a treatment were identified during the first 5 years of the CHAMPIONS study.[158]

In the REFLEX trial,[64] the most commonly reported adverse events were influenza-like illness (54%), injection-site erythema (29%), and headache (27%) in the interferon beta-1a group. In the placebo group, the most commonly reported adverse events were influenza-like illness (20%) and headache (27%).[64] In the CHAMPS trial[87] and the trial by Pakdaman et al.,[90] patients in the interferon beta-1a groups were significantly more likely to experience influenza-like illness compared with patients in the placebo groups (P < .05). In the REFLEX trial, 3 serious events were judged to be related to the study drug (1 case of varicella and 1 spontaneous abortion in the interferon beta-1a once a week group, and 1 spontaneous abortion in the placebo group).[64] Patients in the interferon beta-1a 3 times a week group also had higher rates of hepatic disorders than in the interferon beta-1a once a week group, or placebo (9% vs. 6% vs. 6%).[64] The

number of patients who tested positive for neutralizing antibodies at month 24 or at their last test was 14.8% in the interferon beta-1a 3 times a week group and 16.7% in the interferon beta-1a once a week group.[64]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the 4 eligible RCTs.[64,87,90,97]

Teriflunomide vs. Placebo

Study Characteristics

We identified 1 eligible RCT comparing teriflunomide and placebo in people with a first clinical episode suggestive of MS (Table 57).[94] In the TOPIC trial,[94] 617 participants were randomized to teriflunomide 7 mg daily, teriflunomide 14 mg daily, or placebo, for up to 108 weeks.[94] The TOPIC trial was stopped early because of changes in the diagnostic criteria.[94] We assessed the TOPIC trial as of fair methodological quality because of concerns about high loss to follow-up, author conflict of interest, and funding by industry.

Patients who completed the TOPIC trial (including those still in the study at early termination) or who progressed to clinically definite MS after at least 24 weeks in the initial trial were eligible to participate in the extension.[161] Patients in the teriflunomide groups continued with their allocated dose and patients in the placebo group were rerandomized to teriflunomide 7 mg daily or teriflunomide 14 mg daily.[161] The extension period continued until teriflunomide was commercially available in the patient's country of residence, or until the sponsor stopped the study (planned after a period of 390 weeks).[161]

Table 57. Summary Table of Included RCTs for CIS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Teriflunomide vs. Placebo				
Miller et al., 2014[94] 112 sites in 20 countries, including the U.S. NCT00622700 TOPIC	• Adults with a first neurological event consistent with demyelination • Total N = 618 randomized; n = 205, teriflunomide 7 mg; n = 216, teriflunomide 14 mg; n = 197, placebo	Teriflunomide 7 mg oral, daily; teriflunomide 14 mg oral, daily	Placebo	Up to 108 weeks

Abbreviations. CIS: clinically isolated syndrome; mg: milligram; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial.

Progression to a Diagnosis of MS

Patients in the teriflunomide groups experienced fewer relapses (indicating conversions to clinically definite MS) than patients in the placebo group (19% teriflunomide 7 mg [HR, 0.63; 95% CI, 0.42 to 0.95 vs. placebo] vs. 18% teriflunomide 14 mg [HR, 0.57; 95% CI, 0.38 to 0.87 vs. placebo] vs. 28% placebo).[94] Rates of relapse were also lower in the teriflunomide groups but the differences were not significantly different to those in the placebo group (ARR, 0.19

teriflunomide 7 mg [RR, 0.67; 95% CI, 0.11 to 1.01 vs. placebo] vs. 0.19 teriflunomide 14 mg [RR, 0.68; 95% CI, 0.46 to 1.01 vs. placebo] vs. 0.28 placebo).[94] In the teriflunomide groups, patients had a cumulative rate of relapse of 27.6% in the teriflunomide 7 mg group and 24.0% in the teriflunomide 14 mg group, compared with 35.9% in the placebo group (*P* value not reported).[94]

During the core and extension periods, the number of patients who did not experience a relapse (indicating a conversion to clinically definite MS) was 75.0% in the delayed teriflunomide 7 mg group, 64.1% in the early teriflunomide 7 mg group, 62.7% in the delayed teriflunomide 14 mg group, and 76.0% in the early teriflunomide 14 mg group.[161]

Disability

Patients in the teriflunomide groups and patients in the placebo group had similar rates of disability progression (10% teriflunomide 7 mg [HR, 0.98; 95% CI, 0.52 to 1.83 vs. placebo] vs. 7% teriflunomide 14 mg [HR, 0.70; 95% CI, 0.36 to 1.37 vs. placebo] vs. 10% placebo).[94] However, patients in the teriflunomide groups had significantly greater improvements in disability (EDSS) compared with patients in the placebo group (mean change, -0.25 teriflunomide 7 mg vs. -0.27 teriflunomide 14 mg vs. -0.06 placebo; mean difference of -0.26 for teriflunomide 7 mg vs. placebo; mean difference of -0.23 for teriflunomide 14 mg vs. placebo; *P* < .05 for both comparisons).[94]

In the extension study, the estimated numbers of patients free from disability progression at week 384 was 84.4% in the delayed teriflunomide 7 mg group, 74.7% in the early teriflunomide 7 mg group, 77.0% in the delayed teriflunomide 14 mg group, and 80.6% in the early teriflunomide 14 mg group.[161]

Functional Outcomes

Patients in the teriflunomide groups and patients in the placebo group had similar reductions in fatigue, as measured by the Fatigue Impact Scale (mean change, -2.73 teriflunomide 7 mg vs. -4.49 teriflunomide 14 mg vs. -3.54 placebo; *P* > .05 for both mean differences to placebo).[94]

Persistence

Overall, 73.2% (150 of 205) of participants in the teriflunomide 7 mg group, 75.5% (163 of 216) in the teriflunomide 14 mg group, and 71.6% (141 of 197) in the placebo group completed the study (up to 108 weeks).[94] Persistence was not significantly different between groups.

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the TOPIC trial.[94]

Effectiveness by Subgroup

We did not identify any evidence of effectiveness by subgroup in the TOPIC trial.[94]

Adverse Events

In the teriflunomide 7 mg group, 12% of patients withdrew because of adverse events and 9% experienced a serious adverse event.[94] In the teriflunomide 14 mg group, 8% of patients withdrew because of adverse events and 11% experienced a serious adverse event.[94] In the placebo group, 10% of patients withdrew because of adverse events and 9% experienced a

serious adverse event.[94] In the placebo group, 1 patient died by suicide and no deaths occurred in either of the teriflunomide groups.[94]

The most commonly reported adverse events in the teriflunomide groups were raised alanine transferase levels (17% to 19%), nasopharyngitis (14% to 17%), headache (13% to 14%), diarrhea (11% to 14%), hair thinning (6% to 12%), and upper respiratory tract infection (9% to 11%).[94] The most commonly reported adverse events in the placebo group were raised alanine transferase levels (14%), nasopharyngitis (17%), and headache (13%).[94] Patients in all groups experienced serious hepatic disorders (2% teriflunomide 7 mg, vs. 3% teriflunomide 14 mg, vs. 2% placebo).[94]

In the extension study, 75.8% of patients in the combined delayed and early teriflunomide 7 mg treatment groups and 81.9% of patients in the combined delayed and immediate teriflunomide 14 mg experienced adverse events.[161] The most frequently reported adverse events were nasopharyngitis, headache, upper respiratory tract infection, and diarrhea, which were similar to those reported in the initial trial.[161] Diarrhea, hair thinning, and elevated alanine aminotransferase tended to occur in the first 48 weeks of treatment, and were generally mild.[161]

Harms by Subgroup

We did not identify any evidence of harms by subgroup in the TOPIC trial.[94]

Different Dosing Schedule for Interferon Beta-1a

Study Characteristics

We identified 1 eligible RCT comparing different dosing schedules of interferon beta-1a in people with a first clinical demyelinating event (Table 58).[64] In the REFLEX trial,[64] 346 participants were randomized to subcutaneous injections of interferon beta-1a 44 µg 3 times a week or subcutaneous interferon beta-1a 44 µg once a week, for 24 months. A further 171 participants were also randomized to placebo; however, the comparison of interferon beta-1b and placebo is not relevant for this report, so no results for this comparison are reported.[64] We assessed the REFLEX trial as of fair methodological quality because of concerns about author conflict of interest and funding by industry.

Progression to a Diagnosis of MS

Participants in both the interferon beta-1a 3 times a week and once a week groups had similar rates of conversion to clinically definite MS (HR, 0.90; 95% CI, 0.56 to 1.43).[64] However patients in the interferon beta-1a 3 times a week had a lower rate of progression to MS according to the McDonald criteria[179] (HR, 0.71; 95% CI, 0.54 to 0.91).[64]

Table 58. Summary Table of Included RCTs for CIS

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
Interferon Beta-1a				
Comi et al., 2012[64] 80 sites in 28 countries, no sites in the U.S.	See characteristics reported in the head-to-head section (Table 56)			

Citation Location NCT Number Trial Name	Patient Characteristics	Intervention	Comparator(s)	Study Duration
NCT00404352 REFLEX				

Abbreviations: CIS: clinically isolated syndrome; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial.

Disability

No disability-related outcomes were reported in the REFLEX trial.[64]

Functional Outcomes

No functional outcomes were reported in the REFLEX trial.[64]

Persistence

At 24 months, 85% (146 of 171) of participants in the interferon beta-1a 3 times a week and 89% (156 of 175) in the interferon beta-1a once 1 week group completed the study, and the difference was not statistically significant.[64]

Other Outcomes of Effectiveness

No other relevant outcomes were reported in the REFLEX trial.[64]

Effectiveness by Subgroup

We did not identify any evidence of effectiveness by subgroup for the different dosing schedules of interferon beta-1a from the REFLEX trial.[64]

Adverse Events

Patients in both interferon beta-1a groups withdrew because of adverse events (24% interferon beta-1a 3 times a week group, vs. 27% once a week group).[64] The rates of serious adverse events were similar between the 2 groups.[64] No participants in the interferon beta-1a groups died during the study.[64]

The most commonly reported adverse events were influenza-like illness (54% vs. 71%), injection-site erythema (29% vs. 20%), and headache (27% vs. 21%) in the interferon beta-1a groups.[64] Patients in the interferon beta-1a 3 times a week group had higher rates of hepatic disorders than in the once a week group (9% vs. 6%).[64] Patients in the interferon beta-1a 3 times a week group had higher rates of hepatic disorders than in the once a week group (9% vs. 6%).[64]

Harms by Subgroup

We did not identify any evidence of harms by subgroup for the different dosing schedules of interferon beta-1a from the REFLEX trial.[64]

Comparative Harms from Cohort Studies

We identified 30 eligible cohort studies reported in 31 publications[100-130] reporting on the comparative harms of disease-modifying therapies for MS. We assessed the majority of studies

as fair-methodological quality because of concerns about author conflicts of interest and industry funding. We assessed the remainder of the studies as poor-methodological quality because of concerns about appropriate adjustment for confounding.

Treatment Discontinuation and Switch

We identified 24 eligible cohort studies (reported in 25 publications) comparing treatment discontinuation or treatment switch by disease-modifying therapy (Table 59).[101-110,112-114,116,118-120,122,124-130]

Table 59. Study Characteristics and Findings from Eligible Nonrandomized Studies

Citation Study Description and Location	Data Collection Date	Key Patient Characteristics	Therapies of Interest
Discontinuation or Treatment Switch			
Braune et al., 2018[101] National registry in Germany	Not reported	• Adults with RRMS • Total N = 878 patients in the dimethyl fumarate-interferon matched group • Total N = 776 patients in the dimethyl fumarate-teriflunomide matched group • Total N = 914 patients in the dimethyl fumarate-fingolimod matched group	• Dimethyl fumarate • Interferon • Teriflunomide • Fingolimod
Buron et al., 2019[102] National registry from Denmark	October 1, 2013 to May 6, 2018	• People with RRMS • Total N = 2,236	• Teriflunomide • Dimethyl fumarate
Degli Esposti et al., 2017[103] Retrospective cohort from administrative databases in Italy	July 2009 and October 2012	• Adults with MS treated with an injectable DMT (interferon beta or glatiramer acetate) • Total N = 1,698	• Interferon beta-1a • Interferon beta-1b • Glatiramer acetate
Duquette et al., 2019[104] Retrospective analysis of claims data in Canada	January 2013 to January 2017	• People with RRMS • Total N = 32,795	• Fingolimod • Dimethyl fumarate • Teriflunomide • BRACE (Betaseron, Rebif, Avonex, Copaxone, and Extavia)
Evans et al., 2012[124] Retrospective cohort from 4 sites in Canada	January 1, 1995 to December 31, 2008	• People with MS • Total N = 1,896	• Interferon beta-1a SC • Interferon beta-1b SC • Interferon beta-1b IM • Glatiramer acetate
Evans et al., 2016[105] Population-based health administrative databases in Canada	January 1996 to December 2011, March 2012, or March 2014 depending on the province	• People with MS • Total N = 4,830	• Interferon beta-1b • Interferon beta-1a SC • Interferon beta-1a IM • Glatiramer acetate

Citation Study Description and Location	Data Collection Date	Key Patient Characteristics	Therapies of Interest
Granqvist et al., 2019[106] Retrospective cohort from a national registry in Sweden	January 1 2014 to December 31, 2016	• People with RRMS • Total N = 2,093	• Interferons • Glatiramer acetate • Dimethyl fumarate • Fingolimod
Johnson et al., 2017[107] Retrospective analysis of administrative claims in the U.S.	April 2013 to June 2013	• Adults with MS who were newly prescribed a DMT • Total N = 1,498	• Fingolimod • Dimethyl fumarate • Teriflunomide
Kalincik et al., 2019[108] Analysis from an international cohort study (MSBase)	Not reported	• People with definite relapse-onset MS • Total N = 3,728	• Teriflunomide • Dimethyl fumarate • Fingolimod
Laplaud et al., 2019[109] Prospective registry from 34 sites in France	Data extracted on Dec 15, 2017	• Adults with RRMS, starting treatment with teriflunomide or dimethyl fumarate • Total N = 1,770	• Teriflunomide • Dimethyl fumarate
Laroni et al., 2017[110] Retrospective cohort from 20 sites in Italy, NCT03302442	2010 to 2016	• People with newly-diagnosed MS • Total N = 1,877	• Interferon beta • Glatiramer acetate • Fingolimod
Limmroth et al., 2007[125] Retrospective, controlled cohort study from 510 sites in Germany, Austria, and Switzerland	October 2002 to May 2003	• Adults with RRMS • Total N = 4,754	• Interferon beta-1a • Interferon beta-1b • Interferon beta-1a 22 µg • Interferon beta-1a 44 µg
Marangi et al, 2020[112] Cohort from 10 sites in Italy	Retrospective collection from January 2013 to March 2016 Prospective collection from April 2016 to August 2018	• People with MS • Total N = 3,025	• Interferon beta-1a • Interferon beta-1b • Glatiramer acetate • Dimethyl fumarate • Teriflunomide • Fingolimod
Meyniel et al., 2012[126] Analysis of an international cohort, from 44 sites, including sites in the U.S.	Data extracted on February 7, 2011	• People with a CIS and early RRMS • Total N = 2,314	• Interferon beta-1a IM • Interferon beta-1a SC • Interferon beta-1b • Glatiramer acetate
Milanese et al., 2003[127] Cohort from 65 centers in Italy	February 1996 to June 1999	• People with RRMS • Total N = 1,530	• Interferon beta-1b • Interferon beta-1a
Müller et al., 2019[113]	January 1, 2011 to December 31, 2015	• People with CIS or MS • Total N = 13,333	• Dimethyl fumarate • Fingolimod • Glatiramer acetate

Citation Study Description and Location	Data Collection Date	Key Patient Characteristics	Therapies of Interest
Retrospective cohort analysis of claims data in Germany			• Teriflunomide • Peginterferon beta-1a • Interferon beta-1b • Alemtuzumab
Munsell et al., 2016[114] Retrospective analysis of U.S.-based claims data	July 1, 2010 to June 10, 2014	• Adults with MS • Total N = 8,382	• Self-injectable DMT (interferon beta-1a, interferon beta-1b, glatiramer acetate) • Oral DMT (teriflunomide, fingolimod, dimethyl fumarate)
Reynolds et al., 2010[128] Retrospective analysis of a U.S.-based claims database	January 1, 1996 to June 30, 2005	• People with MS • Total N = 6,134	• Interferon beta-1a IM • Interferon beta-1b SC • Glatiramer acetate • Interferon beta-1a SC
Sacca et al., 2019[116] Retrospective cohort from 24 sites in Italy	January 2010 to June 2017	• People with newly-diagnosed RRMS • Total N = 2,954	• Interferon • Glatiramer acetate • Fingolimod • Dimethyl fumarate • Teriflunomide
Sorensen et al., 2006[129] Prospective, national registry in Denmark	1996 to 2003	• People starting therapy for RRMS • Total N = 2,393	• Interferon beta-1b • Interferon beta-1a • Glatiramer acetate
Trojano et al., 2005[130] Prospective cohort from a single center in Italy	January 1998 to February 2005	• People with MS • Total N = 1,173	• Interferon beta-1b • Interferon beta-1a • Interferon beta-1a 22 µg • Interferon beta-1a 44 µg
Viera et al, 2020[118] Retrospective analysis of U.S.-based claims data (including Medicare)	September 12, 2012 to September 30, 2015	• People with MS • Total N = 4,563	• Fingolimod • Teriflunomide
Vollmer et al., 2018[119,122] Retrospective cohort from 2 sites in the U.S.	Not reported	• People with MS • Total N = 1,272	• Fingolimod • Dimethyl fumarate
Warrender-Sparkes et al., 2016[120] International, prospective, multi-center cohort, including 1 site in the U.S.	December 2004 to January 2015	• People with CIS and early RRMS • Total N = 2,640	• Interferon beta-1a IM • Interferon beta-1a SC • Interferon beta-1b • Glatiramer acetate • Fingolimod

Abbreviations. µg: microgram; CIS: clinically isolated syndrome; DMT: disease modifying therapy; IM: intramuscular; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SC: subcutaneous.

Alemtuzumab

We did not identify any eligible cohort studies comparing discontinuation or treatment switches for alemtuzumab.

Cladribine

We did not identify any eligible cohort studies comparing discontinuation or treatment switches for cladribine.

Dimethyl Fumarate

Based on evidence from 9 cohort studies[101,102,106-109,112,116,119]:
- In 2 studies, discontinuations tended to be significantly lower with dimethyl fumarate than with interferons or glatiramer acetate,[106,112] but in 4 other studies, discontinuations were significantly higher than with fingolimod.[106-108,119,122]
- In 1 study, dimethyl fumarate was associated with higher rates of discontinuation because of adverse events than fingolimod (statistical significance not reported),[101] and in another study was associated with significantly more discontinuations for intolerance than with teriflunomide.[109] However, 1 study found no differences for discontinuations for inefficacy or intolerance with dimethyl fumarate compared with interferons, glatiramer acetate, and fingolimod.[106] In 1 study, compared with teriflunomide, dimethyl fumarate was associated with significantly fewer discontinuations because of disease breakthroughs and similar numbers of discontinuations because of intolerance (P value not reported).[102]
- The risk of switching treatment was significantly lower for inefficacy and intolerance with dimethyl fumarate compared with interferons in 1 study.[116]
- Time to discontinuation of index treatment was similar between dimethyl fumarate and interferon beta, glatiramer acetate, and teriflunomide in 1 study.[101] However, the time to discontinuation was significantly longer for fingolimod compared with dimethyl fumarate in another study.[101]

Diroximel Fumarate

We did not identify any eligible cohort studies comparing discontinuation or treatment switches for diroximel fumarate.

Fingolimod

Based on evidence from 10 cohort studies[101,104,106-108,110,116,118-120]:
- Discontinuations tended to be significantly lower with fingolimod compared with BRACE therapies (Betaseron [interferon beta-1b], Rebif [interferon beta-1a], Avonex [interferon beta-1a], Copaxone [glatiramer acetate], and Extavia [interferon beta-1b]) in 1 study,[104] dimethyl fumarate in 3 studies,[106,107,119] and injectable interferon beta-1a in 1 study.[120] Discontinuation rates were also significantly lower with fingolimod than teriflunomide in 2 studies,[107,108] but another study found no difference between fingolimod and teriflunomide.[104]
- In 1 study, fingolimod was associated with significantly lower rates of discontinuation because of adverse events than dimethyl fumarate.[116] Dimethyl fumarate was associated with higher rates of discontinuation because of adverse events than fingolimod in 1 study (P value not reported).[101]

- In 2 studies, fingolimod was associated with significantly lower rates of discontinuation or switches because of inefficacy than interferons.[101,116] However, 1 study found no differences for discontinuations for inefficacy or intolerance with dimethyl fumarate compared with interferons, glatiramer acetate, and fingolimod.[106]
- The time to discontinuation was significantly longer with fingolimod compared with dimethyl fumarate in 1 study.[101]
- In 1 study, the time to treatment failure was significantly longer with fingolimod compared with teriflunomide.[118]
- The risk of continuing glatiramer acetate without switching was no different in people with comorbidities than in people without comorbidities in 1 study.[110]

Glatiramer Acetate

Based on evidence from 11 cohort studies[101,103,105,110,112,113,116,124,126,128,129]:
- Discontinuations tended to be similar between glatiramer acetate and interferon beta-1b in 2 studies[105,113] and interferon beta-1a in another study.[105,113,126] However, 1 study found glatiramer acetate had the highest proportion of discontinuations compared with interferons (*P* value not reported).[129] In another study, persistence was higher with dimethyl fumarate than glatiramer acetate at time points up to 24 months, but after 24 months glatiramer acetate appeared to be associated with higher persistence (*P* value not reported).[112]
- Switches in treatment were significantly lower with glatiramer acetate than with intramuscular interferon beta-1a in 1 study,[128] and the rate of switching for adverse events was significantly lower with glatiramer acetate than with interferons in another study.[116]
- When comparing glatiramer acetate with individual interferons, subcutaneous interferon beta-1b had the highest rate of treatment switch, and intramuscular interferon beta-1a had the highest frequency of temporary discontinuation and permanent interruption compared with other interferons and glatiramer acetate in 1 study.[103] However, these differences were not statistically significant.[103]
- Time to discontinuation was similar with glatiramer acetate compared with dimethyl fumarate in 1 study[101] and with interferon beta-1b in another study.[124]
- The risk of continuing glatiramer acetate without switching was no different in people with comorbidities than in people without comorbidities in 1 study.[110]

Interferon Beta

Based on evidence from 14 cohort studies[101,103,105,110,113,116,124-130]:
- In 2 studies, discontinuations were similar for interferon beta-1b and subcutaneous interferon beta-1a, intramuscular interferon beta-1a, and glatiramer acetate.[105,113] However, 1 study found that intramuscular interferon beta-1a and subcutaneous interferon beta-1a had significantly higher rates of discontinuation than glatiramer acetate in 1 study.[126]
- When comparing individual interferons, subcutaneous interferon beta-1b had the highest rate of treatment switch, and intramuscular interferon beta-1a had the highest frequency of temporary discontinuation and permanent interruption, compared with other interferons and glatiramer acetate in 1 study.[103] However, these differences were not statistically significant.[103] Interruptions in treatment were significantly higher with interferon beta-1b than with interferon beta-1a, and the incidence of adverse events was higher in patients treated with interferon beta-1b in another study (*P* value not reported).[127] In 1 study,

stopping treatment was also significantly more likely with subcutaneous interferon beta-1b vs. intramuscular interferon beta-1b.[128] In another study, interferon beta-1b was associated with significantly more withdrawals compared with intramuscular interferon beta-1a and subcutaneous interferon beta-1a.[130]

- Rates of switching for inefficacy or intolerance were significantly higher with interferons than with fingolimod, dimethyl fumarate, and glatiramer acetate in 1 study.[116] Another study found that rates of switching were significantly higher with intramuscular interferon beta-1b compared with glatiramer acetate.[128] In 1 study, subcutaneous interferon beta-1a had the highest proportion of treatment switch compared with other interferons and glatiramer acetate, but no *P* value was reported.[129]
- Discontinuations because of inefficacy were significantly higher with subcutaneous interferon beta-1a than with intramuscular interferon beta-1a in 1 study. [125]
- Discontinuations because of flu-like symptoms were significantly higher with interferon beta-1b than with subcutaneous interferon beta-1a in 1 study.[125] Discontinuations because of injection-site reactions were also lower for intramuscular interferon beta-1a compared with interferon beta-1b or subcutaneous interferon beta-1a.[125]
- The time to discontinuation was similar with interferon beta compared with dimethyl fumarate in 1 study [101] and with interferon beta-1b in 1 study.[124] Interferon beta-1b, as index therapy, had a significantly longer time to discontinuation than subcutaneous interferon beta-1a in another study.[124]
- The risk of continuing interferon beta without switching was significantly higher in people with comorbidities than in people without comorbidities in 1 study.[110]

Ocrelizumab
We did not identify any eligible cohort studies comparing discontinuation or treatment switches for ocrelizumab.

Ozanimod
We did not identify any eligible cohort studies comparing discontinuation or treatment switches for ozanimod.

Peginterferon Beta-1a
We did not identify any eligible cohort studies comparing discontinuation or treatment switches for peginterferon beta-1a.

Siponimod
We did not identify any eligible cohort studies comparing discontinuation or treatment switches for siponimod.

Teriflunomide
Based on evidence from 6 cohort studies[101,102,104,112,116,118]:
- Discontinuations were similar for teriflunomide and fingolimod in 1 study.[104]
- Compared with dimethyl fumarate, teriflunomide was associated with significantly more discontinuations because of disease breakthroughs, and similar numbers of discontinuations because of intolerance in 1 study (*P* value not reported).[102] In another study, teriflunomide had the highest numbers of discontinuations compared with other disease-modifying

therapies (*P* value not reported).[112] Teriflunomide also had significantly lower rates of discontinuations for inefficacy, but not for tolerance, than interferon in 1 study.[116]Time to discontinuation was similar with teriflunomide compared with dimethyl fumarate in 1 study,[101] with a lack of efficacy cited more commonly as a reason in the teriflunomide population.[101]

- The time to treatment failure was significantly shorter with teriflunomide compared with fingolimod in 1 study.[118]

Injectable Therapies

We identified 2 cohort studies comparing injectable and oral therapies[114,120]:

- In 1 study, treatment switches from self-injectable therapies were significantly higher than switches from oral therapies.[114] There were no differences between self-injectable therapies than from oral therapies for discontinuations and time to discontinuation.[114]
- In 1 study, following the availability of fingolimod, patients were more likely to discontinue injectable treatments.[120] Patients who switched to fingolimod were more likely to do so for convenience.[120] Persistence was significantly improved on fingolimod compared to other medications.[120]

Serious Adverse Events

We identified 6 eligible cohort studies comparing serious adverse events, including infection and cancer, by disease-modifying therapy (Table 60).[100,111,115,117,121,123]

Table 60. Study Characteristics and Findings from Eligible Nonrandomized Studies

Citation Study Description and Location	Data Collection Date	Key Patient Characteristics	Therapies of Interest
Serious Adverse Events - Nonspecific			
Simbrich et al., 2019[117] Analysis of a national claims database in Germany	January 1, 2006 to December 31, 2013	• People with MS • Total N = 15,377	• Interferon beta-1a • Glatiramer acetate • Fingolimod
Specific Adverse Events - Liver Injury			
Antonazzo et al., 2019[100] Analysis of the FDA Adverse Event Reporting System	Over a 13-year period	• Cases/non-cases of liver injury • Total cases N = 8,862,213	• Dimethyl fumarate • Fingolimod • Interferon beta-1a • Interferon beta-1b • Peginterferon beta-1a • Teriflunomide • Alemtuzumab
Specific Adverse Events - Drug-associated Progressive Multifocal Leukoencephalopathy			
Oshima et al., 2019[115] Analysis of the FDA Adverse Event Reporting System	July 1, 2015 to June 31, 2017	• People with MS • Total N = 78,281	• Fingolimod • Dimethyl fumarate • Glatiramer acetate • Interferon beta
Specific Adverse Events - Infection Risk			
Luna et al., 2019[111] National, prospective registry in Sweden	January 2011 to December 2017	• People with RRMS • Total N = 6,421	• Interferon beta and glatiramer acetate • Fingolimod

Citation Study Description and Location	Data Collection Date	Key Patient Characteristics	Therapies of Interest
Wijnands et al., 2017[121] Retrospective analysis of prospective population-based administrative data in Canada	April 1996 to December 2013	• People with MS • Total N = 6,793	• Interferon beta • Glatiramer acetate • Oral DMT (fingolimod or dimethyl fumarate)
Specific Adverse Events - Cancer			
Achiron et al., 2006[123] Analysis of linked data from a national cancer registry and MS records in Israel	1960 to December 31, 2003	• People with MS • Total N = 1,338	• Glatiramer acetate • Interferon beta

Abbreviations. DMT: disease modifying therapy; FDA: U.S. Food and Drug Administration; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis.

Non-specific Serious Adverse Events

We identified 1 cohort study comparing the risk of serious adverse events by treatment, and overall, there was no significant differences between interferon beta-1a, glatiramer acetate, and fingolimod.[117]

Liver Injury

We identified 1 cohort study evaluating liver injury which found that the risk of liver injury was increased with MS therapies, including interferons and newer therapies, specifically alemtuzumab, teriflunomide, and fingolimod.[100]

Drug-associated Progressive Multifocal Leukoencephalopathy

We identified 1 cohort study evaluating the risk of progressive multifocal leukoencephalopathy.[115] The analysis found that fingolimod and dimethyl fumarate were associated with an increased risk of progressive multifocal leukoencephalopathy.[115]

Infection Risk

We identified 2 cohort studies evaluating infection risk[111,121]:
- In 1 study, the rate of infections was lowest with interferon beta and glatiramer acetate.[111] Fingolimod was associated with a higher crude rate of infection but when confounders were adjusted for, the increase was no longer significant.[111] Similarly, in another study, compared to no disease-modifying therapy, exposure to any first-generation disease-modifying therapy (beta interferon or glatiramer acetate) or by each drug class individually was not associated with infection-related physician claims.[121]
- Compared to no disease-modifying therapy, exposure to any second-generation disease-modifying therapy (fingolimod, dimethyl fumarate or natalizumab) was associated with a significantly increased risk of an infection-related physician claim.[121] When assessed individually, the association was not significant for fingolimod and dimethyl fumarate.[121]

Cancer

We identified 1 cohort study evaluating the risk of cancer, which found that women with MS treated with glatiramer acetate had an increased risk of breast cancer, though the increase was not statistically significant.[123] All individuals with MS who were treated with interferon beta

showed an increased risk of non-breast cancers, though the increase was not statistically significant, although the effect was large.[123]

Ongoing Studies

We identified 2 ongoing RCTs and 5 ongoing cohort studies focusing on harms. The RCTs both include adults with RRMS and are due to complete in 2020 (Table 61). Of particular interest is the RCT comparing peginterferon beta-1a with interferon beta-1a or 1b, as this is a comparison for which we did not identify any eligible RCTs. The cohort studies range in sample size from 1,125 to 200,000 and the majority of studies are due to complete before the end of 2020.

Table 61. Ongoing Trials of Disease-modifying Drugs

NCT Number Trial Name	Population	Intervention(s)	Eligible Outcomes	Enrollment	Primary Completion Date
Randomized Controlled Trials					
NCT02744222[180] Not reported	Adults with RRMS	• Interferon beta-1a • Peginterferon biosimilar	• Relapse • MRI outcomes • Disability progression • Functional capacity • Adverse events	399 (actual)	January 2020 (estimated)
NCT03177083[181] PLENO	Adults with RRMS	• Peginterferon beta-1a • Interferon beta-1a or beta-1b	• Adverse events • Quality of life • Work productivity and activity impairment • Disability • Fatigue • Relapses	80 (actual)	September 2020 (estimated)
Observational Studies					
NCT03302442[182] COMP-RMS	Adults and children with RRMS	• Dimethyl fumarate • Teriflunomide	• Adverse events	3,000 (actual)	August 2017 (actual)
NCT02749396[183] EPID MS Pregnancy Study	Pregnant women with MS	• Interferon beta-1a • Interferon beta-1b • Peginterferon beta-1a	• Pregnancy outcomes • Live births	2,089 (actual)	August, 2018 (actual)
NCT04237337[184] PVSEPK	Adults and children with MS	• MS drugs (not specified)	• Cancer	200,000 (estimated)	February 2020 (estimated)
NCT01442194[185] PASSAGE	Adults and children with relapsing MS	• Fingolimod • Other disease-modifying therapy	• Adverse events	3,620 (estimated)	March 2020 (estimated)

NCT Number Trial Name	Population	Intervention(s)	Eligible Outcomes	Enrollment	Primary Completion Date
NCT01911767[186] Biogen MS Pregnancy Exposure Registry	Pregnant women with MS	• Dimethyl fumarate • Peginterferon beta-1a	• Pregnancy loss • Live births	1,125 (estimated)	May, 2028 (estimated)

Abbreviations. MS: multiple sclerosis; MRI: magnetic resonance imaging; NCT: U.S. National Clinical Trial number; RRMS: relapsing-remitting multiple sclerosis.

Discussion

Overall, this update includes 42 RCTs and 30 observational studies. Evidence from the RCTs comprises:

- 11 head-to-head comparisons in MS evaluated in 23 RCTs
  - 12 RCTs were assessed as being of fair methodological quality and 11 RCTs as being of poor methodological quality
- 4 comparisons of different dosing schedules in MS evaluated in 9 RCTs
  - 2 RCTs were assessed as being of fair methodological quality and 7 RCTs as being of poor methodological quality
- 5 placebo-controlled comparisons in MS evaluated in 5 RCTs
  - 3 RCTs were assessed as being of fair methodological quality and 2 RCTs as being of poor methodological quality
  - No RCTs met our eligibility criteria for diroximel fumarate
- 1 comparison of different dosing schedules in CIS evaluated in 1 fair-methodological-quality RCT
- 5 placebo-controlled comparisons in CIS evaluated in 8 RCTs
  - 6 RCTs were assessed as being of fair methodological quality and 2 RCTs as being of poor methodological quality

When comparing the disease-modifying therapies directly, alemtuzumab, fingolimod, ocrelizumab, and teriflunomide significantly reduce relapses and are not associated with increased serious adverse events, compared with other disease-modifying therapies assessed in the eligible trials. However, we did not identify head-to-head trials for every possible comparison of the relevant interventions, so we are not able to state conclusively that other therapies are not any more or less effective overall. In this situation, network meta-analyses (NMAs) can be useful models to rank treatments where direct evidence is not available for all interventions of interest.

In 2017, the Institute for Clinical and Economic Review (ICER)[41] conducted a NMA comparing disease-modifying therapies for RRMS and PPMS. The analysis included 33 RCTs, representing 21,768 patients with RRMS and 1,171 patients with PPMS, with 16 comparators including placebo.[41] Newer drugs (cladribine, siponimod, and diroximel) were not included in this analysis.[41] ICER concluded that:

- All active treatments were more effective than placebo in lowering the risk of relapse.[41] Alemtuzumab, natalizumab, and ocrelizumab had the greatest reduction in ARR compared with placebo.[41] Fingolimod, daclizumab, rituximab, and dimethyl fumarate were the next

most effective, with interferon beta, glatiramer acetate 20 mg, and teriflunomide being least effective.[41] However, there was no clear evidence that any active treatment was more effective than another active comparator.[41]

- Ocrelizumab and alemtuzumab had the greatest reduction in disability progression compared with placebo.[41] Interferon beta-1a 30 μg, interferon beta-1a 22 μg, teriflunomide 7 mg, and glatiramer acetate 40 mg did reduce disability progression when compared with placebo.[41] Again, there was no clear evidence that any active treatment was more effective than another active comparator.[41]

In 2018, 2 NMAs were published which included cladribine, but not siponimod or diroximel fumarate.[46,54] In general, the 2 analyses had similar results, with infusion therapies (alemtuzumab and ocrelizumab) remaining the most effective, and cladribine and other oral disease-modifying therapies (fingolimod and dimethyl fumarate) having an intermediate level of effectiveness.[46,54]

We note some of the limitations of NMAs, including that not all available treatments can be compared because of limited studies within the network. Further, important assumptions about the included studies must be met for results from an NMA to be valid, including similar study and intervention characteristics among studies within the network and consistency between direct and indirect evidence. In addition, we did not undertake a formal quality assessment of the NMAs, but simply report the main results for information.

The newer drugs with FDA approval, cladribine and siponimod, are significantly more effective than placebo for MS, although cladribine is highlighted as having some safety concerns with a black box warning related to malignancies and teratogenicity.[10] However, ozanimod at 0.5 mg and 1 mg doses (currently not approved by the FDA) do not appear to be an effective treatment for MS.

The presence of neutralizing antibodies does not appear to be associated with a reduction in the effectiveness of treatment. Patient factors, such as age and prior treatment, may change the effectiveness of treatment, but subgroup analyses are not reported consistently across studies, limiting our ability to draw robust conclusions.

For CIS, each of the active therapies reviewed (cladribine, glatiramer acetate, interferon beta-1b, interferon beta-1b, and teriflunomide) significantly reduced conversion to MS compared with placebo and did not appear to be associated with more serious adverse events. A recent NMA found similar results. Armoiry et al.[26] evaluated the short- and long-term clinical effectiveness of interferon beta and glatiramer acetate in people with CIS.[26] The analysis included 5 RCTs, representing 1,845 participants.[26]

- Overall, interferon beta (interferon beta-1a 44 μg 3 times a week, interferon beta-1b 250 μg every other day, interferon beta-1a 30 μg once a week, and glatiramer acetate 20 mg daily) was associated with a longer time to progression than placebo, and there was no evidence suggesting superiority of any one active drug over another.[26]
- Rankings from the NMA suggested that subcutaneous interferon beta-1a 44 μg 3 times a week was ranked highest, followed by subcutaneous interferon beta-1b 250 μg every other day, intramuscular interferon beta-1a 30 μg once a week, and subcutaneous glatiramer acetate 20 mg daily, with placebo being ranked as the least effective.[26]

As with therapies for MS, subgroup analyses are not reported consistently across studies, but there is some evidence that women may benefit more than men from glatiramer acetate and interferon beta-1a for CIS.

We did not identify any eligible RCTs comparing diroximel fumarate with placebo. The FDA approval in 2019 was based on bioavailability studies comparing oral dimethyl fumarate delayed-release capsules to diroximel fumarate delayed-release capsules, and 2 placebo-controlled trials of dimethyl fumarate.[24] We found 1 ongoing study and 1 published RCT evaluating the efficacy and safety of diroximel fumarate since FDA approval; however, neither study met our inclusion criteria for this report.

Disease-modifying therapies do have adverse events and they differ in their safety profile. From the cohort studies, treatment discontinuations or switches appear to be significantly lower with fingolimod and dimethyl fumarate. The route of administration (oral or injectable) is also likely to affect patient adherence, and therefore clinical outcomes. However, the evidence is not consistent in which therapies are compared, limiting our ability to draw conclusions. Overall, the risk of specific adverse events is higher with some disease-modifying therapies:

- The risk of liver injury was higher for alemtuzumab, teriflunomide, and fingolimod
- The risk of progressive multifocal leukoencephalopathy was higher with fingolimod and dimethyl fumarate
- The risk of infection was lower with interferon beta and glatiramer acetate

Disease-modifying therapies do not appear to be associated with an increased risk of cancer. However, the evidence is from only 1 retrospective study in a specific population, and may not be generalizable to the U.S. Medicaid population. Different dosing schedules are unlikely to show benefit in effectiveness and safety, based on the evidence reviewed in this report. In summary, the choice of disease-modifying therapy might depend on the values and preferences of the patient and the prescriber.

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Appendix A. Clinical Evidence Methods

Search Strategy

We searched Drug Effectiveness Review Project (DERP) clinical evidence sources to identify systematic reviews (with and without meta-analyses), technology assessments, randomized controlled trials (RCTs), and cohort studies using the terms *multiple sclerosis*, *clinically isolated syndrome*, and *first demyelinating event* in combination with generic and brand names of the relevant drugs. Systematic reviews and technology assessments were only used for reference list searching. We limited searches of evidence sources to citations published after January 1, 2016 (the search date in the previous update report).

We searched the following DERP evidence sources:
- Agency for Healthcare Research and Quality (AHRQ)
  - Evidence-based Practice Centers (EPC) Reports
  - Effective Health Care (EHC) Program
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- National Institute for Health and Care Excellence (NICE) Evidence
- Ovid MEDLINE
- Veterans Administration Evidence-based Synthesis Program (ESP)

We used Google and Google Scholar to conduct targeted gray literature searches using the following search terms *multiple sclerosis* and *clinically isolated syndrome* in combination with generic and brand names of the relevant drugs.

Ovid MEDLINE Search Strategy

1	Multiple sclerosis.mp. or Multiple Sclerosis/
2	clinically isolated syndrome.mp.
3	first demyelinating event.mp.
4	or/1-3
5	cladribine/
6	mavenclad.mp.
7	siponimod.mp.
8	mayzent.mp.
9	ocrelizumab.mp.
10	Ocrevus.mp.
11	glatiramer.mp.
12	glatiramer acetate.mp.
13	copaxone.mp.
14	interferon-alpha/

15   interferon-beta/

16   avonex.mp.

17   interferon-beta-1a/

18   interferon-beta-1b/

19   Betaseron.mp.

20   betaferon.mp.

21   extavia.mp.7

22   peginterferon beta.mp.

23   plegridy.mp.

24   Dimethyl Fumarate.mp.

25   BG-12.mp.

26   BAF-312.mp.

27   tecfidera.mp.

28   teriflunomide.mp.

29   aubagio.mp.

30   fingolimod.mp.

31   Fingolimod Hydrochloride/

32   gilenya.mp.

33   ALKS8700.mp.

34   Diroximel fumarate.mp.

35   interferon beta.mp.

36   Rebif.mp.

37   alemtuzumab.mp.

38   alemtuzumab/

39   lemtrada.mp.

40   vumerity.mp.

41   copaxone.mp.

42   glatopa.mp.

43   glatiramer acetate.mp.

44   teva-glatiramer acetate.mp.

45   glatect.mp.

46   ozanimod.mp.

47   BIIB098.mp.

48   rpc1063.mp.

49   laquinimod.mp.

50   ublituximab.mp.

51   ponesimod.mp.

52   cladribine.mp.

53   or/5-52

54   4 and 53

55   limit 54 to english language

Cochrane Library Search Strategy

#1   MeSH descriptor: [Multiple Sclerosis] explode all trees

#2   Multiple Sclerosis

#3   clinically isolated syndrome

#4   first demyelinating event

#5   MeSH descriptor: [Cladribine] explode all trees

#6   mavenclad

#7   siponimod

#8   mayzent

#9   ocrelizumab

#10   Ocrevus

#11   MeSH descriptor: [Glatiramer Acetate] explode all trees

#12   glatiramer

#13   copaxone

#14   avonex

#15   Betaseron

#16   MeSH descriptor: [Interferon beta-1b] explode all trees

#17   MeSH descriptor: [Interferon beta-1a] explode all trees

#18   betaferon

#19   extavia

#20   peginterferon beta

#21   plegridy

#22   MeSH descriptor: [Dimethyl Fumarate] explode all trees

#23	BG-128
#24	MeSH descriptor: [Interferon-beta] explode all trees
#25	Rebif
#26	MeSH descriptor: [Alemtuzumab] explode all trees
#27	lemtrada
#28	vumerity
#29	copaxone
#30	glatopa
#31	teva-glatiramer acetate
#32	glatect
#33	ozanimod
#34	BIIB098
#35	rpc1063
#36	laquinimod
#37	ublituximab
#38	ponesimod
#39	MeSH descriptor: [Interferon-alpha] explode all trees
#40	interferon-alpha
#41	glatiramer acetate
#42	interferon-beta
#43	alemtuzumab
#44	dimethyl fumarate
#45	cladribine
#46	interferon beta-1a
#47	interferon beta-1b
#48	#1 OR #2 OR #3 OR #4
#49	#48 AND #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #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 #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
#50	#49 with Cochrane Library publication date Between Jan 2016 and Dec 2019, in Cochrane Reviews, Trials

Ongoing Studies

We searched the following DERP sources for ongoing studies using the search terms *multiple sclerosis*, *clinically isolated syndrome*, and *first demyelinating event* in combination with generic names of the relevant drugs:

- ClinicalTrials.gov
- ISRCTN Registry
- U.S. Food and Drug Administration

Inclusion Criteria

Population

- Adult outpatients (age ≥ 18 years) with multiple sclerosis
  - Relapsing-remitting multiple sclerosis
  - Secondary progressive multiple sclerosis
  - Primary progressive multiple sclerosis
  - Progressive relapsing MS
- Adult outpatients with a clinically isolated syndrome (also known as "first demyelinating event," first clinical attack suggestive of multiple sclerosis, or monosymptomatic presentation)

Interventions

Table A1. Included Interventions by Date of FDA Approval

Generic Name	Brand Name	Dose, Route of Administration, and Frequency	FDA Approval Date
FDA-approved Drugs			
Diroximel fumarate	**Vumerity**	**462 mg orally twice daily (maintenance)**	**10/30/2019**
Cladribine	**Mavenclad**	**Cumulative dose of 3.5 mg/kg, orally in 2 treatment courses**	**3/29/2019**
Siponimod	**Mayzent**	**2 mg orally once daily (maintenance)** **1 mg orally once daily (maintenance) for patients with a CYP2C9*1/*3 or *2/*3 genotype**	**3/27/2019**
Ocrelizumab	Ocrevus	600 mg intravenous infusion every 6 months (maintenance)	3/28/2017
Glatiramer acetate	Glatopa (branded generic)	20 mg subcutaneously daily 40 mg subcutaneously 3 times a week	4/16/2015
Peginterferon beta-1a	Plegridy	125 µg subcutaneously every 14 days	8/15/2014
Dimethyl fumarate	Tecfidera	240 mg orally twice daily (maintenance)	3/27/2013
Teriflunomide	Aubagio	7 mg or 14 mg orally once daily	9/12/2012
Fingolimod	Gilenya	0.5 mg orally once daily	9/21/2010
Interferon beta-1a	Rebif	22 µg or 44 µg subcutaneously 3 times a week	3/7/2002
Alemtuzumab	Lemtrada	12 mg/day by intravenous infusion for 5 days, then 12 mg/day for 3 consecutive days, 12 months after the first treatment course	5/7/2001

Generic Name	Brand Name	Dose, Route of Administration, and Frequency	FDA Approval Date
Glatiramer acetate	Copaxone	20 mg subcutaneously daily 40 mg subcutaneously 3 times a week	12/20/1996
Interferon beta-1a	Avonex	30 µg intramuscularly once a week	5/17/1996
Interferon beta-1b	Betaseron Extavia	250 µg subcutaneously every other day	7/23/1993
Pipeline Drugs			
Ozanimod (RPC1063)	N/A	Oral	N/A

Note. Bold text indicates newly approved drugs for multiple sclerosis. Abbreviations. µg: microgram; FDA: U.S. Food and Drug Administration; kg: kilogram; mg: milligram; N/A: not applicable.

Comparators

- Another listed intervention (head-to-head comparison)
- Placebo (interventions that lack head-to-head comparisons and for pipeline drugs)

Outcomes

- Health outcomes
  - Disability
  - Clinical exacerbation/relapse
  - Quality of life (QoL)
  - Functional outcomes (e.g., wheelchair use, time lost from work)
  - Persistence (discontinuation rates)
  - Clinically isolated syndrome: progression to multiple sclerosis diagnosis
- Harms
  - Overall adverse events
  - Serious adverse events
  - Withdrawals due to adverse events
  - Specific adverse events (e.g., hepatotoxicity)

Study Designs

- Randomized controlled trials
  - ≥ 12 weeks study duration
- Placebo-controlled trials
  - For interventions that do not have head-to-head studies and pipeline drugs
  - ≥ 12 weeks study duration
- Retrospective and prospective cohort studies comparing an intervention type to another for outcomes on harms
  - ≥ 12 weeks study duration
  - Minimum total sample size of 1,000

Exclusion Criteria

We excluded studies if they were not published in English.

Screening

Two experienced researchers independently screened all titles and abstracts of identified documents. In cases in which there was disagreement about eligibility, a third experienced researcher resolved the disagreement. This method was repeated for full-text review of documents that could not be excluded by title and abstract screening.

Data Abstraction

One experienced researcher abstracted and entered data from eligible studies in a standardized way using Microsoft Word. A second experienced researcher reviewed all the data entered. We attempted to resolve discrepancies through discussion. When discussion did not resolve the issue, a third experienced researcher settled disagreements.

Quality Assessment

Methodological Quality of Included Studies

We assessed the methodological quality of the included RCTs and cohort studies using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[17-21] Two experienced researchers independently rated all included studies. In cases in which there was disagreement about the methodological quality of a study, a third rater resolved the disagreement.

Randomized Controlled Trials

Good-quality randomized controlled trials include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good-quality randomized controlled trials also have low potential for bias from conflicts of interest and funding source(s). Fair-quality randomized controlled trials have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. Poor-quality randomized controlled trials have clear flaws that could introduce significant bias.

Cohort Studies

Good-quality cohort studies include a sample that is representative of the source population, have low loss to follow-up, and measure and consider relevant confounding factors. Good-quality cohort studies also list their funding source(s) and have a low potential of bias from conflicts of interest. Fair-quality cohort studies might not have measured all relevant confounding factors or adjusted for them in statistical analyses, have loss to follow-up that could bias findings, consist of a sample that is not representative of the source population, or have potential conflicts of interest that are not addressed. Poor-quality cohort studies have a clear, high risk of bias that would affect findings.

Quality of Evidence Assessment

Overall Quality of Evidence

We assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[22,23] Two independent experienced researchers assigned

ratings, with disagreements resolved by a third rater. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are randomized controlled trials with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are randomized controlled trials with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are randomized controlled trials with serious limitations or nonrandomized studies without special strengths.
- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables

See attachment for the full evidence tables (pages B1-B212).

Appendix C. Bibliography of Included Studies

Randomized Controlled Trials

- Cadavid D, Wolansky LJ, Skurnick J, et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology.* 2009;72(23):1976-1983. doi: 10.1212/01.wnl.0000345970.73354.17.
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Sister Publications of Included Randomized Controlled Trials

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Appendix D. Excluded Studies With Reason for Exclusion

Reference	Reason for Exclusion
(2016). Fulminant Central Nervous System Nocardiosis in a Patient Treated With Alemtuzumab For Relapsing-Remitting Multiple Sclerosis JAMA Neurology	Not relevant publication type
(2016). How do immunomodulators and immunosuppressants compare in people with relapsing-remitting multiple sclerosis?	Not relevant publication type
(2016). In adults with multiple sclerosis, how does alemtuzumab compare with other drug therapies?	Not relevant publication type
(2016). In people with relapsing-remitting multiple sclerosis, what are the benefits and harms of dimethyl	Not relevant publication type
(2016). Peginterferon beta-1a in the management of relapsingremitting multiple sclerosis in Italy: elements of health technology assessment Global and regional health technology assessment, 3(1), 52-	Not relevant publication type
(2016). Persistence and adherence in multiple sclerosis patients starting glatiramer acetate treatment: assessment of relationship with care received from multiple disciplines Patient Preference and Adherence,	Not sample size of interest (< 1,000 for NRS)
(2016). Rebound Syndrome in Patients With Multiple Sclerosis After Cessation of Fingolimod Treatment JAMA Neurology	Not sample size of interest (< 1,000 for NRS)
(2016). Safety and efficacy of amiselimod in relapsing multiple sclerosis (MOMENTUM): a randomised, double-blind, placebo-controlled phase 2 trial The Lancet Neurology,	Not intervention of interest
(2016). Therapeutic protein–drug interaction assessment for daclizumab high-yield process in patients with multiple sclerosis using a cocktail approach British Journal of Clinical Pharmacology	Not intervention of interest
(2017). ACCLAIM: a randomized trial of abatacept (CTLA4-Ig) for relapsing-remitting multiple sclerosis Multiple sclerosis (houndmills, basingstoke, england),	Not intervention of interest
(2017). Adjusting for treatment switching in the relapsing-remitting multiple sclerosis clarity trial and the clarity extension study Value in health, Conference: ISPOR 20th Annual European Congress. United Kingdom. 20(9), A718	Not relevant publication type
(2017). Baseline EDSS proportions in MS clinical trials affect the overall outcome and power: a cautionary note Multiple sclerosis (houndmills, basingstoke, england),	Not relevant publication type
(2017). Early MRI results and odds of attaining 'no evidence of disease activity' status in MS patients treated with interferon beta-1a in the EVIDENCE study Journal of the neurological sciences, 379(pp 151-156)	Not a sister publication of interest
(2017). Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial The Lancet	Not intervention of interest
(2017). Effect of ocrelizumab on upper limb function in patients with primary progressive multiple sclerosis in the ORATORIO study Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 658-659	Not relevant publication type
(2017). Efficacy and safety of 2 doses of ponesimod (10 and 20 mg o.d.): interim analysis of a phase II extension trial in relapsing-remitting multiple sclerosis Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 606-607	Not relevant publication type

Reference	Reason for Exclusion
(2017). Efficacy and safety of a three-times-weekly dosing regimen of glatiramer acetate in relapsing-remitting multiple sclerosis patients: 3-year results of the Glatiramer Acetate Low-Frequency Administration open-label extension study Multiple sclerosis (houndmills, basingstoke, england),	Not a sister publication of interest
(2017). Efficacy of daclizumab beta vs intramuscular interferon beta-1a on patient-reported outcomes across patient demographic and disease activity subgroups in DECIDE Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 966-967	Not relevant publication type
(2017). How does early initiation compare with late initiation of disease-modifying drugs after a first clinical attack suggestive of multiple sclerosis?	Not intervention of interest
(2017). How does interferon-beta compare with glatiramer acetate in people with relapsing-remitting multiple sclerosis?	Not relevant publication type
(2017). Impact of adherence on subcutaneous interferon beta-1a effectiveness administered by Rebismart(R) in patients with multiple sclerosis Patient Preference And Adherence,	Not sample size of interest (< 1,000 for NRS)
(2017). Infusion-related reactions with ocrelizumab in phase III studies Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 878-879	Not relevant publication type
(2017). Longitudinal changes in lymphocyte subsets of siponimodtreated patients with SPMS Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 660	Not relevant publication type
(2017). Management of flu-like syndrome with cetirizine in patients with relapsing-remitting multiple sclerosis during therapy with interferon beta: results of a randomized, cross-over, placebo-controlled pilot study Plos one,	Not intervention of interest
(2017). No evidence of disease activity in patients receiving daclizumab versus intramuscular interferon beta-1a for relapsing-remitting multiple sclerosis in the DECIDE study Multiple sclerosis (houndmills, basingstoke, england)	Not intervention of interest
(2017). Ocrelizumab reduces disability progression independent of relapse activity in patients with relapsing multiple sclerosis Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 309-310	Not relevant publication type
(2017). Ozanimod demonstrates efficacy and safety in a phase 3 trial of relapsing multiple sclerosis (SUNBEAM) Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 73-74	Not relevant publication type
(2017). Persistence to disease-modifying therapies for multiple sclerosis in a Canadian cohort Patient Preference And Adherence	Not sample size of interest (< 1,000 for NRS)
(2017). Persistence with dimethyl fumarate in relapsing-remitting multiple sclerosis: a population-based cohort study European Journal Of Clinical Pharmacology	Not sample size of interest (< 1,000 for NRS)
(2017). Placebo controlled, phase 2a multicenter study of ublituximab (UTX), a novel glycoengineered anti-CD20 monoclonal antibody (mAb), in patients with relapsing forms of multiple sclerosis (RMS): 6 months analysis of B cell subsets Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 609-610	Not relevant publication type

Reference	Reason for Exclusion
(2017). Preliminary results of phase 2 multicenter study of ublituximab (UTX), a novel glycoengineered anti-CD20 monoclonal antibody (mAb), in patients with relapsing forms of multiple sclerosis (RMS) demonstrates rapid Gd-enhancing lesions decrease Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 410-411	Not relevant publication type
(2017). Reduced brain atrophy rates are associated with lower risk of disability progression in patients with relapsing multiple sclerosis treated with cladribine tablets Multiple sclerosis journal	Not a sister publication of interest
(2017). Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies The Lancet Diabetes & Endocrinology	Not intervention of interest
(2017). Selective and discontinuous reduction of B and T lymphocytes by cladribine tablets in patients with early and relapsing multiple sclerosis (ORACLE-MS, CLARITY and CLARITY Extension) Multiple sclerosis (houndmills, basingstoke, england), Conference: MS Research Australia Progress in MS Research 2017. Australia. 23(13), NP11	Not relevant publication type
(2017). Subgroup analyses of annualised relapse rates in patients with relapsing multiple sclerosis who received ocrelizumab or interferon beta-1a in the Phase III OPERA i and OPERA II studies Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 332-333	Not relevant publication type
(2017). Sustained efficacy of daclizumab beta over up to 6 years of treatment and improvements in efficacy outcomes in relapsing MS patients who switched from intramuscular interferon beta-1a to daclizumab beta: interim results from EXTEND Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 361	Not relevant publication type
(2017). Switching from branded to generic glatiramer acetate: 15-month GATE trial extension results Multiple sclerosis journal	Not comparator of interest
(2017). Temporal variability profile of serum neurofilament light levels in multiple sclerosis patients Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 24-25	Not relevant publication type
(2017). Variability in adverse event reporting and reasons for discontinuations with dimethyl fumarate: results from a generalized linear mixed model Multiple sclerosis journal, Conference: 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France. 23(3 Supplement 1), 408	Not relevant publication type
(2017). What are the effects of disease-modifying drugs in people with a first clinical attack suggestive of multiple sclerosis?	Not relevant publication type
(2018). Adherence to disease-modifying therapies in patients with multiple sclerosis Patient Preference And Adherence	Not sample size of interest (< 1,000 for NRS)
(2018). Adherence to subcutaneous interferon beta-1a treatment using an electronic injection device: a prospective open-label Scandinavian noninterventional study (the ScanSmart study) Patient Preference And Adherence	Not sample size of interest (< 1,000 for NRS)
(2018). Association of Progressive Multifocal Leukoencephalopathy Lesion Volume With JC Virus Polymerase Chain Reaction Results in Cerebrospinal Fluid of Natalizumab-Treated Patients With Multiple Sclerosis JAMA Neurology	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
(2018). Clinical Efficacy Is Sustained in Relapsing Remitting Multiple Sclerosis Following Treatment Switch to Placebo from Cladribine Tablets in Patients with High Disease Activity at Baseline Multiple sclerosis and related disorders, 26, 260-	Not relevant publication type
(2018). Effect of interferon beta-1a subcutaneously three times weekly on clinical and radiological measures and no evidence of disease activity status in patients with relapsing-remitting multiple sclerosis at year 1 BMC neurology,	Not a sister publication of interest
(2018). Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension The Lancet Neurology	Not intervention of interest
(2018). Effect of ocrelizumab on severe progression of upper extremity impairment in patients with primary progressive multiple sclerosis in oratorio Multiple sclerosis journal, Conference: 3rd Annual Americas Committee for Treatment and Research in Multiple Sclerosis Forum, ACTRIMS 2018. United States. 24(1 Supplement 1), 33-34	Not relevant publication type
(2018). Efficacy of cladribine tablets in patients with highly active relapsing-remitting multiple sclerosis: analysis of pooled double-blind data from the clarity and onward studies Journal of neurology, neurosurgery and psychiatry, Conference: Annual Scientific Meeting of the Australian and New Zealand Association of Neurologists, ANZAN 2018. Australia. 89(6), e27-e28	Not relevant publication type
(2018). Erratum: siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study (The Lancet (2018) 391(10127) (1263-1273), (S0140673618304756) (10.1016/S0140-6736(18)30475-6)) Lancet, 392(10160), 2170	Not relevant publication type
(2018). Evaluation of no evidence of progression or active disease (NEPAD) in patients with relapsing multiple sclerosis in the opera i and opera II trials Multiple sclerosis journal, Conference: 3rd Annual Americas Committee for Treatment and Research in Multiple Sclerosis Forum, ACTRIMS 2018. United States. 24(1 Supplement 1), 17	Not relevant publication type
(2018). How does alemtuzumab compare with interferon beta 1a in people with relapsing-remitting multiple sclerosis?	Not relevant publication type
(2018). Improved cognitive outcomes in patients with relapsing-remitting multiple sclerosis treated with daclizumab beta: results from the DECIDE study Multiple sclerosis (Houndmills, Basingstoke, England)	Not intervention of interest
(2018). In Clarity the Severity and Frequency of Relapses are Lower in Patients with Relapsing-remitting Multiple Sclerosis Treated with Cladribine Tablets Versus Placebo Multiple sclerosis and related disorders, 26, 262-	Not relevant publication type
(2018). In people with relapsing-remitting multiple sclerosis, how does fingolimod compare with placebo or interferon for improving outcomes?	Not relevant publication type
(2018). Longer-term Safety with Siponimod Treatment in Multiple Sclerosis: pooled Analysis of Data from the Bold and Expand Trials and their Extensions Multiple sclerosis and related disorders, 26, 255-256	Not relevant publication type
(2018). Long-term effects of cladribine tablets on mri activity outcomes in patients with relapsing-remitting multiple sclerosis: the clarity extension study Therapeutic advances in neurological disorders, 11(no pagination),	Not a sister publication of interest
(2018). Long-term Efficacy and Safety of Teriflunomide: an Analysis of Pooled Clinical Trials Multiple sclerosis and related disorders, 26, 257-	Not relevant publication type

Reference	Reason for Exclusion
(2018). Long-term predictors of relapse or disability progression in patients with multiple sclerosis in the transforms and freedoms/freedoms II studies Multiple sclerosis journal, Conference: 3rd Annual Americas Committee for Treatment and Research in Multiple Sclerosis Forum, ACTRIMS 2018. United States. 24(1 Supplement 1), 104	Not relevant publication type
(2018). Long-term Reduction in Brain MRI Disease Activity and Atrophy after 5 years of Ocrelizumab Treatment in Patients with Relapsing Multiple Sclerosis Multiple sclerosis and related disorders, 26, 265-	Not relevant publication type
(2018). Long-term Reduction of Relapse Rate and Confirmed Disability progression after 5 years of Ocrelizumab Treatment in Patients with Relapsing Multiple Sclerosis Multiple sclerosis and related disorders, 26, 265-266	Not relevant publication type
(2018). No Evidence of Disease Activity-3 Status Is Durable in Patients with Relapsing Multiple Sclerosis Receiving Cladribine Tablets: clarity Extension Multiple sclerosis and related disorders, 26, 259-260	Not relevant publication type
(2018). Ocrelizumab reduces progression of upper extremity impairment in patients with primary progressive multiple sclerosis: findings from the phase III randomized ORATORIO trial Multiple sclerosis journal, 24(14), 1862-1870	Not a sister publication of interest
(2018). Ocrelizumab safety in patients with multiple sclerosis: updated analyses with a focus on infusion-related reactions Multiple sclerosis journal, Conference: 3rd Annual Americas Committee for Treatment and Research in Multiple Sclerosis Forum, ACTRIMS 2018. United States. 24(1 Supplement 1), 46	Not relevant publication type
(2018). Ocrelizumab: a Review in Multiple Sclerosis CNS drugs	Not relevant publication type
(2018). Peginterferon beta-1a demonstrated better clinical outcomes than teriflunomide in newly diagnosed rms patients: a matching-adjusted comparison Multiple sclerosis journal, Conference: 3rd Annual Americas Committee for Treatment and Research in Multiple Sclerosis Forum, ACTRIMS 2018. United States. 24(1 Supplement 1), 25	Not relevant publication type
(2018). Persistence and adherence to interferon and glatiramer acetate in patients with multiple sclerosis European Journal of Hospital Pharmacy,	Not sample size of interest (< 1,000 for NRS)
(2018). Predictive value of early magnetic resonance imaging measures is differentially affected by the dose of interferon beta-1a given subcutaneously three times a week: an exploratory analysis of the PRISMS study BMC neurology, 18(1),	Not a sister publication of interest
(2018). Pregnancy Outcomes During the Clinical Development of Cladribine in Multiple Sclerosis: an Integrated Analysis of Safety Multiple sclerosis and related disorders, 26, 260-261	Not relevant publication type
(2018). Rapid onset of ocrelizumab suppression of brain MRI activity in relapsing-remitting multiple sclerosis Multiple sclerosis journal, Conference: 4th Middle East North Africa Committee for Research and Treatment in Multiple Sclerosis, MENACTRIMS 2018. United Arab Emirates. 24(2), NP14-NP15	Not relevant publication type
(2018). Rapidity of onset of ocrelizumab clinical efficacy in relapsing multiple sclerosis Multiple sclerosis journal, Conference: 4th Middle East North Africa Committee for Research and Treatment in Multiple Sclerosis, MENACTRIMS 2018. United Arab Emirates. 24(2), NP13-NP14	Not relevant publication type

Reference	Reason for Exclusion
(2018). Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis New England journal of medicine,	Not population of interest
(2019). An exploratory analysis of the efficacy of cladribine tablets 3.5 mg/kg in patients with relapsing multiple sclerosis stratified according to age above and below 45 years in the clarity study Multiple sclerosis journal, 25(3), 465-466	Not relevant publication type
(2019). Clarity: an analysis of severity and frequency of relapses in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets or placebo Multiple sclerosis journal, 25(3), 466-467	Not relevant publication type
(2019). Delayed-release Dimethyl Fumarate demonstrates sustained efficacy over nine years in newly diagnosed patients with relapsing-remitting multiple Sclerosis Revue neurologique, 175, S101-	Not relevant publication type
(2019). Durability of neda-3 status in patients with relapsing multiple sclerosis receiving cladribine tablets: clarity extension Multiple sclerosis journal, 25(3), 467-	Not relevant publication type
(2019). Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis Multiple sclerosis and related disorders, 29, 168-174	Not a sister publication of interest
(2019). Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial Journal of the American Medical Association,	Not comparator of interest
(2019). Effects of cladribine tablets on heart rate, atrio-ventricular conduction and cardiac repolarization in patients with relapsing multiple sclerosis British journal of clinical pharmacology,	Not a sister publication of interest
(2019). Efficacy and safety of dimethyl fumarate in Japanese MS patients who had the history of treatment with fingolimod: apex part 1+2 interim analysis Multiple sclerosis journal, 25(3), 457-458	Not relevant publication type
(2019). Efficacy of dimethyl fumarate in Japanese MS patient in phase 3 apex study and the open label extension study: 72 weeks interim analysis Multiple sclerosis journal, 25(3), 457-	Not relevant publication type
(2019). Longer-term safety with siponimod treatment in multiple sclerosis: pooled analysis from the bold and expand trial and their extensions Multiple sclerosis journal, 25(3), 460-	Not relevant publication type
(2019). Multiple sclerosis: effect of beta interferon treatment on survival Brain,	Not comparator of interest
(2019). Peginterferon beta-1a reduces the number of black holes evolved from acute MRI lesions in newly diagnosed patients with relapsing-remitting multiple sclerosis: a post hoc analysis ADVANCE Revue neurologique, 175, S96-	Not relevant publication type
(2019). Safety of dimethyl fumarate in Japanese patients with relapse-remitting ms for 72 weeks in the apex part 1 and part 2 studies Multiple sclerosis journal, 25(3), 456-	Not relevant publication type
(2019). The interim sub-analysis from apex part 1+2 studies; efficacy and safety of dimethyl fumarate in treatment-naïve Japanese patients with relapse-remitting ms Multiple sclerosis journal, 25(3), 456-457	Not relevant publication type
(2019). The magnify-MS study: mavenclad tablets in active RMS Multiple sclerosis journal, 25(3), 469-470	Not relevant publication type
Aarskog, N. K.,Maroy, T.,Myhr, K. M.,Vedeler, C. A.. Antibodies against interferon-beta in multiple sclerosis. J Neuroimmunol. 2009. 212:148-50	Not sample size of interest (< 1,000 for NRS)

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Achiron, A.,Aref, H.,Inshasi, J.,Harb, M.,Alroughani, R.,Bijarnia, M.,Cooke, K.,Yuksel, O. (2017). Effectiveness, safety and health-related quality of life of multiple sclerosis patients treated with fingolimod: results from a 12-month, real-world, observational PERFORMS study in the Middle East BMC Neurology, 17(1), 150	Not sample size of interest (< 1,000 for NRS)
Adler, A. I.,Knight, H. (2019). Ocrelizumab for primary progressive multiple sclerosis 1(9), 816-817	Not relevant publication type
Afolabi, D.,Albor, C.,Altmann, D. R.,Zalewski, L.,Baker, D.,Schmierer, K. (2017). Cladribine tablets treating multiple sclerosis orally (CLARITY): an independent analysis of the quality of life data Multiple sclerosis journal, 23(3), 423-	Not relevant publication type
Alcala, C.,Gascon, F.,Perez-Miralles, F.,Dominguez, J. A.,Gil-Perotin, S.,Casanova, B. (2019). Treatment with alemtuzumab or rituximab after fingolimod withdrawal in relapsing-remitting multiple sclerosis is effective and safe Journal of Neurology, 266(3), 726-734	Not sample size of interest (< 1,000 for NRS)
Alemtuzumab for multiple sclerosis. 2016. http://dx.doi.org/10.1002/14651858.CD011203.pub2.	Systematic review (not checked)
Ali S, Paracha N, Cook S, et al. Reduction in healthcare and societal resource utilization associated with cladribine tablets in patients with relapsing-remitting multiple sclerosis: analysis of economic data from the CLARITY Study. *Clinical drug investigation*. 2012;32(1):15-27. doi: 10.2165/11593310-000000000-00000.	Not sister publication of interest
Alping P., J. Askling, J. Burman, K. Fink, A. Fogdell-Hahn, M. Gunnarsson, J. Hillert, A. Langer-Gould, J. Lycke, P. Nilsson, J. Salzer, A. Svenningsson, M. Vrethem, T. Olsson, F. Piehl, T. Frisell (2020). Cancer Risk for Fingolimod, Natalizumab, and Rituximab in MS Patients Ann Neurol, 13, 13	Not comparator of interest
Alping, P.,Frisell, T.,Novakova, L.,Islam-Jakobsson, P.,Salzer, J.,Bjorck, A.,Axelsson, M.,Malmestrom, C.,Fink, K.,Lycke, J.,Svenningsson, A.,Piehl, F. (2016). Rituximab versus fingolimod after natalizumab in multiple sclerosis patients Annals of Neurology, 79(6), 950-8	Not sample size of interest (< 1,000 for NRS)
Al-Salama, Z. T. (2019). Siponimod: First Global Approval 1(9), 1009-1015	Not relevant publication type
Alsop, J.,Medin, J.,Cornelissen, C.,Vormfelde, S. V.,Ziemssen, T. (2017). Two studies in one: A propensity-score-matched comparison of fingolimod versus interferons and glatiramer acetate using real-world data from the independent German studies, PANGAEA and PEARL PLoS ONE [Electronic Resource], 12(5), e0173353	Not outcomes of interest
Ancau, M.,Berthele, A.,Hemmer, B. (2019). CD20 monoclonal antibodies for the treatment of multiple sclerosis: up-to-date 1(8), 829-843	Not relevant publication type
Andersen O, Elovaara I, Färkkilä M, et al. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry*. 2004;75(5):706-710. doi: 10.1136/jnnp.2003.010090.	Other Not placebo-controlled trial of interest
Andersen, J. B.,Moberg, J. Y.,Spelman, T.,Magyari, M. (2018). Pregnancy Outcomes in Men and Women Treated With Teriflunomide. A Population-Based Nationwide Danish Register Study Frontiers in Immunology, 9, 2706	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
Andrew Chan,Gary Cutter,Robert J Fox,James Xiao,James B Lewin,Michael R Edwards (2017). Comparative effectiveness of delayed-release dimethyl fumarate versus glatiramer acetate in multiple sclerosis patients: results of a matching-adjusted indirect comparison Journal of Comparative Effectiveness Research, 6(4), 313-323	Not a sister publication of interest
Annovazzi, P.,Bertolotto, A.,Brescia Morra, V.,Gasperini, C.,Montanari, E.,Navarra, P.,Patti, F.,Sormani, M. P.,Ghezzi, A. (2017). A Comprehensive Review on Copemyl. [Review] 1(2), 161-173	Not relevant publication type
Anonymous (2019). Fingolimod and changes in hematocrit, hemoglobin and red blood cells of patients with multiple sclerosis [Retraction] Am J Clin Exp Immunol, 8(5), 54	Not relevant publication type
Anonymous, (2018). Ocrelizumab for multiple sclerosis. [Review] 1(4), 125-126	Not relevant publication type
Arbizu, T.,Alvarez-Cermeno, J. C.,Decap, G.,Fernandez, O.,Uria, D. F.,Garcia Merino, A.,Izquierdo, G.,Montalban, X.. Interferon beta-1b treatment in patients with relapsing--remitting multiple sclerosis under a standardized protocol in Spain. Acta Neurol Scand. 2000. 102:209-17	Not comparator of interest
Arends, R. J.,Wang, D.,Buurman, M.,Luten, J.,Koper, N. P.,Wolf, C.,Scheren, M. (2019). Comparison of Copaxone and Synthon's therapeutically equivalent glatiramer acetate 1(8), 449-461	Not relevant publication type
Arnold, D. L.,Barnett, M.,Comi, G.,Giovannoni, G.,Pelletier, D.,Rovira, A.,Schippling, S.,Van Wijmeersch, B.,Margolin, D. H.,Thangavelu, K.,et al., (2016). Durable reduction in MRI disease activity with alemtuzumab in treatment-naive patients with active relapsing-remitting multiple sclerosis: 6-year follow-up of the CARE-MS I study Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 329	Not relevant publication type
Arnold, D. L.,Bar-Or, A.,Comi, G.,Hartung, H. P.,Hauser, S. L.,Kappos, L.,Lublin, F.,Selmaj, K.,Traboulsee, A.,Klingelschmitt, G.,et al., (2016). Effect of ocrelizumab on magnetic resonance imaging markers of neurodegeneration in patients with relapsing multiple sclerosis: analysis of the Phase III, double-blind, double-dummy, interferon beta-1a-controlled OPERA I and OPERA II studies Multiple sclerosis (houndmills, basingstoke, england), 22, 514-515	Not relevant publication type
Arnold, D. L.,Benedict, R. H. B.,Cree, B. A. C.,Meng, X.,Schofield, L.,Tenenbaum, N. (2016). PREFERMS study: post hoc analyses of cross-sectional correlations between oral Symbol Digit Modalities Test scores and clinical, cognitive and radiological outcomes Multiple sclerosis (houndmills, basingstoke, england), 22, 612-	Not relevant publication type
Arnold, D. L.,Cohen, J. A.,Comi, G.,Selmaj, K. W.,Bar-Or, A.,Steinman, L.,Hartung, H. P.,Montalban, X.,Havrdova, E. K.,Cree, B. A. C.,et al., (2017). Ozanimod demonstrates preservation of brain volume at 1 and 2 years in two Phase 3 trials of relapsing multiple sclerosis (SUNBEAM and RADIANCE) Multiple sclerosis journal, 23(3), 986-987	Not relevant publication type

Reference	Reason for Exclusion
Arnold, D. L.,Fisher, E.,Brinar, V. V.,Cohen, J. A.,Coles, A. J.,Giovannoni, G.,Hartung, H. P.,Havrdova, E.,Selmaj, K. W.,Stojanovic, M.,Weiner, H. L.,Lake, S. L.,Margolin, D. H.,Thomas, D. R.,Panzara, M. A.,Compston, D. A.,Care-Ms, I.,Care-Ms Ii Investigators (2016). Superior MRI outcomes with alemtuzumab compared with subcutaneous interferon beta-1a in MS Neurology, 87(14), 1464-1472	Not a sister publication of interest
Arnold, D. L.,Fisher, E.,Brinar, V. V.,Cohen, J. A.,Coles, A. J.,Giovannoni, G.,Hartung, H. P.,Havrdova, E.,Selmaj, K. W.,Stojanovic, M.,et al., (2016). Superior MRI outcomes with alemtuzumab compared with subcutaneous interferon β-1a in MS Neurology, 87(14), 1464-1472	Not a sister publication of interest
Arnold, D.,Shang, S.,Castrillo-Viguera, C.,Fiore, D. (2016). Peginterferon beta-1a every 2 weeks increased achievement of NEDA over 4 years in the ADVANCE and ATTAIN studies in patients with RRMS Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 610-611	Not relevant publication type
Arnold, Douglas,Kappos, Ludwig,Hauser, Stephen,Montalban, Xavier,Traboulsee, Anthony,Wolinsky, Jerry,Levesque, Victoria,Villoslada, Pablo,Belachew, Shibeshih,Model, Fabian,Hubeaux, Stanislas,Bar-Or, Amit (2018). Brain MRI Activity and Atrophy Measures in Patients Receiving Continuous Ocrelizumab or Switching From Interferon Beta-1a to Ocrelizumab Therapy in the Open-Label Extension Period of the Phase III Trials of Ocrelizumab in Patients With Relapsing Multiple Sclerosis (S6.002) Neurology, 90(15 Supplement), S6.002	Not relevant publication type
Arnoldus, J. H.,Killestein, J.,Pfennings, L. E.,Jelles, B.,Uitdehaag, B. M.,Polman, C. H.. Quality of life during the first 6 months of interferon-beta treatment in patients with MS. Mult Scler. 2000. 6:338-42	Not sample size of interest (< 1,000 for NRS)
Aschenbrenner, D. S. (2017). New Drug For Multiple Sclerosis American Journal of Nursing, 117(7), 22	Not relevant publication type
Aschenbrenner, D. S. (2019). New Warning for the Multiple Sclerosis Drug Alemtuzumab 1(3), 21	Not relevant publication type
Auguste P., J. Colquitt, M. Connock, E. Loveman, R. Court, O. Ciccarelli, C. Counsell, X. Armoiry (2020). Ocrelizumab for Treating Patients with Primary Progressive Multiple Sclerosis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal Pharmacoeconomics, 12, 12	Not relevant publication type
Baghbanian, S. M.,Sahraian, M. A. (2018). Induction or aggravation of other immune-mediated disorders by disease-modifying therapy in treatment of multiple sclerosis. [Review] 1(3), 129-136	Not relevant publication type
Baharnoori, M.,Gonzalez, C. T.,Chua, A.,Diaz-Cruz, C.,Healy, B. C.,Stankiewicz, J.,Weiner, H. L.,Chitnis, T. (2018). Predictors of hematological abnormalities in multiple sclerosis patients treated with fingolimod and dimethyl fumarate and impact of treatment switch on lymphocyte and leukocyte count Multiple Sclerosis and Related Disorders, 20, 51-57	Not sample size of interest (< 1,000 for NRS)
Bajrami, A.,Pitteri, M.,Castellaro, M.,Pizzini, F.,Romualdi, C.,Montemezzi, S.,Monaco, S.,Calabrese, M. (2018). The effect of fingolimod on focal and diffuse grey matter damage in active MS patients Journal of Neurology, 265(9), 2154-2161	Not sample size of interest (< 1,000 for NRS)

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Baker, D.,Herrod, S. S.,Alvarez-Gonzalez, C.,Giovannoni, G.,Schmierer, K. (2017). Interpreting Lymphocyte Reconstitution Data From the Pivotal Phase 3 Trials of Alemtuzumab JAMA Neurology, 74(8), 961-969	Not a sister publication of interest
Baker, D.,Herrod, S. S.,Alvarez-Gonzalez, C.,Zalewski, L.,Albor, C.,Schmierer, K. (2017). Both cladribine and alemtuzumab may effect MS via B-cell depletion 1(4), e360	Not a sister publication of interest
Balak, D. M.,Hengstman, G. J.,Hajdarbegovic, E.,van den Brule, R. J.,Hupperts, R. M.,Thio, H. B.. Prevalence of cutaneous adverse events associated with long-term disease-modifying therapy and their impact on health-related quality of life in patients with multiple sclerosis: a cross-sectional study. BMC Neurol. 2013. 13:146	Not sample size of interest (< 1,000 for NRS)
Balcer, L. J.,Hauser, S. L.,Kappos, L.,Leocani, L.,Saidha, S.,Julian, L.,Pei, J.,Comi, G. (2018). Effect of ocrelizumab on visual outcomes in patients with baseline visual impairment in the opera studies in relapsing multiple sclerosis Multiple sclerosis journal, 24(1), 16-17	Not relevant publication type
Barclay, K.,Carruthers, R.,Traboulsee, A.,Bass, A. D.,LaGanke, C.,Bertolotto, A.,Boster, A.,Celius, E. G.,de Seze, J.,Cruz, D. D.,Habek, M.,Lee, J. M.,Limmroth, V.,Meuth, S. G.,Oreja-Guevara, C.,Pagnotta, P.,Vos, C.,Ziemssen, T.,Baker, D. P.,Wijmeersch, B. V. (2019). Best Practices for Long-Term Monitoring and Follow-Up of Alemtuzumab-Treated MS Patients in Real-World Clinical Settings. [Review] 1, 253	Not relevant publication type
Bartolome-Garcia, E.,Usarralde-Perez, A.,Sanmartin-Fenollera, P.,Perez-Encinas, M. (2019). Persistence and adherence to interferon and glatiramer acetate in patients with multiple sclerosis 1(1), 23-28	Not sample size of interest (< 1,000 for NRS)
Bastianello, S.,Pozzilli, C.,D'Andrea, F.,Millefiorini, E.,Trojano, M.,Morino, S.,Gasperini, C.,Bozzao, A.,Gallucci, M.,Andreula, C.,et al.,. A controlled trial of mitoxantrone in multiple sclerosis: serial MRI evaluation at one year. Can J Neurol Sci. 1994. 21:266-70	Not intervention of interest
Battaglini, M.,Vrenken, H.,Tappa Brocci, R.,Gentile, G.,Luchetti, L.,Versteeg, A.,Freedman, M. S.,Uitdehaag, B.,Kappos, L.,Comi, G.,et al., (2016). Treatment with interferon reduces the appearance of lesions in clinically relevant white matter tracts in patients with clinically isolated syndrome Multiple sclerosis. Conference: 32nd congress of the european committee for treatment and research in multiple sclerosis, ECTRIMS 2016. United kingdom. Conference start: 20160914. Conference end: 20160917, 22, 537-538	Not relevant publication type
Baum, K.,O'Leary, C.,Coret Ferrer, F.,Klimova, E.,Prochazkova, L.,Bugge, J.,Bright Study Group. Comparison of injection site pain and injection site reactions in relapsing-remitting multiple sclerosis patients treated with interferon beta-1a or 1b. Mult Scler. 2007. 13:1153-60	Not sample size of interest (< 1,000 for NRS)
Beckmann, Y.,Ture, S. (2019). Headache characteristics in multiple sclerosis Multiple Sclerosis and Related Disorders, 27, 112-116	Not sample size of interest (< 1,000 for NRS)
Beer, K.,Muller, M.,Hew-Winzeler, A. M.,Bont, A.,Maire, P.,You, X.,Foulds, P.,Marlind, J.,Curtius, D.. The prevalence of injection-site reactions with disease-modifying therapies and their effect on adherence in patients with multiple sclerosis: an observational study. BMC Neurol. 2011. 11:144	Not sample size of interest (< 1,000 for NRS)

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Behrangi, N.,Fischbach, F.,Kipp, M. (2019). Mechanism of Siponimod: Anti-Inflammatory and Neuroprotective Mode of Action. [Review] 1(1),	Not relevant publication type
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Bell Gorrod, H.,Latimer, N.,Damian, D.,Hettle, R.,Harty, G. T.,Wong, S. L. (2017). Impact of non-randomised drop-out on treatment switching adjustment in the relapsing-remitting multiple sclerosis clarity trial and the clarity extension study Value in health, 20(9), A769-	Not relevant publication type
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Berenguer-Ruiz, L.,Gimenez-Martinez, J.,Palazon-Bru, A.,Sempere, A. P. (2019). Relapses and obstetric outcomes in women with multiple sclerosis planning pregnancy 1(10), 2512-2517	Not sample size of interest (< 1,000 for NRS)
Berger T., B. Brochet, L. Brambilla, P. S. Giacomini, X. Montalban, A. Vasco Salgado, R. Su, A. Bretagne (2019). Effectiveness of delayed-release dimethyl fumarate on patient-reported outcomes and clinical measures in patients with relapsing-remitting multiple sclerosis in a real-world clinical setting: PROTEC Mult Scler J Exp Transl Clin, 5(4), 2055217319887191	Not comparator of interest

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Bertoglio, J. C.,Baumgartner, M.,Palma, R.,Ciampi, E.,Carcamo, C.,Caceres, D. D.,Acosta-Jamett, G.,Hancke, J. L.,Burgos, R. A. (2016). Andrographis paniculata decreases fatigue in patients with relapsing-remitting multiple sclerosis: a 12-month double-blind placebo-controlled pilot study BMC Neurology, 16, 77	Not intervention of interest
Bhan, V.,Lapierre, Y.,Devonshire, V.,Emond, F.,Morrow, S. A.,Burton, J. M.,Oh, J.,Haddad, P.,Schecter, R. (2016). Fingolimod in routine clinical practice: canadian experience Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 302-303	Not relevant publication type
Bhargava, P.,Newsome, S. D. (2016). An update on the evidence base for peginterferon beta1a in the treatment of relapsing-remitting multiple sclerosis. [Review] 1(6), 483-490	Not relevant publication type
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Boiko, A. N.,Bosenko, L. P.,Vasilovskii, V. V.,Volkova, L. I.,Zakharova, M. N.,Kotov, S. V.,Lekomtseva, E. V.,Negrich, T. I.,Parshina, E. V.,Patrusheva, O. P.,et al., (2018). A Comparative Placebo-Controlled Clinical Trial of the Efficacy and Safety of Interferon β-1a Formulations for S.C. Administration in Patients with Remitting Multiple Sclerosis: first-Year Results Neuroscience and behavioral physiology, 48(7), 883-889	Not comparator of interest
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Buck, D.,Andlauer, T. F.,Igl, W.,Wicklein, E. M.,Muhlau, M.,Weber, F.,Kochert, K.,Pohl, C.,Arnason, B.,Comi, G.,Cook, S.,Filippi, M.,Hartung, H. P.,Jeffery, D.,Kappos, L.,Barkhof, F.,Edan, G.,Freedman, M. S.,Montalban, X.,Muller-Myhsok, B.,Hemmer, B.,Beyond,,Benefit Study Groups (2019). Effect of HLA-DRB1 alleles and genetic variants on the development of neutralizing antibodies to interferon beta in the BEYOND and BENEFIT trials 1(4), 565-573	Not outcomes of interest
Burkill S., P. Vattulainen, Y. Geissbuehler, M. Sabido Espin, C. Popescu, K. Suzart-Woischnik, J. Hillert, M. Artama, A. Verkkoniemi-Ahola, K. M. Myhr, S. Cnattingius, P. Korhonen, S. Montgomery, S. Bahmanyar (2019). The association between exposure to interferon-beta during pregnancy and birth measurements in offspring of women with multiple sclerosis PLoS One, 14(12), e0227120	Not comparator of interest
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Cocco, E.,Sardu, C.,Gallo, P.,Capra, R.,Amato, M. P.,Trojano, M.,Uccelli, A.,Marrosu, M. G.,Femims Group. Frequency and risk factors of mitoxantrone-induced amenorrhea in multiple sclerosis: the FEMIMS study. Mult Scler. 2008. 14:1225-33	Not sample size of interest (< 1,000 for NRS)
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Cohan, S.,Chen, C.,Baraban, E.,Stuchiner, T.,Grote, L. (2016). MRI utility in the detection of disease activity in clinically stable patients with multiple sclerosis: a retrospective analysis of a community based cohort BMC Neurology, 16(1), 184	Not sample size of interest (< 1,000 for NRS)
Cohan, S.,Kappos, L.,Giovannoni, G.,Wiendl, H.,Selmaj, K.,Havrdova, E. K.,Rose, J.,Greenberg, S.,Phillips, G.,Ma, W.,Wang, P.,Lima, G.,Sabatella, G. (2017). Efficacy of daclizumab beta versus intramuscular interferon beta-1a on disability progression across patient demographic and disease activity subgroups in DECIDE Multiple Sclerosis, 1352458517735190	Not a sister publication of interest
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Cohen, J. A.,Bar-Or, A.,Cree, B. A. C.,Mao-Draayer, Y.,Han, M. H.,Singer, B.,Jannu, A.,Kolodny, S.,Meng, X.,Winger, R. C. (2019). The FLUENT study design: investigating immune cell subset and neurofilament changes in patients with relapsing multiple sclerosis treated with fingolimod 1(1), 2055217318819245	Not relevant publication type
Cohen, J. A.,Comi, G.,Selmaj, K. W.,Bar-Or, A.,Arnold, D. L.,Steinman, L.,Hartung, H. P.,Montalban, X.,Havrdova, E. K.,Cree, B. A. C.,et al., (2017). Ozanimod vs interferon β-1a: clinical and MRI results of RADIANCE part B - A 2-year Phase 3 trial in relapsing multiple sclerosis Multiple sclerosis journal, 23(3), 981-982	Not relevant publication type

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Cohen, J. A.,Tenenbaum, N.,Bhatt, A.,Zhang, Y.,Kappos, L. (2019). Extended treatment with fingolimod for relapsing multiple sclerosis: the 14-year LONGTERMS study results 1, 1756286419878324	Not comparator of interest
Cohen, J.,Barkhof, F.,Comi, G. et al.,. Oral fingolimod (FTY720) treatment improves the performance of daily activities compared with intramuscular interferon β-1a: Patient-Reported Indices for Multiple Sclerosis (PRIMUS)-Activities results from a Phase III study (TRANSFORMS) [poster]. The American Academy of Neurology Annual Meeting. 2010. :	Not relevant publication type
Coles, A. J.,Boyko, A. N.,Cohen, J. A.,De Seze, J.,Fox, E. J.,Havrdova, E.,Hartung, H. P.,Inshasi, J. S.,McCombe, P.,Selmaj, K. W.,et al., (2016). Alemtuzumab provides durable improvements in clinical outcomes in treatment-naive patients with active relapsingremitting multiple sclerosis over 6 years in the absence of continuous treatment (CARE-MS I) Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 75-76	Not relevant publication type
Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. *Annals of neurology*. 2001;49(3):290-297. doi: 10.1002/ana.64.	Other Not placebo-controlled trial of interest
Comi, G.,Arnold, D. L.,Cree, B. A.,Kappos, L.,Selmaj, K. W.,Bar-Or, A.,Steinman, L.,Hartung, H. P.,Montalban, X.,Havrdova, E. K.,et al., (2018). Ozanimod demonstrates efficacy and safety in a phase 3 trial of relapsing multiple sclerosis (SUNBEAM) Multiple sclerosis journal, 24(1), 20-21	Not relevant publication type
Comi, G.,Cohen, J.,Arnold, D.,Bar-Or, A.,Gujrathi, S.,Hartung, J.,Olson, A.,Cravets, M.,Frohna, P.,Selmaj, K.. Efficacy results of the phase 2 portion of the radiance trial: a randomized, double-blind, placebo-controlled trial of oral RPC1063 in adults with relapsing multiple sclerosis. Neurology. 2015. 84:	Not relevant publication type
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Comi, G.,Cook, S.,Rammohan, K.,Soelberg Sorensen, P.,Vermersch, P.,Adeniji, A. K.,Dangond, F.,Giovannoni, G. (2018). Long-term effects of cladribine tablets on MRI activity outcomes in patients with relapsing-remitting multiple sclerosis: the CLARITY Extension study 1, 1756285617753365	Not a sister publication of interest
Comi, G.,Freedman, M. S.,Kappos, L.,Olsson, T. P.,Miller, A. E.,Wolinsky, J. S.,O'Connor, P. W.,Benamor, M.,Dukovic, D.,Truffinet, P.,Leist, T. P. (2016). Pooled safety and tolerability data from four placebo-controlled teriflunomide studies and extensions Multiple Sclerosis and Related Disorders, 5, 97-104	Not a sister publication of interest

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Comi, G.,Kappos, L.,Hartung, H. P.,Arnold, D. L.,Bar-Or, A.,Selmaj, K. W.,Steinman, L.,Havrdova, E.,Cree, B. A. C.,Montalban, X.,et al., (2017). Cardiac safety of ozanimod in a QT/QTc trial and a phase 2 trial in RMS Multiple sclerosis journal, 23(3), 377-378	Not relevant publication type
Comi, G.,Leist, T.,Freedman, M. S.,Cree, B. A. C.,Coyle, P. K.,Hartung, H. P.,Vermersch, P.,Damian, D.,Dangond, F. (2016). Cladribine tablets in the ORACLE-MS study open-label maintenance period: analysis of efficacy in patients after conversion to clinically definite multiple sclerosis (CDMS) Multiple sclerosis (houndmills, basingstoke, england), 22, 15-16	Not relevant publication type
Comi, G.,Miller, A. E.,Benamor, M.,Truffinet, P.,Poole, E. M.,Freedman, M. S. (2019). Characterizing lymphocyte counts and infection rates with long-term teriflunomide treatment: Pooled analysis of clinical trials Multiple Sclerosis, 1352458519851981	Not a sister publication of interest
Comi, G.,Vollmer, T. L.,Boyko, A.,Vermersch, P.,Ziemssen, T.,Montalban, X.,Lublin, F. D.,Sasson, N.,Dadon, Y.,Steinerman, J. R.,et al., (2017). CONCERTO: a placebo-controlled trial of oral laquinimod in patients with relapsing-remitting multiple sclerosis Multiple sclerosis journal, 23(3), 74-75	Not relevant publication type
Conde, S.,Moisset, X.,Pereira, B.,Zuel, M.,Colamarino, R.,Maillet-Vioud, M.,Lauxerois, M.,Taithe, F.,Clavelou, P.,Reseau Neuro, S. E. P. Auvergne (2019). Dimethyl fumarate and teriflunomide for multiple sclerosis in a real-life setting: a French retrospective cohort study European Journal of Neurology, 26(3), 460-467	Not sample size of interest (< 1,000 for NRS)
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Cook, S.,Comi, G.,Giovannoni, G.,Rieckmann, P.,Soelberg-Sorensen, P.,Vermersch, P.,Dangond, F.,Hicking, C. (2017). Rates of lymphopenia year-by-year in patients with relapsing multiple sclerosis treated and retreated with cladribine tablets 3.5mg/kg Multiple sclerosis journal, 23(3), 317-318	Not relevant publication type
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Cortes, J. E.,Goldberg, S. L.,Feldman, E. J.,Rizzeri, D. A.,Hogge, D. E.,Larson, M.,Pigneux, A.,Recher, C.,Schiller, G.,Warzocha, K.,et al.,. Phase II, multicenter, randomized trial of CPX-351 (cytarabine: daunorubicin) liposome injection versus intensive salvage therapy in adults with first relapse AML. Cancer. 2015. 121:234-242	Not population of interest
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Coyle, P. K.,Khatri, B.,Edwards, K. R.,Meca-Lallana, J. E.,Cavalier, S.,Rufi, P.,Benamor, M.,Thangavelu, K.,Robinson, M.,Gold, R.,Teri, P. R. O. Trial Group (2018). Patient-reported outcomes in patients with relapsing forms of MS switching to teriflunomide from other disease-modifying therapies: Results from the global Phase 4 Teri-PRO study in routine clinical practice Multiple Sclerosis and Related Disorders, 26, 211-218	Not comparator of interest
Coyle, P. K.,Khatri, B.,Edwards, K. R.,Meca-Lallana, J. E.,Cavalier, S.,Rufi, P.,Benamor, M.,Poole, E. M.,Robinson, M.,Gold, R. (2019). Teriflunomide real-world evidence: Global differences in the phase 4 Teri-PRO study 1, 157-164	Not comparator of interest
Coyle, P. K.,Reder, A. T.,Freedman, M. S.,Fang, J.,Dangond, F. (2017). Early MRI results and odds of attaining 'no evidence of disease activity' status in MS patients treated with interferon β-1a in the EVIDENCE study Journal of the neurological sciences, 379, 151-156	Not a sister publication of interest
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Cree, B. A. C.,Bar-Or, A.,Comi, G.,Selmaj, K. W.,Arnold, D. L.,Steinman, L.,Hartung, H. P.,Montalban, X.,Havrdova, E. K.,Sheffield, J. K.,et al., (2018). Safety of ozanimod versus interferon β-1a in phase 3 studies in relapsing multiple sclerosis (sunbeam and radi-ance part B) Multiple sclerosis journal, 24(1), 24-25	Not relevant publication type
Cree, B. A. C.,Cohen, J. A.,Selmaj, K.,Kopicko, J.,Ziemssen, T.,Carus, C. G.,De Stefano, N.,Bar-Or, A.,Comi, G.,Arnold, D. L.,et al., (2017). The RADIANCE and SUNBEAM phase 3 studies of ozanimod in relapsing multiple sclerosis: study design and baseline characteristics Multiple sclerosis (houndmills, basingstoke, england), 23, 24-25	Not relevant publication type
Cree, B. A. C.,Mares, J.,Hartung, H. P. (2019). Current therapeutic landscape in multiple sclerosis: an evolving treatment paradigm 1(3), 365-377	Not relevant publication type

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Cree, B.,Cohen, J.,Silva, D.,Ritter, S.,Piani Meier, D.,Tomic, D.,Leppert, D.,Kappos, L. (2017). Confirmed disability improvement in patients treated with fingolimod in phase 3 and extension trial programmes for up to 96 months Multiple sclerosis journal, 23(3), 322-	Not relevant publication type
Crescenzo, F.,Marastoni, D.,Zuco, C.,Pitteri, M.,Magliozzi, R.,Monaco, S.,Calabrese, M. (2019). Effect of glatiramer acetate on cerebral grey matter pathology in patients with relapsing-remitting multiple sclerosis Multiple Sclerosis and Related Disorders, 27, 305-311	Not sample size of interest (< 1,000 for NRS)
Cursiefen, S.,Flachenecker, P.,Toyka, K. V.,Rieckmann, P.. Escalating immunotherapy with mitoxantrone in patients with very active relapsing-remitting or progressive multiple sclerosis. Eur Neurol. 2000. 43:186-7	Not intervention of interest
Daigl, M.,Jhuti, G. S.,McDougall, F.,Bennett, I. (2017). Impact of disease activity measures and patient characteristics on health utilities in RMS Value in health, 20(9), A728-	Not relevant publication type
Daigl, M.,Jhuti, G. S.,McDougall, F.,Bennett, I. (2017). Impact of disease activity measures on health utilities in PPMS Value in health, 20(9), A727-A728	Not relevant publication type
D'Ambrosio, D.,Freedman, M. S.,Prinz, J. (2016). Ponesimod, a selective S1P1 receptor modulator: a potential treatment for multiple sclerosis and other immune-mediated diseases. [Review] 1(1), 18-33	Not intervention of interest
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D'Amico, E.,Zanghi, A.,Sciandra, M.,Borriello, G.,Callari, G.,Gallo, A.,Salemi, G.,Cottone, S.,Buccafusca, M.,Valentino, P.,Bossio, R. B.,Grimaldi, L. M. E.,Pozzilli, C.,Tedeschi, G.,Zappia, M.,Patti, F. (2019). Discontinuation of teriflunomide and dimethyl fumarate in a large Italian multicentre population: a 24-month real-world experience Journal of Neurology, 266(2), 411-416	Not sample size of interest (< 1,000 for NRS)
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Dargahi, N.,Katsara, M.,Tselios, T.,Androutsou, M. E.,de Courten, M.,Matsoukas, J.,Apostolopoulos, V. (2017). Multiple Sclerosis: Immunopathology and Treatment Update. [Review] 1(7),	Not relevant publication type
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De Angelis, F.,Plantone, D.,Chataway, J. (2018). Pharmacotherapy in Secondary Progressive Multiple Sclerosis: An Overview CNS Drugs, 32(6), 499-526	Not relevant publication type
de Flon, P.,Gunnarsson, M.,Laurell, K.,Soderstrom, L.,Birgander, R.,Lindqvist, T.,Krauss, W.,Dring, A.,Bergman, J.,Sundstrom, P.,Svenningsson, A. (2016). Reduced inflammation in relapsing-remitting multiple sclerosis after therapy switch to rituximab Neurology, 87(2), 141-7	Not sample size of interest (< 1,000 for NRS)

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de Jong, H. J. I.,Kingwell, E.,Shirani, A.,Cohen Tervaert, J. W.,Hupperts, R.,Zhao, Y.,Zhu, F.,Evans, C.,van der Kop, M. L.,Traboulsee, A.,Gustafson, P.,Petkau, J.,Marrie, R. A.,Tremlett, H.,British Columbia Multiple Sclerosis Clinic, Neurologists (2017). Evaluating the safety of beta-interferons in MS: A series of nested case-control studies Neurology, 88(24), 2310-2320	Not comparator of interest
De Luca, J.,Huang, D. R.,Cohen, J. A.,Cree, B. A. C.,Chen, Y.,Campagnolo, D.,Harvey, D.,Sheffield, J. K.,Comi, G.,Kappos, L. (2019). Assessment of cognitive processing speed in the phase 3 sunbeam trial demonstrates sustained improvement in ozanimod-treated patients Multiple sclerosis journal, 25, 129-	Not relevant publication type
De Seze, J.,Arnold, D. L.,Bar-Or, A.,Giovannoni, G.,Hartung, H. P.,Hauser, S. L.,Hemmer, B.,Kappos, L.,Lublin, F.,Montalban, X.,et al., (2016). Infusion-related reactions with ocrelizumab in relapsing multiple sclerosis and primary progressive multiple sclerosis Multiple sclerosis (houndmills, basingstoke, england), 22, 351-352	Not relevant publication type
De Seze, J.,Montalban, X.,McDougall, F.,Julian, L.,Sauter, A.,Deol-Bhullar, G.,Wolinsky, J. (2017). Patient-reported outcomes in the phase III double-blind, placebo-controlled ORATORIO study of ocrelizumab in primary progressive multiple sclerosis Multiple sclerosis (houndmills, basingstoke, england), 23, 84-	Not relevant publication type
De Seze, J.,Montalban, X.,McDougall, F.,Sauter, A.,Deol-Bhullar, G.,Wolinsky, J. (2016). Patient-reported outcomes in the phase III double-blind, placebo-controlled ORATORIO study of ocrelizumab in primary progressive multiple sclerosis Multiple sclerosis (houndmills, basingstoke, england), 22, 677-678	Not relevant publication type
De Stefano N., G. Comi, L. Kappos, M. S. Freedman, C. H. Polman, B. M. J. Uitdehaag, B. Hennessy, F. Casset-Semanaz, L. Lehr, B. Stubinski,et al. (2014). Efficacy of subcutaneous interferon beta-1a on MRI outcomes in a randomised controlled trial of patients with clinically isolated syndromes Journal of neurology, neurosurgery and psychiatry, 85(6), 647-653	Not a sister publication of interest
De Stefano, N.,Giorgio, A.,De Leucio, A.,Hamlett, A.,Scaramozza, M.,Stubinski, B.. Oral cladribine treatment reduces brain atrophy rates in relapsing-remitting multiple sclerosis: exploratory analysis of the clarity study. Neurology. 2013. 80:	Not relevant publication type
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De Stefano, Nicola,Giorgio, Antonio,Battaglini, Marco,De Leucio, Alessandro,Hicking, Christine,Dangond, Fernando,Giovannoni, Gavin,Sormani, Maria Pia (2018). Reduced brain atrophy rates are associated with lower risk of disability progression in patients with relapsing multiple sclerosis treated with cladribine tablets Multiple Sclerosis Journal, 24(2), 222-226	Not a sister publication of interest
Debouverie, M.,Moreau, T.,Lebrun, C.,Heinzlef, O.,Brudon, F.,Msihid, J.. A longitudinal observational study of a cohort of patients with relapsing-remitting multiple sclerosis treated with glatiramer acetate. Eur J Neurol. 2007. 14:1266-74	Not sample size of interest (< 1,000 for NRS)
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Reference	Reason for Exclusion
Deeks, E. D. (2018). Cladribine Tablets: A Review in Relapsing MS 1(8), 785-796	Not relevant publication type
Deftereos, S. N.,Koutlas, E.,Koutsouraki, E.,Kyritsis, A.,Papathanassopoulos, P.,Fakas, N.,Tsimourtou, V.,Vlaikidis, N.,Tavernarakis, A.,Voumvourakis, K.,Arvanitis, M.,Sakellariou, D.,DeLorenzo, F. (2018). Seasonal adherence to, and effectiveness of, subcutaneous interferon beta-1a administered by RebiSmart in patients with relapsing multiple sclerosis: results of the 1-year, observational GEPAT-SMART study BMC Neurology, 18(1), 186	Not sample size of interest (< 1,000 for NRS)
Deleu, D.,Mesraoua, B.,Canibano, B.,Melikyan, G.,Al Hail, H.,El-Sheikh, L.,Ali, M.,Al Hussein, H.,Ibrahim, F.,Hanssens, Y. (2019). Oral disease-modifying therapies for multiple sclerosis in the Middle Eastern and North African (MENA) region: an overview 1(2), 249-260	Not relevant publication type
Deleu, D.,Mesraoua, B.,El Khider, H.,Canibano, B.,Melikyan, G.,Al Hail, H.,Mhjob, N.,Bhagat, A.,Ibrahim, F.,Hanssens, Y. (2017). Optimization and stratification of multiple sclerosis treatment in fast developing economic countries: a perspective from Qatar Current Medical Research & Opinion, 33(3), 439-458	Not relevant publication type
DeLuca, J.,Cohen, J. A.,Cree, B. A. C.,Chen, Y.,Harvey, D.,Sheffield, J. K.,Silva, D.,Comi, G.,Kappos, L. (2019). Sustained improvement in cognitive processing speed in multiple sclerosis patients completing 18 months of ozanimod treatment: results from the phase 3 SUNBEAM Trial Multiple sclerosis journal, 25(8), NP22-	Not relevant publication type
Demir G. A., R. Turkoglu, S. Saip, N. Yuceyar, H. Efendi, O. F. Turan, K. Agan, M. Terzi, C. Boz, A. Tuncer, B. Kocer, M. Kasap, Z. Caliskan, Group Fine Study (2019). A 12-month, Open Label, Multicenter Pilot Study Evaluating Fingolimod Treatment in terms of Patient Satisfaction in Relapsing Remitting Multiple Sclerosis Patients - FINE Trial Noropsikiyatri Arsivi, 56(4), 253-257	Not sample size of interest (< 1,000 for NRS)
Desai, R. J.,Mahesri, M.,Gagne, J. J.,Hurley, E.,Tong, A.,Chitnis, T.,Minden, S.,Spettell, C. M.,Matlin, O. S.,Shrank, W. H.,Choudhry, N. K. (2019). Utilization Patterns of Oral Disease-Modifying Drugs in Commercially Insured Patients with Multiple Sclerosis Journal of Managed Care & Specialty Pharmacy, 25(1), 113-121	Not outcomes of interest
Disanto, G.,Benkert, P.,Lorscheider, J.,Mueller, S.,Vehoff, J.,Zecca, C.,Ramseier, S.,Achtnichts, L.,Findling, O.,Nedeltchev, K.,Radue, E. W.,Sprenger, T.,Stippich, C.,Derfuss, T.,Louvion, J. F.,Kamm, C. P.,Mattle, H. P.,Lotter, C.,Du Pasquier, R.,Schluep, M.,Pot, C.,Lalive, P. H.,Yaldizli, O.,Gobbi, C.,Kappos, L.,Kuhle, J.,Smsc Scientific Board (2016). The Swiss Multiple Sclerosis Cohort-Study (SMSC): A Prospective Swiss Wide Investigation of Key Phases in Disease Evolution and New Treatment Options PLoS ONE [Electronic Resource], 11(3), e0152347	Not sample size of interest (< 1,000 for NRS)
Druart, C.,El Sankari, S.,van Pesch, V. (2018). Long-term safety and real-world effectiveness of fingolimod in relapsing multiple sclerosis. [Review] 1, 1-10	Not relevant publication type
Drulovic, J.,Ivanovic, J.,Mesaros, S.,Martinovic, V.,Kisic-Tepavcevic, D.,Dujmovic, I.,Pekmezovic, T. (2019). Long-term disability outcomes in relapsing-remitting multiple sclerosis: a 10-year follow-up study 1(8), 1627-1636	Not sample size of interest (< 1,000 for NRS)
Du, F. H.,Mills, E. A.,Mao-Draayer, Y. (2017). Next-generation anti-CD20 monoclonal antibodies in autoimmune disease treatment 1(1), 12	Not relevant publication type

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Dubois, B. D.,Keenan, E.,Porter, B. E.,Kapoor, R.,Rudge, P.,Thompson, A. J.,Miller, D. H.,Giovannoni, G.. Interferon beta in multiple sclerosis: experience in a British specialist multiple sclerosis centre. J Neurol Neurosurg Psychiatry. 2003. 74:946-9	Not sample size of interest (< 1,000 for NRS)
Duchini, A.. Autoimmune hepatitis and interferon beta-1a for multiple sclerosis. Am J Gastroenterol. 2002. 97:767-8	Not relevant publication type
Duchovskiene, N.,Mickeviciene, D.,Jurkeviciene, G.,Dirziuviene, B.,Balnyte, R. (2017). Factors associated with adherence to disease modifying therapy in multiple sclerosis: An observational survey from a referral center in Lithuania Multiple Sclerosis and Related Disorders, 13, 107-111	Not sample size of interest (< 1,000 for NRS)
Duddy, M.,Palace, J. (2016). The UK Risk-Sharing Scheme for interferon-beta and glatiramer acetate in multiple sclerosis. Outcome of the year-6 analysis 1(1), 4-6	Not relevant publication type
Duddy, M.,Palace, J.,Lilford, R.,Bregenzer, T.,Lawton, M.,Zhu, F.,Piske, B.,Oger, J.,Boggild, M.,Robertson, N.,et al., (2016). The United Kingdom multiple sclerosis risk-sharing scheme: final 10 year results Multiple sclerosis (houndmills, basingstoke, england), 22, 74-75	Not relevant publication type
Dupuy, S. L.,Tauhid, S.,Hurwitz, S.,Chu, R.,Yousuf, F.,Bakshi, R. (2016). The Effect of Dimethyl Fumarate on Cerebral Gray Matter Atrophy in Multiple Sclerosis 1(2), 215-229	Not sample size of interest (< 1,000 for NRS)
Duquette P, Girard M, Despault L, et al. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology.* 2001;57(12 SUPPL. 5):S3-S9. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00425421/full.	Other Not placebo-controlled trial of interest
Durelli, L.,Barbero, P.,Cucci, A.,Ferrero, B.,Ricci, A.,Contessa, G.,De Mercanti, S.,Ripellino, P.,Lapuma, D.,Viglietta, E.,Bergui, M.,Versino, E.,Clerico, M.,Optims Trial NAb Sub-Study Group. Neutralizing antibodies in multiple sclerosis patients treated with 375 micrograms interferon-beta-1b. Expert Opin Biol Ther. 2009. 9:387-97	Not comparator of interest
Durelli, L.,Ferrero, B.,Oggero, A.,Verdun, E.,Bongioanni, M. R.,Gentile, E.,Isoardo, G. L.,Ricci, A.,Rota, E.,Bergamasco, B.,Durazzo, M.,Saracco, G.,Biava, M. A.,Brossa, P. C.,Giorda, L.,Pagni, R.,Aimo, G.. Autoimmune events during interferon beta-1b treatment for multiple sclerosis. J Neurol Sci. 1999. 162:74-83	Not sample size of interest (< 1,000 for NRS)
Durelli, L.,Ferrero, B.,Oggero, A.,Verdun, E.,Ghezzi, A.,Montanari, E.,Zaffaroni, M.. Liver and thyroid function and autoimmunity during interferon-beta 1b treatment for MS. Neurology. 2001. 57:1363-70	Not sample size of interest (< 1,000 for NRS)
Durelli, L.,Ferrero, B.,Oggero, A.,Verdun, E.,Ghezzi, A.,Montanari, E.,Zaffaroni, M.. Thyroid function and autoimmunity during interferon beta-1b treatment: a multicenter prospective study. J Clin Endocrinol Metab. 2001. 86:3525-32	Not sample size of interest (< 1,000 for NRS)
Eagle, T.,Stuart, F.,Chua, A. S.,LaRussa, A.,Leclaire, K.,Cook, S. L.,Chitnis, T.,Weiner, H. L.,Glanz, B. I.,Healy, B. C. (2017). Treatment satisfaction across injectable, infusion, and oral disease-modifying therapies for multiple sclerosis Multiple Sclerosis and Related Disorders, 18, 196-201	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
Ebers GC, Hommes O, Hughes RAC, et al. Randomised double blind placebo controlled study of interferon beta 1a in relapsing/remitting multiple sclerosis. *Lancet*. 1998;352:1498-1504. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00225610/full.	Other Not placebo-controlled trial of interest
Ebrahimi Monfared M., S. Shapoori, G. Mosayebi, B. Khansarinejad, A. Ghazavi, M. Rezagholizamenjany, A. Ganji (2019). Assessment of CCL27 and IL-11 in Multiple Sclerosis Patients Treated with Interferon-beta and Glatiramer Acetate Neuroimmunomodulation, 26(6), 301-306	Not outcomes of interest
Edgar, C. M.,Brunet, D. G.,Fenton, P.,McBride, E. V.,Green, P.. Lipoatrophy in patients with multiple sclerosis on glatiramer acetate. Can J Neurol Sci. 2004. 31:58-63	Not sample size of interest (< 1,000 for NRS)
Elliott, C.,Belachew, S.,Wolinsky, J. S.,Hauser, S. L.,Kappos, L.,Barkhof, F.,Bernasconi, C.,Fecker, J.,Model, F.,Wei, W.,Arnold, D. L. (2019). Chronic white matter lesion activity predicts clinical progression in primary progressive multiple sclerosis 1(9), 2787-2799	Not a sister publication of interest
Enjeti, A. K.,D'Crus, A.,Melville, K.,Verrills, N. M.,Rowlings, P. (2016). A systematic evaluation of the safety and toxicity of fingolimod for its potential use in the treatment of acute myeloid leukaemia Anti-Cancer Drugs, 27(6), 560-8	Not population of interest
Erbay, O.,Usta Yesilbalkan, O.,Yuceyar, N. (2018). Factors Affecting the Adherence to Disease-Modifying Therapy in Patients With Multiple Sclerosis Journal of Neuroscience Nursing, 50(5), 291-297	Not sample size of interest (< 1,000 for NRS)
Eriksson, I.,Komen, J.,Piehl, F.,Malmstrom, R. E.,Wettermark, B.,von Euler, M. (2018). The changing multiple sclerosis treatment landscape: impact of new drugs and treatment recommendations European Journal of Clinical Pharmacology, 74(5), 663-670	Not outcomes of interest
Ernst, F. R.,Barr, P.,Elmor, R.,Wong, S. L. (2017). Relapse outcomes, safety, and treatment patterns in patients diagnosed with relapsing-remitting multiple sclerosis and initiated on subcutaneous interferon beta-1a or dimethyl fumarate: a real-world study Current Medical Research & Opinion, 33(12), 2099-2106	Not sample size of interest (< 1,000 for NRS)
Etemadifar, M.,Janghorbani, M.,Shaygannejad, V.. Comparison of interferon beta products and azathioprine in the treatment of relapsing-remitting multiple sclerosis. J Neurol. 2007. 254:1723-8	Not comparator of interest
Evangelopoulos, M. E.,Miclea, A.,Schrewe, L.,Briner, M.,Salmen, A.,Engelhardt, B.,Huwiler, A.,Chan, A.,Hoepner, R. (2018). Frequency and clinical characteristics of Multiple Sclerosis rebounds after withdrawal of Fingolimod CNS Neuroscience & Therapeutics, 24(10), 984-986	Not relevant publication type
Evans, C.,Marrie, R. A.,Zhu, F.,Leung, S.,Lu, X.,Kingwell, E.,Zhao, Y.,Tremlett, H. (2017). Adherence to disease-modifying therapies for multiple sclerosis and subsequent hospitalizations Pharmacoepidemiology & Drug Safety, 26(6), 702-711	Not comparator of interest
Evdoshenko E. P., N. A. Neofidov, K. Z. Bakhtiyarova, M. V. Davydovskaya, E. I. Kairbekova, Y. M. Kolontareva, N. A. Malkova, M. M. Odinak, E. V. Popova, D. V. Sazonov, I. D. Stolyarov, I. V. Smagina, A. S. Fedyanin, F. A. Habirov, T. I. Khaibullin, N. V. Khachanova, I. A. Shchukin, A. N. Boyko (2019). [The efficacy and safety of siponimod in the Russian population of patients with secondary progressive multiple sclerosis] Zh Nevrol Psikhiatr Im S S Korsakova, 119(10. Vyp. 2), 110-119	Not in English

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Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. *Neurology*. 1999;53(4):679-686. doi: 10.1212/wnl.53.4.679.	Other Not placebo-controlled trial of interest
Faissner, S.,Gold, R. (2019). Oral Therapies for Multiple Sclerosis. [Review] 1(1),	Not relevant publication type
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Farley, S.,Gottesman, M. H.,Friedman-Urevich, S.,Ye, J.,Shen, M.,Grueneberg, D.,Martone, L.,Calixte, R. (2019). Anti-John Cunningham virus antibody index levels in multiple sclerosis patients treated with rituximab, fingolimod, and dimethyl fumarate 1, 59	Not sample size of interest (< 1,000 for NRS)
Farrell, R.,Kapoor, R.,Leary, S.,Rudge, P.,Thompson, A.,Miller, D.,Giovannoni, G.. Neutralizing anti-interferon beta antibodies are associated with reduced side effects and delayed impact on efficacy of Interferon-beta. Mult Scler. 2008. 14:212-8	Not sample size of interest (< 1,000 for NRS)
Fernández, Ó,Giovannoni, G.,Fox, R. J.,Gold, R.,Phillips, J. T.,Potts, J.,Okwuokenye, M.,Marantz, J. L. (2017). Efficacy and Safety of Delayed-release Dimethyl Fumarate for Relapsing-remitting Multiple Sclerosis in Prior Interferon Users: an Integrated Analysis of DEFINE and CONFIRM Clinical therapeutics, 39(8), 1671-1679	Not comparator of interest
Fernandez, O. (2017). Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS? Multiple Sclerosis and Related Disorders, 17, 75-83	Not relevant publication type
Fernandez, O.,Arbizu, T.,Izquierdo, G.,Martinez-Yelamos, A.,Gata, J. M.,Luque, G.,de Ramon, E.. Clinical benefits of interferon beta-1a in relapsing-remitting MS: a phase IV study. Acta Neurol Scand. 2003. 107:7-11	Not sample size of interest (< 1,000 for NRS)
Fernandez, O.,Duran, E.,Ayuso, T.,Hernandez, L.,Bonaventura, I.,Forner, M.,Stick Study Investigators Group (2017). Treatment satisfaction with injectable disease-modifying therapies in patients with relapsing-remitting multiple sclerosis (the STICK study) PLoS ONE [Electronic Resource], 12(10), e0185766	Not sample size of interest (< 1,000 for NRS)
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Fernandez, O.,Mayorga, C.,Luque, G.,Guerrero, M.,Guerrero, R.,Leyva, L.,Leon, A.,Blanca, M.. Study of binding and neutralising antibodies to interferon-beta in two groups of relapsing-remitting multiple sclerosis patients. J Neurol. 2001. 248:383-8	Not sample size of interest (< 1,000 for NRS)
Ferraro, D.,Camera, V.,Baldi, E.,Vacchiano, V.,Curti, E.,Guareschi, A.,Malagu, S.,Montepietra, S.,Strumia, S.,Santangelo, M.,Caniatti, L.,Foschi, M.,Lugaresi, A.,Granella, F.,Pesci, I.,Motti, L.,Neri, W.,Immovilli, P.,Montanari, E.,Vitetta, F.,Simone, A. M.,Sola, P. (2018). First-line disease-modifying drugs in relapsing-remitting multiple sclerosis: an Italian real-life multicenter study on persistence 1(10), 1803-1807	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
Ferraro, D.,Camera, V.,Vitetta, F.,Zennaro, M.,Ciolli, L.,Nichelli, P. F.,Sola, P. (2018). Acute coronary syndrome associated with alemtuzumab infusion in multiple sclerosis Neurology, 90(18), 852-854	Not relevant publication type
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Findling O., L. Hauer, T. Pezawas, P. S. Rommer, W. Struhal, J. Sellner (2020). Cardiac Autonomic Dysfunction in Multiple Sclerosis: A Systematic Review of Current Knowledge and Impact of Immunotherapies J Clin Med, 9(2), 24	Not relevant publication type
Fingolimod for relapsing-remitting multiple sclerosis. 2016. http://dx.doi.org/10.1002/14651858.CD009371.pub2.	Other
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Flechter, S.,Vardi, J.,Pollak, L.,Rabey, J. M.. Comparison of glatiramer acetate (Copaxone) and interferon beta-1b (Betaferon) in multiple sclerosis patients: an open-label 2-year follow-up. J Neurol Sci. 2002. 197:51-5	Not sample size of interest (< 1,000 for NRS)
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Forsberg, L.,Johansson, S.,Hillert, J.,Nilsson, P.,Dahle, C.,Sveningsson, A.,Lycke, J.,Landtblom, A. M.,Burman, J.,Walentin, F.,et al., (2016). A Swedish nationwide pharmaco-epidemiological and genetic study of the long-term safety and effectiveness of dimethyl fumarate (IMSE 5) Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 338-339	Not relevant publication type
Forster, M.,Kury, P.,Aktas, O.,Warnke, C.,Havla, J.,Hohlfeld, R.,Mares, J.,Hartung, H. P.,Kremer, D. (2019). Managing Risks with Immune Therapies in Multiple Sclerosis. [Review] 1(5), 633-647	Not relevant publication type
Fox R. J., R. Gold, J. T. Phillips, M. Okwuokenye, A. Zhang, J. L. Marantz (2017). Efficacy and Tolerability of Delayed-release Dimethyl Fumarate in Black, Hispanic, and Asian Patients with Relapsing-Remitting Multiple Sclerosis: Post Hoc Integrated Analysis of DEFINE and CONFIRM 1(2), 175-187	Not comparator of interest

Reference	Reason for Exclusion
Fox, E. J.,Markowitz, C.,Applebee, A.,Montalban, X.,Wolinsky, J. S.,Belachew, S.,Fiore, D.,Pei, J.,Musch, B.,Giovannoni, G. (2018). Ocrelizumab reduces progression of upper extremity impairment in patients with primary progressive multiple sclerosis: Findings from the phase III randomized ORATORIO trial Multiple Sclerosis, 24(14), 1862-1870	Not a sister publication of interest
Fox, E. J.,Wynn, D.,Coles, A. J.,Palmer, J.,Margolin, D. H.,Camms Investigators (2016). Alemtuzumab improves neurological functional systems in treatment-naive relapsing-remitting multiple sclerosis patients Journal of the Neurological Sciences, 363, 188-94	Not a sister publication of interest
Fox, E.,Lovett-Racke, A.,Inglese, M.,Wray, S.,Racke, M.,Shubin, R.,Eubanks, J.,Su, W. (2017). Patient characteristics, safety, and preliminary results of a placebo controlled, phase 2a multicenter study of ublituximab (UTX), a novel glycoengineered anti-CD20 monoclonal antibody (mAb), in patients with relapsing forms of multiple sclerosis Multiple sclerosis journal, 23(3), 407-	Not relevant publication type
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Fox, R. J.,Chan, A.,Zhang, A.,Xiao, J.,Levison, D.,Lewin, J. B.,Edwards, M. R.,Marantz, J. L. (2017). Comparative effectiveness using a matching-adjusted indirect comparison between delayed-release dimethyl fumarate and fingolimod for the treatment of multiple sclerosis Current Medical Research & Opinion, 33(2), 175-183	Not a sister publication of interest
Fox, R. J.,Coffey, C. S.,Conwit, R.,Cudkowicz, M. E.,Gleason, T.,Goodman, A.,Klawiter, E. C.,Matsuda, K.,McGovern, M.,Naismith, R. T.,et al., (2018). Phase 2 trial of ibudilast in progressive multiple sclerosis New england journal of medicine, 379(9), 846-855	Not intervention of interest
Fox, R. J.,Coffey, C. S.,Cudkowicz, M. E.,Gleason, T.,Goodman, A.,Klawiter, E. C.,Matsuda, K.,McGovern, M.,Conwit, R.,Naismith, R.,et al., (2016). Design, rationale, and baseline characteristics of the randomized double-blind phase II clinical trial of ibudilast in progressive multiple sclerosis Contemporary clinical trials, 50, 166-177	Not relevant publication type
Fox, R.,Arnold, D. L.,Bar-Or, A.,Cree, B.,Giovannoni, G.,Gold, R.,Vermersch, P.,Pohlmann, H.,Sidorenko, T.,Wolf, C.,et al., (2017). Effects of siponimod on MRI outcomes in patients with secondary progressive multiple sclerosis: results of the phase 3 EXPAND study Multiple sclerosis journal, 23(3), 34-35	Not relevant publication type
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Reference	Reason for Exclusion
Frau, J.,Sacca, F.,Signori, A.,Baroncini, D.,Fenu, G.,Annovazzi, P.,Capobianco, M.,Signoriello, E.,Laroni, A.,La Gioia, S.,Sartori, A.,Maniscalco, G. T.,Bonavita, S.,Clerico, M.,Russo, C. V.,Gallo, A.,Lapucci, C.,Carotenuto, A.,Sormani, M. P.,Cocco, E.,i-Mu, S. T. study group (2019). Outcomes after fingolimod to alemtuzumab treatment shift in relapsing-remitting MS patients: a multicentre cohort study 1(10), 2440-2446	Not sample size of interest (< 1,000 for NRS)
Frau, J.,Sormani, M. P.,Signori, A.,Realmuto, S.,Baroncini, D.,Annovazzi, P.,Signoriello, E.,Maniscalco, G. T.,La Gioia, S.,Cordioli, C.,Frigeni, B.,Rasia, S.,Fenu, G.,Grasso, R.,Sartori, A.,Lanzillo, R.,Stromillo, M. L.,Rossi, S.,Forci, B.,Cocco, E.,i-Mu, S. T. study group (2018). Clinical activity after fingolimod cessation: disease reactivation or rebound? European Journal of Neurology, 25(10), 1270-1275	Not sample size of interest (< 1,000 for NRS)
Freedman M. S., G. Comi, P. K. Coyle, J. Aldridge, L. Chen, K. Marhardt, L. Kappos (2019). No evidence of disease activity status in patients treated with early vs. delayed subcutaneous interferon beta-1a Multiple Sclerosis and Related Disorders, 39, 101891	Not a sister publication of interest
Freedman MS, Francis GS, Sanders EA, et al. Randomized study of once-weekly interferon beta-1la therapy in relapsing multiple sclerosis: three-year data from the OWIMS study. *Multiple sclerosis (houndmills, basingstoke, england).* 2005;11(1):41-45. doi: 10.1191/1352458505ms1126oa.	Not sister publication of interest
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Freedman MS, Wolinsky JS, Wamil B, et al. Teriflunomide added to interferon-β in relapsing multiple sclerosis: a randomized phase II trial. *Neurology.* 2012;78(23):1877-1885. doi: 10.1212/WNL.0b013e318258f7d4.	Other Not placebo-controlled trial of interest
Freedman, M. S.,Brod, S.,Singer, B. A.,Cohen, B. A.,Hayward, B.,Dangond, F.,Coyle, P. K. (2019). Clinical and MRI efficacy of sc IFN beta-1a tiw in patients with relapsing MS appearing to transition to secondary progressive MS: post hoc analyses of PRISMS and SPECTRIMS Journal of Neurology, 26, 26	Not a sister publication of interest
Freedman, M. S.,Duquette, P.,Grand'Maison, F.,Lee, L.,Vorobeychik, G.,Lara, N.,Khurana, V.,Nakhaipour, H. R.,Schecter, R.,Haddad, P. (2019). The clinical and cost impact of switching to fingolimod versus other first line injectable disease-modifying therapies in patients with relapsing multiple sclerosis 1(5), 767-776	Not sample size of interest (< 1,000 for NRS)
Freedman, M. S.,Kappos, L.,Edan, G.,Hartung, H. P.,Montalban, X.,Barkhof, F.,Wicklein, E. M.,Koelbach, R. (2019). Long-term clinical outcomes in patients with CIS treated with interferon beta-1B: first results from benefit 15 Multiple sclerosis journal, 25, 50-51	Not relevant publication type
Freedman, M. S.,Montalban, X.,Miller, A. E.,Dive-Pouletty, C.,Hass, S.,Thangavelu, K.,Leist, T. P. (2016). Comparing outcomes from clinical studies of oral disease-modifying therapies (dimethyl fumarate, fingolimod, and teriflunomide) in relapsing MS: Assessing absolute differences using a number needed to treat analysis Multiple Sclerosis and Related Disorders, 10, 204-212	Not a sister publication of interest
Freedman, M. S.,Morawski, J.,Thangavelu, K. (2018). Clinical efficacy of teriflunomide over a fixed 2-year duration in the TOWER study 1(2), 2055217318775236	Not a sister publication of interest

Reference	Reason for Exclusion
Freedman, M. S.,Wolinsky, J. S.,Comi, G.,Kappos, L.,Olsson, T. P.,Miller, A. E.,Thangavelu, K.,Benamor, M.,Truffinet, P.,O'Connor, P. W.,Temso,,Tower Study Groups (2018). The efficacy of teriflunomide in patients who received prior disease-modifying treatments: Subgroup analyses of the teriflunomide phase 3 TEMSO and TOWER studies Multiple Sclerosis, 24(4), 535-539	Not a sister publication of interest
Freedman, M.,Comi, G.,Coyle, P. K.,Aldridge, J.,Marhardt, K.,Kappos, L. (2018). Impact of Gadolinium-enhancing (GD+) Lesions on No Evidence of Disease Activity (NEDA) Status in Subcutaneous Interferon Beta-1a (SC IFNβ-1a)-treated Patients Multiple sclerosis and related disorders, 26, 239-240	Not relevant publication type
Freeman, S.,Selmaj, K.,Fernandez, O.,Grimaldi, L.,Silber, E.,Pardo, G.,Freedman, S. M.,Zhang, Y.,Xu, L.,Mellion, M.,et al., (2016). Safety and tolerability of opicinumab in relapsing multiple sclerosis: the Phase 2b SYNERGY trial Multiple sclerosis (houndmills, basingstoke, england), 22, 323-324	Not relevant publication type
Gaetano, L.,Haring, D. A.,Radue, E. W.,Mueller-Lenke, N.,Thakur, A.,Tomic, D.,Kappos, L.,Sprenger, T. (2018). Fingolimod effect on gray matter, thalamus, and white matter in patients with multiple sclerosis Neurology, 90(15), e1324-e1332	Not a sister publication of interest
Gaines, A. R.,Varricchio, F.. Interferon beta-1b injection site reactions and necroses. Mult Scler. 1998. 4:70-3	Not comparator of interest
Gaitan, M. I.,Ysrraelit, M. C.,Correale, J. (2017). Neutropenia in Patients With Multiple Sclerosis Treated With Alemtuzumab JAMA Neurology, 74(9), 1143-1144	Not relevant publication type
Gajofatto, A. (2017). Spotlight on siponimod and its potential in the treatment of secondary progressive multiple sclerosis: the evidence to date Drug design, development & therapy, 11, 3153-3157	Not relevant publication type
Gasim M, Bernstein CN, Graff LA, et al. Adverse psychiatric effects of disease-modifying therapies in multiple Sclerosis: A systematic review. *Multiple Sclerosis and Related Disorders*. 2018;26:124-156. doi: https://dx.doi.org/10.1016/j.msard.2018.09.008.	Other
Gasperini, C.,Prosperini, L.,Tintore, M.,Sormani, M. P.,Filippi, M.,Rio, J.,Palace, J.,Rocca, M. A.,Ciccarelli, O.,Barkhof, F.,Sastre-Garriga, J.,Vrenken, H.,Frederiksen, J. L.,Yousry, T. A.,Enzinger, C.,Rovira, A.,Kappos, L.,Pozzilli, C.,Montalban, X.,De Stefano, N.,the, Magnims Study Group (2019). Unraveling treatment response in multiple sclerosis: A clinical and MRI challenge. [Review] 1(4), 180-192	Not relevant publication type
Ghalie, R. G.,Edan, G.,Laurent, M.,Mauch, E.,Eisenman, S.,Hartung, H. P.,Gonsette, R. E.,Butine, M. D.,Goodkin, D. E.. Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. Neurology. 2002. 59:909-13	Not intervention of interest
Ghalie, R. G.,Mauch, E.,Edan, G.,Hartung, H. P.,Gonsette, R. E.,Eisenmann, S.,Le Page, E.,Butine, M. D.,De Goodkin, D. E.. A study of therapy-related acute leukaemia after mitoxantrone therapy for multiple sclerosis. Mult Scler. 2002. 8:441-5	Not intervention of interest
Ghasami, K.,Faraji, F.,Fazeli, M.,Ghazavi, A.,Mosayebi, G. (2016). Interferon β-1a and Atorvastatin in the Treatment of Multiple Sclerosis Iranian journal of immunology, 13(1), 16-26	Not intervention of interest

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Ghezzi, A.,Chitnis, T.,K. Laflamme A,Meinert, R.,Haring, D. A.,Pohl, D. (2019). Long-Term Effect of Immediate Versus Delayed Fingolimod Treatment in Young Adult Patients with Relapsing-Remitting Multiple Sclerosis: Pooled Analysis from the FREEDOMS/FREEDOMS II Trials Neurology & Therapy, 19, 19	Not a sister publication of interest
Giovannni, G.,Comi, G.,Cook, S.. Analysis of clinical and radiological disease activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets, in the doulbe-blind, 96-week CLARITY study. Jornal of neurology. 2010. 257:S21, Abstract	Not relevant publication type
Giovannoni G, Barbarash O, Casset-Semanaz F, et al. Safety and immunogenicity of a new formulation of interferon (beta)-1a (Rebif(registered trademark) New Formulation) in a Phase IIIb study in patients with relapsing multiple sclerosis: 96-week results. *Multiple sclerosis (houndmills, basingstoke, england).* 2009;15(2):219-228. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00691435/full.	Not sister publication of interest
Giovannoni G., P. A. Brex, D. Dhiraj, J. Fullarton, M. Freddi, B. Rodgers-Gray, K. Schmierer (2019). Glatiramer acetate as a clinically and cost-effective treatment of relapsing multiple sclerosis over 10 years of use within the National Health Service: Final results from the UK Risk Sharing Scheme Mult Scler J Exp Transl Clin, 5(4), 2055217319893103	Not relevant publication type
Giovannoni, G. (2017). Cladribine to Treat Relapsing Forms of Multiple Sclerosis Neurotherapeutics, 14(4), 874-887	Not relevant publication type
Giovannoni, G.,Arnold, D. L.,Bar-Or, A.,Comi, G.,Hartung, H. P.,Havrdova, E.,Kappos, L.,Lublin, F.,Selmaj, K.,Traboulsee, A.,et al., (2016). NEDA epoch analysis of patients with relapsing multiple sclerosis treated with ocrelizumab: results from OPERA I and OPERA II, phase III studies Multiple sclerosis (houndmills, basingstoke, england), 22, 837-838	Not relevant publication type
Giovannoni, G.,Arnold, D. L.,Bar-Or, A.,De Seze, J.,Hemmer, B.,Montalban, X.,Rammohan, K. W.,Belachew, S.,Bernasconi, C.,Chin, P.,et al., (2016). An exploratory analysis of 12-and 24-week composite confirmed disability progression in patients with primary progressive multiple sclerosis in the ORATORIO trial Multiple sclerosis (houndmills, basingstoke, england), 22, 371-372	Not relevant publication type
Giovannoni, G.,Cohen, J. A.,Coles, A. J.,Hartung, H. P.,Havrdova, E.,Selmaj, K. W.,Margolin, D. H.,Lake, S. L.,Kaup, S. M.,Panzara, M. A.,et al., (2016). Alemtuzumab improves preexisting disability in active relapsing-remitting MS patients Neurology, 87(19), 1985-1992	Not a sister publication of interest
Giovannoni, G.,Comi, G.,Cook, S.,Rammohan, K.,Rieckmann, P.,Soelberg-Sorensen, P.,Vermersch, P.,Hicking, C.,Adeniji, A.,Dangond, F. (2016). Durable efficacy of cladribine tablets in patients with multiple sclerosis: analysis of relapse rates and relapse-free patients in the CLARITY and CLARITY Extension studies Multiple sclerosis (houndmills, basingstoke, england), 22, 48-49	Not relevant publication type
Giovannoni, G.,Comi, G.,Cook, S.,Rammohan, K.,Rieckmann, P.,Soelberg-Sorensen, P.,Vermersch, P.,Hicking, C.,Adeniji, A.,Dangond, F.,et al., (2018). Analysis of relapse rates and relapse-free patients in the CLARITY and CLARITY extension studies Multiple sclerosis journal, 24(3), 396-	Not relevant publication type
Giovannoni, G.,Comi, G.,Cook, S.,Rammohan, K.,Rieckmann, P.,Soelberg-Sorensen, P.. Safety and efficacy of oral cladribine in patients with relapsing-	Not relevant publication type

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remitting multiple sclerosis: results from the 96 week phase IIIB extension trial to the clarity study. . 2013. 80:	
Giovannoni, G.,Comi, G.,Cook, S.,Rieckmann, P.,Rammohan, K.,Soelberg-Soerensen, P.,Vermersch, P.,Martin, E.,Dangond, F. (2018). Efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis (RRMS) in the 120-week extension to the CLARITY study Multiple sclerosis journal, 24(2), NP6-NP7	Not relevant publication type
Giovannoni, G.,Comi, G.,Cook, S.,Rieckmann, P.,Rammohan, K.,Soelberg-Sorensen, P.,Vermersch, P.,Adeniji, A.,Dangond, F. (2016). Benefits of cladribine tablets on the proportion of patients with multiple sclerosis free from clinical and radiological indicators of disease activity in the CLARITY EXTENSION study Multiple sclerosis (houndmills, basingstoke, england), 22, 300-301	Not relevant publication type
Giovannoni, G.,Comi, G.,Cook, S.. Clinical outcomes of short-course oral treatment with cladribine tablets for relapsing-remitting multiple sclerosis (RRMS) in the 96-week, phase III, double-blind, placebo-controlled CLARITY study. Journal of the neurological sciences. 2009. 285:S114, Abstract	Not relevant publication type
Giovannoni, G.,Comi, G.,Montalban, X.,Hicking, C.,Dangond, F. (2016). Benefits of cladribine tablets on magnetic resonance imaging (MRI) outcomes in patients with multiple sclerosis: analysis of pooled double-blind data from the CLARITY and ONWARD studies Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 304	Not relevant publication type
Giovannoni, G.,Montalban, X.,Hicking, C.,Dangond, F. (2016). Benefits of cladribine tablets on the achievement of no evidence of disease activity (NEDA) status in patients with multiple sclerosis: analysis of pooled double-blind data from the CLARITY and ONWARD studies Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 303-304	Not relevant publication type
Giovannoni, G.,Montalban, X.,Hicking, C.,Dangond, F. (2016). Benefits of cladribine tablets on relapse rates and disability progression in patients with multiple sclerosis: analysis of pooled double-blind data from the CLARITY and ONWARD studies Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 305	Not relevant publication type
Giovannoni, G.,Rammohan, K.,Cook, S.,Comi, G.,Rieckmann, P.,Soelberg-Sorensen, P.,Vermersch, P.,Dangond, F.,Hicking, C. (2017). Effects of cladribine tablets on radiological outcomes in high disease activity (HDA) subgroups of patients with relapsing multiple sclerosis (RMS) in the CLARITY study Multiple sclerosis journal, 23(3), 613-614	Not relevant publication type
Giovannoni, G.,Rammohan, K.,Cook, S.,Comi, G.,Rieckmann, P.,Soelberg-Sorensen, P.,Vermersch, P.,Dangond, F.,Hicking, C.,King, J. (2018). Efficacy of cladribine tablets 3.5 mg/kg in high disease activity (HDA) subgroups of patients with relapsing multiple sclerosis (RMS) in the CLARITY study Multiple sclerosis journal, 24(3), 396-397	Not relevant publication type

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Giovannoni, G.,Soelberg Sorensen, P.,Butzkueven, H.,Comi, G.,Cook, S.,Rammohan, K.,Rieckmann, P.,Vermersch, P.,Bock, D.,Weiner, J.,et al.,. Mitigating severe lymphopenia: post hoc analysis of data from the 96-week CLARITY study. Multiple sclerosis.. 2011. 17:S454-S455	Not relevant publication type
Gobbi, C.,Zecca, C.,Linnebank, M.,Muller, S.,You, X.,Meier, R.,Borter, E.,Traber, M.. Swiss analysis of multiple sclerosis: a multicenter, non-interventional, retrospective cohort study of disease-modifying therapies. Eur Neurol. 2013. 70:35-41	Not sample size of interest (< 1,000 for NRS)
Gold, R.,Giovannoni, G.,Phillips, J. T.,Fox, R. J.,Xiao, J.,Taylor, C.,Marantz, J. L. (2016). Seven-year follow-up of the efficacy of delayed-release dimethyl fumarate in newly diagnosed patients with relapsing-remitting multiple sclerosis: integrated analysis of DEFINE, CONFIRM, and ENDORSE Multiple sclerosis (houndmills, basingstoke, england), 22, 296-297	Not relevant publication type
Gold, R.,Giovannoni, G.,Phillips, J. T.,Fox, R. J.,Yang, L.,Taylor, C. (2017). Efficacy of delayed-release dimethyl fumarate in newly diagnosed patients with relapsing-remitting multiple sclerosis: eight-year follow-up of an integrated analysis of DEFINE, CONFIRM, and ENDORSE Multiple sclerosis journal, 23(3), 313-314	Not relevant publication type
Gold, R.,Giovannoni, G.,Selmaj, K.,Havrdova, E.,Montalban, X.,Radue, E. W.,Stefoski, D.,Robinson, R.,Riester, K.,Rana, J.,Elkins, J.,O'Neill, G.,Select study investigators. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. Lancet. 2013. 381:2167-75	Not intervention of interest
Gold, R.,Schlegel, E.,Elias-Hamp, B.,Albert, C.,Schmidt, S.,Tackenberg, B.,Xiao, J.,Schaak, T.,Salmen, H. C. (2018). Incidence and mitigation of gastrointestinal events in patients with relapsing-remitting multiple sclerosis receiving delayed-release dimethyl fumarate: a German phase IV study (TOLERATE) 1, 1756286418768775	Not comparator of interest
Goodin D, O'Connor P, Hartung HP. Neutralizing antibodies during treatment with interferon beta-1b in 1745 patients with relapsing-remitting multiple sclerosis. *Neurology*. 2009;72(11 Suppl 3):A317, Abstract. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00775587/full.	Other Systematic review (not checked)
Goodin, D. S.,Reder, A. T.,Koelbach, R.,Pohl, C.,Wicklein, E. M. (2016). Contribution of clinical and MRI to evaluation of NEDA (No Evidence of Disease Activity) from the pivotal trial of interferon beta-1b in multiple sclerosis Multiple sclerosis (houndmills, basingstoke, england), 22, 837-	Not relevant publication type
Goodin, D. S.,Reder, A. T.,Traboulsee, A. L.,Li, D. K. B.,Langdon, D.,Cutter, G.,Cook, S.,O'Donnell, T.,Kremenchutzky, M.,Oger, J.,et al., (2018). Predictive validity of NEDA in the 16- and 21-year follow-up from the pivotal trial of interferon beta-1b Multiple sclerosis journal,	Not a sister publication of interest
Goodin, D. S.,Reder, A. T.,Traboulsee, A. L.,Li, D. K.,Langdon, D.,Cutter, G.,Cook, S.,O'Donnell, T.,Kremenchutzky, M.,Oger, J.,Koelbach, R.,Pohl, C.,Wicklein, E. M.,Ifnb Multiple Sclerosis Study Group,the,,Year, L. T. F. Investigators (2019). Predictive validity of NEDA in the 16- and 21-year follow-up from the pivotal trial of interferon beta-1b 1(6), 837-847	Not a sister publication of interest
Gorrod, H. B.,Latimer, N. R.,Damian, D.,Hettle, R.,Harty, G. T.,Wong, S. L. (2019). Impact of Nonrandomized Dropout on Treatment Switching Adjustment in the Relapsing-Remitting Multiple Sclerosis CLARITY Trial and the CLARITY Extension Study 1(7), 772-776	Not relevant publication type

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Gottberg, K.,Gardulf, A.,Fredrikson, S.. Interferon-beta treatment for patients with multiple sclerosis: the patients' perceptions of the side-effects. Mult Scler. 2000. 6:349-54	Not sample size of interest (< 1,000 for NRS)
Granqvist, M.,Boremalm, M.,Poorghobad, A.,Svenningsson, A.,Salzer, J.,Frisell, T.,Piehl, F. (2018). Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis JAMA Neurology, 75(3), 320-327	Not sample size of interest (< 1,000 for NRS)
Grebenciucova, E.,Pruitt, A. (2017). Infections in Patients Receiving Multiple Sclerosis Disease-Modifying Therapies Current Neurology & Neuroscience Reports, 17(11), 88	Not relevant publication type
Guarnera, C.,Bramanti, P.,Mazzon, E. (2017). Alemtuzumab: a review of efficacy and risks in the treatment of relapsing remitting multiple sclerosis. [Review] 1, 871-879	Not relevant publication type
Guarnera, C.,Bramanti, P.,Mazzon, E. (2017). Comparison of efficacy and safety of oral agents for the treatment of relapsing-remitting multiple sclerosis Drug design, development & therapy, 11, 2193-2207	Not relevant publication type
Guger, M.,Enzinger, C.,Leutmezer, F.,Kraus, J.,Kalcher, S.,Kvas, E.,Berger, T.,Austrian, M. S. Treatment Registry (2019). Real-life use of oral disease-modifying treatments in Austria Acta Neurologica Scandinavica, 140(1), 32-39	Not sample size of interest (< 1,000 for NRS)
Guger, M.,Enzinger, C.,Leutmezer, F.,Kraus, J.,Kalcher, S.,Kvas, E.,Berger, T.,Austrian, M. S. Treatment Registry (2019). Switching from natalizumab to fingolimod treatment in multiple sclerosis: real life data from the Austrian MS Treatment Registry Journal of Neurology, 16, 16	Not sample size of interest (< 1,000 for NRS)
Guger, M.,Enzinger, C.,Leutmezer, F.,Kraus, J.,Kalcher, S.,Kvas, E.,Berger, T. (2019). Real-life use of oral disease-modifying treatments in Austria Acta neurologica Scandinavica, 140(1), 32-39	Not sample size of interest (< 1,000 for NRS)
Guo, J. D.,Das Gupta, R. J.,Fahrbach, K.,Wissinger, E.,Cox, F. M. (2016). A network meta-analysis comparing alemtuzumab to natalizumab in patients with relapsing-remitting multiple sclerosis with rapidly evolving severe disease Multiple sclerosis (houndmills, basingstoke, england), 22, 772-	Not relevant publication type
Haartsen, J.,Spelman, T.,Baker, J.,Agland, S.,Lechner-Scott, J.,Burke, T.,Vucic, S.,Rath, L.,Skibina, O.,Toubia, M.,et al., (2016). MSFIRST-utilising a longitudinal, prospective, comparative drug safety module for use in everyday MS clinical practice to evaluate and track incidence and characteristics of safety outcomes in MS patients on therapy over the long term Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 342-343	Not relevant publication type
Haas, J.,Firzlaff, M.. Twenty-four-month comparison of immunomodulatory treatments - a retrospective open label study in 308 RRMS patients treated with beta interferons or glatiramer acetate (Copaxone). Eur J Neurol. 2005. 12:425-31	Not sample size of interest (< 1,000 for NRS)
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Haase, R.,Kullmann, J. S.,Ziemssen, T. (2016). Therapy satisfaction and adherence in patients with relapsing-remitting multiple sclerosis: the THEPA-MS survey 1(4), 250-63	Not outcomes of interest
Halpern, A. B.,Anwar, A.,Scott, B. L.,Becker, P. S.,Othus, M.,Hendrie, P. C.,Ranker, E. M.,Perdue, A.,Heather, A. Smith,Chen, T. L.,et al.,. Phase 1 trial of G-CSF, cladribine, cytarabine, and dose-escalated mitoxantrone (G-CLAM) in adults with newly diagnosed AML or high-risk MDS. Clinical lymphoma, myeloma & leukemia. 2015. 15:S11	Not relevant publication type
Halpern, R.,Agarwal, S.,Borton, L.,Oneacre, K.,Lopez-Bresnahan, M. V.. Adherence and persistence among multiple sclerosis patients after one immunomodulatory therapy failure: retrospective claims analysis. Adv Ther. 2011. 28:761-75	Not comparator of interest
Hang, Y.,Hu, X.,Zhang, J.,Liu, S.,Deykin, A.,Nestorov, I. (2016). Analysis of peginterferon β-1a exposure and Gd-enhanced lesion or T2 lesion response in relapsing-remitting multiple sclerosis patients Journal of pharmacokinetics and pharmacodynamics, 43(4), 371-383	Not a sister publication of interest
Hartung D. M., K. A. Johnston, J. Geddes, D. N. Bourdette (2020). Effect of generic glatiramer acetate on spending and use of drugs for multiple sclerosis Neurology, 15, 15	Not outcomes of interest
Hartung, H. P.,Arnold, D. L.,Bar-Or, A.,Comi, G.,De Seze, J.,Giovannoni, G.,Hauser, S. L.,Hemmer, B.,Kappos, L.,Lublin, F.,et al., (2016). Infections and serious infections with ocrelizumab in relapsing multiple sclerosis and primary progressive multiple sclerosis Multiple sclerosis (houndmills, basingstoke, england), 22, 658-659	Not relevant publication type
Hartung, H. P.,Graf, J.,Kremer, D. (2019). Long-term follow-up of multiple sclerosis studies and outcomes from early treatment of clinically isolated syndrome in the BENEFIT 11 study Journal of Neurology, 04, 04	Not relevant publication type
Hartung, H. P.,Pigeolet, E.,Li, D.,Hemmer, B.,Kappos, L.,Freedman, M. S.,Stuve, O.,Rieckmann, P.,Montalban, X.,Ziemssen, T.,et al.,. The selective sphingosine 1-phosphate receptor modulator siponimod (BAF312): magnetic resonance imaging lesion and lymphocyte relationship in a phase 2 study in relapsingremitting multiple sclerosis. Multiple sclerosis.. 2012. 18:426-427	Not relevant publication type
Hartung, H. P.,Selmaj, K.,Li, D.,Hemmer, B.,Freedman, M.,Stuve, O.. Phase 2 bold extension study safety results for siponimod (BAF312) in patients with relapsing-remitting multiple sclerosis. . 2013. 80:	Not relevant publication type
Hatam, N.,Bastani, P.,Shahtaheri, R. S. (2016). Quality of life in relapsing-remitting multiple sclerosis patients receiving CinnoVex compared with Avonex 1(3), 181-5	Not sample size of interest (< 1,000 for NRS)
Hauser, S. L.,Comi, G.C.,Hartung, H. P.. Efficacy and safety of ocrelizumab in relapsing multiple sclerosis -results of the Phase III double-blind, interferon beta-1a-controlled OPERA I and II studies. 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis. 2015. :	Not relevant publication type
Hauser, S. L.,Kappos, L.,Montalban, X.,Guittari, C. J.,Koendgen, H.,Li, C.,Marcillat, C.,Wormser, D.,Wolinsky, J. (2018). Safety of ocrelizumab in multiple sclerosis: updated analysis in patients with relapsing and primary progressive multiple sclerosis Multiple sclerosis journal, 24(2), NP13-	Not relevant publication type
Hauser, S. L.,Kappos, L.,Montalban, X.,Guittari, C. J.,Koendgen, H.,Li, C.,Marcillat, C.,Wormser, D.,Wolinsky, J. S. (2017). Safety of ocrelizumab in multiple sclerosis: updated analysis in patients with relapsing and primary progressive multiple sclerosis Multiple sclerosis journal, 23(3), 324-325	Not relevant publication type

Reference	Reason for Exclusion
Hauser, S. L.,Wolinsky, J. S.,Brochet, B.,Montalban, X.,Naismith, R. T.,Manfrini, M.,Garas, M.,Villoslada, P.,Model, F.,Hubeaux, S.,et al., (2018). Sustained Reduction in Confirmed Disability Progression in Patients with Primary Progressive Multiple Sclerosis Treated with Ocrelizumab in the Open-label Extension Period of the Phase III ORATORIO trial Multiple sclerosis and related disorders, 26, 264-265	Not relevant publication type
Hauser, Stephen,Arnold, Douglas,Bar-Or, Amit,Comi, Giancarlo,Hartung, Hans-Peter,Lublin, Fred,Selmaj, Krzysztof,Traboulsee, Anthony,Klingelschmitt, Gaelle,Masterman, Donna,Fontoura, Paulo,Chin, Peter,Garren, Hideki,Kappos, Ludwig (2016). Efficacy of Ocrelizumab in Patients with Relapsing Multiple Sclerosis: Pooled Analysis of Two Identical Phase III, Double-Blind, Double-Dummy, Interferon Beta-1a-Controlled Studies (S49.003) Neurology, 86(16 Supplement), S49.003	Not relevant publication type
Hauser, Stephen,Brochet, Bruno,Montalban, Xavier,Naismith, Robert,Wolinsky, Jerry,Manfrini, Marianna,Garas, Monika,Villoslada, Pablo,Model, Fabian,Hubeaux, Stanislas,Kappos, Ludwig (2018). Annualized Relapse Rate and Confirmed Disability Progression in Patients Receiving Continuous Ocrelizumab or Switching From Interferon Beta-1a to Ocrelizumab Therapy in the Open-Label Extension Period of the Phase III Trials of Ocrelizumab in Patients With Relapsing Multiple Sclerosis (P1.366) Neurology, 90(15 Supplement), P1.366	Not relevant publication type
Havrdova, E.,Arnold, D. L.,Bar-Or, A.,Comi, G.,Hartung, H. P.,Kappos, L.,Lublin, F.,Selmaj, K.,Traboulsee, A.,Belachew, S.,Bennett, I.,Buffels, R.,Garren, H.,Han, J.,Julian, L.,Napieralski, J.,Hauser, S. L.,Giovannoni, G. (2018). No evidence of disease activity (NEDA) analysis by epochs in patients with relapsing multiple sclerosis treated with ocrelizumab vs interferon beta-1a 1(1), 2055217318760642	Not a sister publication of interest
Havrdova, E.,Cohen, J. A.,Horakova, D.,Kovarova, I.,Meluzinova, E. (2017). Understanding the positive benefit:risk profile of alemtuzumab in relapsing multiple sclerosis: perspectives from the Alemtuzumab Clinical Development Program. [Review] 1, 1423-1437	Not relevant publication type
Healy, B. C.,Glanz, B. I.,Zurawski, J. D.,Mazzola, M.,Chitnis, T.,Weiner, H. L. (2018). Long-term follow-up for multiple sclerosis patients initially treated with interferon-beta and glatiramer acetate Journal of the Neurological Sciences, 394, 127-131	Not sample size of interest (< 1,000 for NRS)
Healy, B.C. ,Glanz, B.I. ,Zurawski, J.D.,Mazzola, M. ,Chitnis, T. ,Weiner, H.L. (2018). Interferon-beta Versus Glatiramer Acetate as Initial Treatment for Multiple Sclerosis: Long-term Follow-up American Journal of Managed Care, 394, 127-131	Not sample size of interest (< 1,000 for NRS)
Hegen, H.,Walde, J.,Bsteh, G.,Auer, M.,Wurth, S.,Zinganell, A.,Di Pauli, F.,Deisenhammer, F.,Berger, T. (2018). Impact of Disease-Modifying Treatments on the Longitudinal Evolution of Anti-JCV Antibody Index in Multiple Sclerosis Frontiers in Immunology, 9, 2435	Not sample size of interest (< 1,000 for NRS)
Hellwig, K.,Haghikia, A.,Gold, R.. Parenthood and immunomodulation in patients with multiple sclerosis. J Neurol. 2010. 257:580-3	Not sample size of interest (< 1,000 for NRS)
Hendin, B.,Naismith, R. T.,Wray, S. E.,Huang, D.,Dong, Q.,Livingston, T.,Jones, D. L.,Watson, C.,Jhaveri, M. (2018). Treatment satisfaction significantly improves in patients with multiple sclerosis switching from interferon beta therapy to peginterferon beta-1a every 2 weeks 1, 1289-1297	Not a sister publication of interest

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Herbstritt, S.,Langer-Gould, A.,Rockhoff, M.,Haghikia, A.,Queisser-Wahrendorf, A.,Gold, R.,Hellwig, K. (2016). Glatiramer acetate during early pregnancy: A prospective cohort study Multiple Sclerosis, 22(6), 810-6	Not sample size of interest (< 1,000 for NRS)
Hermann, R.,Karlsson, M. O.,Novakovic, A. M.,Terranova, N.,Fluck, M.,Munafo, A. (2019). Correction to: The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis 1(3), 401	Not relevant publication type
Hermann, R.,Karlsson, M. O.,Novakovic, A. M.,Terranova, N.,Fluck, M.,Munafo, A. (2019). The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis. [Review] 1(3), 283-297	Not relevant publication type
Herndon RM, Rudick RA, Munschauer Iii FE, et al. Eight-year immunogenicity and safety of interferon beta-1a-Avonex® treatment in patients with multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2005;11(4):409-419. doi: 10.1191/1352458505ms1209oa.	Not sister publication of interest
Hersh, C. M.,Love, T. E.,Bandyopadhyay, A.,Cohn, S.,Hara-Cleaver, C.,Bermel, R. A.,Fox, R. J.,Cohen, J. A.,Ontaneda, D. (2017). Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 24-month follow-up 1(3), 2055217317715485	Not sample size of interest (< 1,000 for NRS)
Hersh, C. M.,Love, T. E.,Cohn, S.,Hara-Cleaver, C.,Bermel, R. A.,Fox, R. J.,Cohen, J. A.,Ontaneda, D. (2016). Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 12-month follow-up Multiple sclerosis and related disorders, 10, 44-52	Not sample size of interest (< 1,000 for NRS)
Hersh, C. M.,Vollmer, B.,Bandyopadhyay, A.,Cohn, S.,Nair, K.,Sillau, S.,Bermel, R.,Corboy, J.,Fox, R.,Vollmer, T.,et al., (2017). Comparative effectiveness and discontinuation of dimethyl fumarate and fingolimod in two large academic medical centers at 24-month follow-up Multiple sclerosis journal, 23(3), 314-315	Not relevant publication type
Hocevar, K.,Ristic, S.,Peterlin, B. (2019). Pharmacogenomics of Multiple Sclerosis: A Systematic Review. [Review] 1, 134	Not outcomes of interest
Holmoy, T.,Fevang, B.,Olsen, D. B.,Spigset, O.,Bo, L. (2019). Adverse events with fatal outcome associated with alemtuzumab treatment in multiple sclerosis 1(1), 497	Not sample size of interest (< 1,000 for NRS)
Honce, J. H.,Nair, K. V.,Stefan, S.,Brooke, V.,Ildiko, T.,Miravalle, A.,Alvarez, E.,Teri, S.,Bennett, J. L.,Corboy, J. R.,et al., (2016). Comparing rituximab induction therapy followed by glatiramer acetate therapy to glatiramer acetate monotherapy in MS patients on clinical and imaging Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 620-621	Not relevant publication type
Hosseini, A.,Masjedi, A.,Baradaran, B.,Hojjat-Farsangi, M.,Ghalamfarsa, G.,Anvari, E.,Jadidi-Niaragh, F. (2019). Dimethyl fumarate: Regulatory effects on the immune system in the treatment of multiple sclerosis. [Review] 1(7), 9943-9955	Not relevant publication type
Hu H., S. Reddell, S. Riminton, C. Chan, N. Urriola (2020). Refractory chronic spontaneous urticaria after the use of alemtuzumab in multiple sclerosis Neurol Neuroimmunol Neuroinflamm, 7(2),	Not relevant publication type
Hua, L. H.,Harris, H.,Conway, D.,Thompson, N. R. (2019). Changes in patient-reported outcomes between continuers and discontinuers of disease modifying therapy in patients with multiple sclerosis over age 60 Multiple Sclerosis and Related Disorders, 30, 252-256	Not sample size of interest (< 1,000 for NRS)

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Huber J. E., Y. Chang, I. Meinl, T. Kumpfel, E. Meinl, D. Baumjohann (2020). Fingolimod Profoundly Reduces Frequencies and Alters Subset Composition of Circulating T Follicular Helper Cells in Multiple Sclerosis Patients J Immunol, 204(5), 1101-1110	Not comparator of interest
Hunter, S. F.,Agius, M.,Miller, D. M.,Cutter, G.,Barbato, L.,McCague, K.,Meng, X.,Agashivala, N.,Chin, P.,Hollander, E. (2016). Impact of a switch to fingolimod on depressive symptoms in patients with relapsing multiple sclerosis: an analysis from the EPOC (Evaluate Patient OutComes) trial Journal of the neurological sciences, 365, 190-198	Other Study excluded from prior report
Hunter, S. F.,Cascione, M.,Thomas, F. P.,Cree, B. A. C.,Meng, X.,Schofield, L.,Tenenbaum, N. (2016). PREFERMS study: fingolimod switch effect on patient retention, key clinical outcomes and patient satisfaction Multiple sclerosis (houndmills, basingstoke, england), 22, 782-	Not relevant publication type
Hunter, S. F.,Cascione, M.,Thomas, F. P.,Fox, E.,Cree, B. A. C.,Meng, X.,Schofield, L.,Boulos, F.,Tenenbaum, N. (2017). Effect of smoking and excess body weight on safety outcomes in the PREFERMS study of treatment retention in multiple sclerosis Multiple sclerosis (houndmills, basingstoke, england), 23, 95-	Not relevant publication type
Hunter, S. F.,Cree, B. A. C.,Meng, X.,Schofield, L.,Kolodny, S.,Tenenbaum, N.,Thomas, F. P. (2017). Radiological and cognitive outcomes among patients randomized to interferon beta, glatiramer acetate or fingolimod in PREFERMS Multiple sclerosis journal, 23(3), 874-875	Not relevant publication type
Hunter, S. F.,Cree, B. A.,Meng, X.,Schofield, L.,Kolodny, S.,Tenenbaum, N.,Thomas, F. P. P. (2018). Satisfaction and efficacy outcomes when switching from injectable disease-modifying therapies to fingolimod in preferms: effect of previous treatment Multiple sclerosis journal, 24(1), 19-	Not relevant publication type
Hunter, S. F.,Thomas, F. P.,Cree, B. A.,Meng, X.,Schofield, L.,Boulos, F.,Tenenbaum, N. (2017). PREFERMS Study: fingolimod switch effect on volumetric MRI and cognitive outcomes Multiple sclerosis journal, 23(3), 614-	Not relevant publication type
Hunter, S. F.,Thomas, F. P.,Meng, X.,Schofield, L.,Tenenbaum, N.,Cree, B. A. C. (2019). Effect of treatment naiveté on MRI outcomes with fingolimod or injectable disease-modifying therapies in patients with multiple sclerosis: preferms Multiple sclerosis journal, 25, 35-36	Not relevant publication type
Hupperts, R.,Smolders, J.,Vieth, R.,Holmoy, T.,Marhardt, K.,Schluep, M.,Killestein, J.,Barkhof, F.,Beelke, M.,Grimaldi, L. M. E.,Solar Study Group (2019). Randomized trial of daily high-dose vitamin D_3 in patients with RRMS receiving subcutaneous interferon beta-1a Neurology, 08, 08	Not intervention of interest
Hutchinson M, Bar-Or A, Fox RJ, et al. Effect of BG-12 (dimethyl fumarate) in subgroups of patients with relapsing-remitting multiple sclerosis: findings from Two Phase 3 Studies (DEFINE and CONFIRM). *Multiple sclerosis*. 2013;19(5):682-683. doi: 10.1177/1352458513477288.	Other Systematic review (not checked)
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Izquierdo, G.,Damas, F.,Paramo, M. D.,Ruiz-Pena, J. L.,Navarro, G. (2017). The real-world effectiveness and safety of fingolimod in relapsing-remitting multiple sclerosis patients: An observational study PLoS ONE [Electronic Resource], 12(4), e0176174	Not sample size of interest (< 1,000 for NRS)

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Jacobs LD, Cookfair DL, Rudick RA, et al. A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: design and conduct of study and baseline characteristics of patients. Multiple Sclerosis Collaborative Research Group (MSCRG). *Multiple sclerosis (houndmills, basingstoke, england).* 1995;1(2):118-135. doi: 10.1177/135245859500100210.	Not sister publication of interest
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Jakimovski, D.,Kolb, C.,Ramanathan, M.,Zivadinov, R.,Weinstock-Guttman, B. (2018). Interferon beta for Multiple Sclerosis. [Review] 1(11),	Not relevant publication type
Jarvinen E., A. Murtonen, M. Tervomaa, M. L. Sumelahti (2019). Interferon beta-1a subcutaneously 3 times/week clinical outcome in relapsing multiple sclerosis in Finland Neurology International, 11(4), 8177	Not comparator of interest
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Jordy, S. S.,Tilbery, C. P.,Fazzito, M. M.. Immunomodulator therapy migration in relapsing remitting multiple sclerosis: a study of 152 cases. Arq Neuropsiquiatr. 2008. 66:11-4	Not sample size of interest (< 1,000 for NRS)
Juanatey, A.,Blanco-Garcia, L.,Tellez, N. (2018). Ocrelizumab: its efficacy and safety in multiple sclerosis Revista de Neurologia, 66(12), 423-433	Not relevant publication type

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Kalincik, T.,Jokubaitis, V.,Spelman, T.,Horakova, D.,Havrdova, E.,Trojano, M.,Lechner-Scott, J.,Lugaresi, A.,Prat, A.,Girard, M.,Duquette, P.,Grammond, P.,Solaro, C.,Grand'Maison, F.,Hupperts, R.,Prevost, J.,Sola, P.,Ferraro, D.,Terzi, M.,Butler, E.,Slee, M.,Kermode, A.,Fabis-Pedrini, M.,McCombe, P.,Barnett, M.,Shaw, C.,Hodgkinson, S.,Butzkueven, H.,M. SBase Study Group (2018). Cladribine versus fingolimod, natalizumab and interferon beta for multiple sclerosis Multiple Sclerosis, 24(12), 1617-1626	Not outcomes of interest
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Kapica-Topczewska K., J. Tarasiuk, F. Collin, W. Brola, M. Chorazy, A. Czarnowska, M. Kwasniewski, H. Bartosik-Psujek, M. Adamczyk-Sowa, J. Kochanowicz, A. Kulakowska (2019). The effectiveness of interferon beta versus glatiramer acetate and natalizumab versus fingolimod in a Polish real-world population PLoS One, 14(10), e0223863	Not outcomes of interest

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Kappos, L.,Bar-Or, A.,Cree, B.,Fox, R.,Giovannoni, G.,Gold, R.,Vermersch, P.,Arnould, S.,Sidorenko, T.,Wolf, C.,et al., (2016). Efficacy and safety of siponimod in secondary progressive multiple sclerosis-Results of the placebo controlled, double-blind, Phase III EXPAND study Multiple sclerosis (houndmills, basingstoke, england), 22, 828-829	Not relevant publication type
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Kaufmann, M.,Haase, R.,Proschmann, U.,Ziemssen, T.,Akgun, K. (2018). Real World Lab Data: Patterns of Lymphocyte Counts in Fingolimod Treated Patients Frontiers in Immunology, 9, 2669	Not sample size of interest (< 1,000 for NRS)
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Khatri, B. O. (2016). Fingolimod in the treatment of relapsing-remitting multiple sclerosis: long-term experience and an update on the clinical evidence. [Review] 1(2), 130-47	Not relevant publication type
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Kim, H.,Lee, E. J.,Kim, S. K.,Kim, K. K.,Lim, Y. M. (2019). Efficacy and safety of alemtuzumab in Korean multiple sclerosis patients Multiple Sclerosis and Related Disorders, 30, 247-251	Not sample size of interest (< 1,000 for NRS)
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Kingwell, E.,Leray, E.,Zhu, F.,Petkau, J.,Edan, G.,Oger, J.,Tremlett, H. (2018). Beta-interferon and mortality in multiple sclerosis: a popu-lation-based international study Multiple sclerosis journal, 24(1), 122-	Not relevant publication type

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Kingwell, E.,Leray, E.,Zhu, F.,Petkau, J.,Edan, G.,Oger, J.,Tremlett, H. (2017). Beta-interferon and mortality in multiple sclerosis: a population- based international study Multiple sclerosis journal, 23(3), 69-70	Not relevant publication type
Kister, I.,Spelman, T.,Alroughani, R.,Lechner-Scott, J.,Duquette, P.,Grand'Maison, F.,Slee, M.,Lugaresi, A.,Barnett, M.,Grammond, P.,Iuliano, G.,Hupperts, R.,Pucci, E.,Trojano, M.,Butzkueven, H.,M. SBase Study Group (2016). Discontinuing disease-modifying therapy in MS after a prolonged relapse-free period: a propensity score-matched study Journal of Neurology, Neurosurgery & Psychiatry, 87(10), 1133-7	Not outcomes of interest
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Kondo, T.,Kawachi, I.,Onizuka, Y.,Hiramatsu, K.,Hase, M.,Yun, J.,Matta, A.,Torii, S. (2019). Efficacy of dimethyl fumarate in Japanese multiple sclerosis patients: interim analysis of randomized, double-blind APEX study and its open-label extension 1(3), 2055217319864974	Not a sister publication of interest
Kondo, T.,Kawachi, I.,Onizuka, Y.,Hiramatsu, K.,Hase, M.,Yun, J.,Ling, Y.,Torii, S. (2017). Efficacy of delayed-release dimethyl fumarate in Japanese patients with relapsing multiple sclerosis in the placebo-controlled phase 3 apex study Journal of the neurological sciences, 381, 439-440	Not relevant publication type
Koralnik, I. J.. New insights into progressive multifocal leukoencephalopathy. Curr Opin Neurol. 2004. 17:365-70	Not relevant publication type
Koscielny, V. (2018). Phase III SUNBEAM and RADIANCE PART B trials for Ozanimod in relapsing multiple sclerosis demonstrate superiority versus interferon-beta-1a (Avonex) in reducing annualized relapse rates and MRI brain lesions Neurodegenerative Disease Management, 8(3), 141-142	Not relevant publication type
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Krueger, J. G.,Kircik, L.,Hougeir, F.,Friedman, A.,You, X.,Lucas, N.,Greenberg, S. J.,Sweetser, M.,Castro-Borrero, W.,McCroskery, P.,et al., (2016). Cutaneous Adverse Events in the Randomized, Double-Blind, Active-Comparator DECIDE Study of Daclizumab High-Yield Process Versus Intramuscular Interferon Beta-1a in Relapsing-Remitting Multiple Sclerosis Advances in therapy, 33(7), 1231-1245	Not a sister publication of interest
Kuerten, S.,Jackson, L. J.,Kaye, J.,Vollmer, T. L. (2018). Impact of Glatiramer Acetate on B Cell-Mediated Pathogenesis of Multiple Sclerosis CNS Drugs, 32(11), 1039-1051	Not relevant publication type
Kuhle, J.,Barro, C.,Edan, G.,Freedman, M. S.,Hartung, H. P.,Montalban, X.,Barkhof, F.,Fox, E. J.,Hemmer, B.,Schippling, S.,et al., (2017). Serum Neurofilament light chain as a predictor of long-term outcomes in patients with CIS in the BENEFIT 11 trial Multiple sclerosis journal, 23(3), 844-845	Not publication type of interest
Kuhle, J.,Daizadeh, N.,Barro, C.,Michalak, Z.,Leppert, D.,Godin, J.,Shankara, S.,Samad, T.,Jacobs, A.,Chung, L.,et al., (2019). Serum neurofilament light chain levels correlate with disease characteristics in patients with relapsing-remitting multiple sclerosis from care-MS I Multiple sclerosis journal, 25, 30-	Not relevant publication type
Kuhle, J.,Hardmeier, M.,Disanto, G.,Gugleta, K.,Ecsedi, M.,Lienert, C.,Amato, M. P.,Baum, K.,Buttmann, M.,Bayas, A.,Brassat, D.,Brochet, B.,Confavreux, C.,Edan, G.,Farkkila, M.,Fredrikson, S.,Frontoni, M.,D'Hooghe, M.,Hutchinson, M.,De Keyser, J.,Kieseier, B. C.,Kumpfel, T.,Rio, J.,Polman, C.,Roullet, E.,Stolz, C.,Vass, K.,Wandinger, K. P.,Kappos, L.,European Long-term Follow-up Study Group in Interferon beta-1b in Secondary-progressive Multiple, Sclerosis (2016). A 10-year follow-up of the European multicenter trial of interferon beta-1b in secondary-progressive multiple sclerosis 1(4), 533-43	Not a sister publication of interest
Kuhle, J.,Nourbakhsh, B.,Grant, D.,Morant, S.,Barro, C.,Yaldizli, O.,Pelletier, D.,Giovannoni, G.,Waubant, E.,Gnanapavan, S. (2017). Serum neurofilament is associated with progression of brain atrophy and disability in early MS Neurology, 88(9), 826-831	Not intervention of interest
La Gioia, S.,Seghezzi, M.,Barcella, V.,Dominoni, P.,Mecca, T.,Frigeni, B.,Conti, M. Z.,Vedovello, M.,Vidali, M.,Rottoli, M.,Buoro, S. (2016). Erythroblastaemia in natalizumab-treated patients with multiple sclerosis Multiple Sclerosis and Related Disorders, 8, 141-4	Not sample size of interest (< 1,000 for NRS)
La Mantia L, Di Pietrantonj C, Rovaris M, et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. *Cochrane Database of Systematic Reviews*. 2016(11). doi: 10.1002/14651858.CD009333.pub3.	Other Systematic review (not checked)
La Mantia L, Tramacere I, Firwana B, Pacchetti I, Palumbo R, Filippini G. Fingolimod for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2016;4(4):CD009371. doi: 10.1002/14651858.CD009371.pub2.	Other
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Lanza, G.,Ferri, R.,Bella, R.,Ferini-Strambi, L. (2017). The impact of drugs for multiple sclerosis on sleep Multiple Sclerosis, 23(1), 5-13	Not relevant publication type

Reference	Reason for Exclusion
Lanzillo, R. (2017). What should we expect from multiple sclerosis therapy? Results of an integrated analysis of delayed-release dimethyl fumarate pivotal trials European Journal of Neurology, 24(5), 661-662	Not relevant publication type
Lanzillo, R.,Quarantelli, M.,Pozzilli, C.,Trojano, M.,Amato, M. P.,Marrosu, M. G.,Francia, A.,Florio, C.,Orefice, G.,Tedeschi, G.,et al., (2016). No evidence for an effect on brain atrophy rate of atorvastatin add-on to interferon β1b therapy in relapsing–remitting multiple sclerosis (The ARIANNA study) Multiple sclerosis journal, 22(9), 1163-1173	Not intervention of interest
Lapierre, Y.,O'Connor, P.,Devonshire, V.,Freedman, M. S.,Kremenchutzky, M.,Yeung, M.,Schecter, R. (2016). Canadian Experience with Fingolimod: Adherence to Treatment and Monitoring Canadian Journal of Neurological Sciences, 43(2), 278-83	Not comparator of interest
Lapointe, E.,Moghaddam, B.,Barclay, K.,Traboulsee, A. L.,Neufeld, P. (2018). Goodpasture's Syndrome Following Alemtuzumab Therapy in Multiple Sclerosis Canadian Journal of Neurological Sciences, 45(6), 712-714	Not relevant publication type
Laribi, B.,Sahraian, M. A.,Shekarabi, M.,Emamnejad, R.,Marzban, M.,Sadaghiani, S.,Izad, M. (2018). Characterization of CD4+ and CD8+ T Cell Subsets and Interferon Regulatory Factor 4 (IRF4) in MS Patients Treated with Fingolimod (FTY-720): A Follow-up Study Iranian Journal of Allergy Asthma & Immunology, 17(4), 346-360	Not sample size of interest (< 1,000 for NRS)
Laroni, A.,Signori, A.,Maniscalco, G.,Lanzillo, R.,Sacca, F.,Clerico, M.,Lo Fermo, S.,Annovazzi, P.,Bonavita, S.,Baroncini, D.,et al., (2016). Comorbidities affect treatment choice and persistence in RRMS: a multicenter study Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 850-851	Not relevant publication type
Lattanzi S., G. Carlini, M. C. Acciarri, M. Danni, M. Silvestrini (2020). Parvovirus B19 infection in a patient with multiple sclerosis treated with ocrelizumab Acta Neurol Belg, 120(1), 231-232	Not relevant publication type
Lattanzi, S.,Danni, M.,Taffi, R.,Cerqua, R.,Carlini, G.,Pulcini, A.,Provinciali, L.,Silvestrini, M. (2017). Persistence to oral disease-modifying therapies in multiple sclerosis patients Journal of Neurology, 264(11), 2325-2329	Not sample size of interest (< 1,000 for NRS)
Lau, A. Y. L.,Chan, E.,Lau, K. K.,Mok, V.,Siu, D. Y. W.,Lee, R. (2019). Neutralising antibodies to interferon-beta therapy in relapsing multiple sclerosis: a pilot study 1(4), 22-25	Not sample size of interest (< 1,000 for NRS)
Le Page, E.,Leray, E.,Taurin, G.,Coustans, M.,Chaperon, J.,Morrissey, S. P.,Edan, G.. Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients. J Neurol Neurosurg Psychiatry. 2008. 79:52-6	Not sample size of interest (< 1,000 for NRS)
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Lebrun-Frenay, C.,Moulignier, A.,Pierrot-Deseilligny, C.,Benrabah, R.,Moreau, T.,Lubetzki, C.,Monchecourt, F.,Copaxone, Observatory (2019). Five-year outcome in the copaxone observatory: a nationwide cohort of patients with multiple sclerosis starting treatment with glatiramer acetate in France Journal of Neurology, 266(4), 888-901	Not sample size of interest (< 1,000 for NRS)

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Lee, A.,Pike, J.,Edwards, M. R.,Petrillo, J.,Waller, J.,Jones, E. (2017). Quantifying the Benefits of Dimethyl Fumarate Over beta Interferon and Glatiramer Acetate Therapies on Work Productivity Outcomes in MS Patients 1(1), 79-90	Not sample size of interest (< 1,000 for NRS)
Leist, T.,Comi, G.,Cree, B.,Coyle, P.,Freedman, M.,Hartung, H.,Vermersch, P.,Orejudos, A.,Lachenal, N.,Scaramozza, M.. Oral cladribine safety profile in patients with a first demyelinating event: top line results from the phase III oracle ms study. Neurology. 2013. 80:	Not relevant publication type
Leist, T.,Comi, G.,Cree, B.,Coyle, P.,Freedman, M.,Hartung, H.,Vermersch, P.,Orejudos, A.,Lachenal, N.,Scaramozza, M.. Oral cladribine delays time to conversion to clinically definite ms in patients with a first demyelinating event: top line results from the phase III oracle ms study. Neurology. 2013. 80:	Not relevant publication type
Leist, T.,Comi, G.,Freedman, M. S.,Cree, B. A. C.,Coyle, P. K.,Hartung, H. P.,Vermersch, P.,Sylvester, E.,Damian, D.,Dangond, F. (2016). Reduction of lymphopenia by cladribine tablets under retreatment guidelines: a long-term follow-up analysis of patients in the ORACLE-MS study Multiple sclerosis (houndmills, basingstoke, england), 22, 306-307	Not relevant publication type
Leurs, C. E.,van Kempen, Z. L.,Dekker, I.,Balk, L. J.,Wattjes, M. P.,Rispens, T.,Uitdehaag, B. M.,Killestein, J. (2018). Switching natalizumab to fingolimod within 6 weeks reduces recurrence of disease activity in MS patients Multiple Sclerosis, 24(11), 1453-1460	Not sample size of interest (< 1,000 for NRS)
Li, D. K. B.,Hemmer, B.,Stuve, O.,Hartung, H. P.,Freedman, M. S.,Rieckmann, P.,Montalban, X.,Zhang-Auberson, L.,Pohlmann, H.,Wallstrom, E.,et al.,. Siponimod (BAF312) treatment leads to early MRI benefits in relapsing-remitting multiple sclerosis patients: results from a phase 2 study. Multiple sclerosis.. 2012. 18:207-208	Not relevant publication type
Li, H.,Zhang, X.. Oral cladribine and fingolimod for relapsing multiple sclerosis. New England Journal of Medicine. 2010. 362:1738-9; author reply 1739-40	Not relevant publication type
Lim, L. L.,Silva, D. G.,Lo, T. C.,Pimentel, R. S.,Butzkueven, H.,Hall, A. J. (2019). Uveitis in Patients with Multiple Sclerosis in Clinical Trials of Fingolimod: Incidence, Prevalence, and Impact on Disease Course 1(3), 438-444	Not a sister publication of interest
Logan-Clubb, L.,Stacy, M.. An open-labelled assessment of adverse effects associated with interferon 1-beta in the treatment of multiple sclerosis. J Neurosci Nurs. 1995. 27:344-7	Not comparator of interest
Longbrake, E. E.,Cross, A. H.,Salter, A. (2016). Efficacy and tolerability of oral versus injectable disease-modifying therapies for multiple sclerosis in clinical practice 1,	Not sample size of interest (< 1,000 for NRS)
Longbrake, E. E.,Kantor, D.,Pawate, S.,Bradshaw, M. J.,von Geldern, G.,Chahin, S.,Cross, A. H.,Parks, B. J.,Rice, M.,Khoury, S. J.,Yamout, B.,Zeineddine, M.,Russell-Giller, S.,Caminero-Rodriguez, A.,Edwards, K.,Lathi, E.,VanderKodde, D.,Meador, W.,Berkovich, R.,Ge, L.,Bacon, T. E.,Kister, I. (2018). Effectiveness of alternative dose fingolimod for multiple sclerosis 1(2), 102-107	Not sample size of interest (< 1,000 for NRS)
Lorscheider, J.,Jokubaitis, V.,Spelman, T.,Izquierdo, G.,Lugaresi, A.,Havrdova, E.,Horakova, D.,Trojano, M.,Duquette, P.,Girard, M.,et al., (2016). Anti-inflammatory disease modifying treatment does not attenuate disability progression in secondary progressive multiple sclerosis Multiple sclerosis (houndmills, basingstoke, england), 22, 367-369	Not relevant publication type

Reference	Reason for Exclusion
Lorscheider, J.,Kuhle, J.,Izquierdo, G.,Lugaresi, A.,Havrdova, E.,Horakova, D.,Hupperts, R.,Duquette, P.,Girard, M.,Prat, A.,Grand'Maison, F.,Grammond, P.,Sola, P.,Ferraro, D.,Trojano, M.,Ramo-Tello, C.,Lechner-Scott, J.,Pucci, E.,Solaro, C.,Slee, M.,Van Pesch, V.,Sanchez Menoyo, J. L.,van der Walt, A.,Butzkueven, H.,Kappos, L.,Kalincik, T.,M. SBase Study Group (2019). Anti-inflammatory disease-modifying treatment and disability progression in primary progressive multiple sclerosis: a cohort study European Journal of Neurology, 26(2), 363-370	Not comparator of interest
Lu E, Wang BW, Guimond C, Synnes A, Sadovnick D, Tremlett H. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. *Neurology*. 2012;79(11):1130-1135. doi: https://dx.doi.org/10.1212/WNL.0b013e3182698c64.	Other Systematic review (not checked)
Lu Y, Zhao J, Zhan Q. Effect of interferon-beta1alpha therapy on multiple sclerosis based on gadolinium-enhancing or active T2 magnetic resonance imaging outcomes: a meta-analysis. *Neurological Research*. 2016;38(10):909-915. doi: https://dx.doi.org/10.1080/01616412.2016.1214417.	Other
Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet. 2016;387(10023):1075-1084. doi: https://dx.doi.org/10.1016/S0140-6736(15)01314-8.	Other Not placebo-controlled trial of interest
Ludwig, M. D.,Turel, A. P.,Zagon, I. S.,McLaughlin, P. J. (2016). Long-term treatment with low dose naltrexone maintains stable health in patients with multiple sclerosis 1, 2055217316672242	Not sample size of interest (< 1,000 for NRS)
Lugaresi, A.,Durastanti, V.,Gasperini, C.,Lai, M.,Pozzilli, C.,Orefice, G.,Sotgiu, S.,Pucci, E.,Ardito, B.,Millefiorini, E.,CoSa Study, Group. Safety and tolerability in relapsing-remitting multiple sclerosis patients treated with high-dose subcutaneous interferon-beta by Rebiject autoinjection over a 1-year period: the CoSa study. Clin Neuropharmacol. 2008. 31:167-72	Not sample size of interest (< 1,000 for NRS)
Lus, G.,Signoriello, E.,Maniscalco, G. T.,Bonavita, S.,Signoriello, S.,Gallo, C. (2016). Treatment withdrawal in relapsing-remitting multiple sclerosis: a retrospective cohort study 1(3), 489-93	Not sample size of interest (< 1,000 for NRS)
MacDonald, S. C.,McElrath, T. F.,Hernandez-Diaz, S. (2019). Use and safety of disease-modifying therapy in pregnant women with multiple sclerosis 1(4), 556-560	Not comparator of interest
MacMillan E. L., J. J. Schubert, I. M. Vavasour, R. Tam, A. Rauscher, C. Taylor, R. White, H. Garren, D. Clayton, V. Levesque, D. K. Li, S. H. Kolind, A. L. Traboulsee (2019). Magnetic resonance spectroscopy evidence for declining gliosis in MS patients treated with ocrelizumab versus interferon beta-1a Mult Scler J Exp Transl Clin, 5(4), 2055217319879952	Not outcomes of interest
Malucchi, S.,Gilli, F.,Caldano, M.,Marnetto, F.,Valentino, P.,Granieri, L.,Sala, A.,Capobianco, M.,Bertolotto, A.. Predictive markers for response to interferon therapy in patients with multiple sclerosis. Neurology. 2008. 70:1119-27	Not sample size of interest (< 1,000 for NRS)
Mancardi, G. L.,Amato, M. P.,D'Alessandro, R.,Drago, F.,Milanese, C.,Popoli, P.,Provinciali, L.,Rossi, P.,Savettieri, G.,Tedeschi, G.,Tola, M. R.,Vanacore, N.,Covezzoli, A.,De Rosa, M.,Piccinni, C.,Montanaro, N.,Periotto, L.,Addis, A.,Martini, N.. Natalizumab: a country-based surveillance program. Neurol Sci. 2008. 29 Suppl 2:S235-7	Not sample size of interest (< 1,000 for NRS)

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Mao-Draayer, Y.,Wu, Q.,Wang, Q.,Dowling, C.,Lundy, S.,Fox, D. (2017). Basic immunological profile changes with BAF312 (siponimod) treatment in secondary progressive multiple sclerosis patients Multiple sclerosis journal, 23(3), 1015-	Not relevant publication type
Mao-Draayer, Y.,Wu, Q.,Wang, Q.,Dowling, C.,Lundy, S.,Fox, D. (2017). Basic immunological profile changes of secondary progressive multiple sclerosis patients treated with BAF312 (SIPONIMOD) Journal of the neurological sciences, 381, 783-	Not relevant publication type
Marangi, A.,Farina, G.,Vicenzi, V.,Forlivesi, S.,Benedetti, M. D. (2018). Pharmacoepidemiology of multiple sclerosis treatment in veneto region: an observational study Neuroepidemiology, 50(1-2), 90-	Not relevant publication type
Marchand, D.K.,Butcher, R. (2019). CADTH RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL Minocycline for RelapsingRemitting Multiple Sclerosisand Clinically Isolated Syndrome: A Review of Clinical Effectiveness and Guidelines	Not intervention of interest
Margolin, D. H.,Karimi-Anderesi, N.,Chirieac, M. C.,Luo, X.,Hueser, A.,Albach, F. N.,Rakhade, S.,Wagner, F. D. (2017). Safety, tolerability, and pharmacodynamics of intravenous and subcutaneous doses of the anti-CD52 antibody GLD52 in patients with progressive MS: a randomised, controlled, single ascending dose trial Multiple sclerosis journal, 23(3), 329-	Not relevant publication type
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Marignier, R.,Durand-Dubief, F.,du Pasquier, R.,Vukusic, S. (2016). Rituximab versus fingolimod after natalizumab in multiple sclerosis: Also consider progressive multifocal leukoencephalopathy risk Annals of Neurology, 80(5), 791	Not relevant publication type
Martinelli, V.,Gironi, M.,Rodegher, M.,Martino, G.,Comi, G.. Occurrence of thyroid autoimmunity in relapsing remitting multiple sclerosis patients undergoing interferon-beta treatment. Ital J Neurol Sci. 1998. 19:65-7	Not sample size of interest (< 1,000 for NRS)
Masuda, H.,Mori, M.,Hirano, S.,Kojima, K.,Uzawa, A.,Uchida, T.,Ohtani, R.,Kuwabara, S. (2019). Relapse numbers and earlier intervention by disease modifying drugs are related with progression of less brain atrophy in patients with multiple sclerosis 1, 78-84	Not sample size of interest (< 1,000 for NRS)
Maurer, M.,Comi, G.,Freedman, M. S.,Kappos, L.,Olsson, T. P.,Wolinsky, J. S.,Miller, A. E.,Dive-Pouletty, C.,Bozzi, S.,O'Connor, P. W. (2016). Multiple sclerosis relapses are associated with increased fatigue and reduced health-related quality of life - A post hoc analysis of the TEMSO and TOWER studies Multiple Sclerosis and Related Disorders, 7, 33-40	Not a sister publication of interest
Maurer, M.,Schuh, K.,Seibert, S.,Baier, M.,Hentschke, C.,Streber, R.,Tallner, A.,Pfeifer, K. (2018). A randomized study to evaluate the effect of exercise on fatigue in people with relapsing-remitting multiple sclerosis treated with fingolimod 1(1), 2055217318756688	Not intervention of interest

Reference	Reason for Exclusion
Mazdeh, M.,Kargar Monhaser, S.,Taheri, M.,Ghafouri-Fard, S. (2019). A non-randomized clinical trial to evaluate the effect of fingolimod on expanded disability status scale score and number of relapses in relapsing-remitting multiple sclerosis patients 1(1), 11	Not sample size of interest (< 1,000 for NRS)
Mazibrada, G.,Sharples, C.,Perfect, I. (2018). Real-world experience of fingolimod in patients with multiple sclerosis (MS Fine): An observational study in the UK 1(4), 2055217318801638	Not sample size of interest (< 1,000 for NRS)
McCarty, D. J. (2017). Treating relapsing multiple sclerosis with dimethyl fumarate Nurse Practitioner, 42(7), 8-10	Not relevant publication type
McCombe, P.,Achiron, A.,Chambers, C.,Fox, E. J.,Otero, S.,Margolin, D. H.,Kasten, L.,Compston, D. A. S. (2016). Pregnancy outcomes in alemtuzumab-treated female patients with active RRMS in the clinical development program Multiple sclerosis. Conference: 9th congress of the pan-asian committee for treatment and research in multiple sclerosis, PACTRIMS 2016. Thailand, 22(3), 420-421	Not relevant publication type
McGinley, M.,Fox, R. J. (2018). Prospects of siponimod in secondary progressive multiple sclerosis 1, 1756286418788013	Not relevant publication type
Meca-Lallana, J.,Oreja-Guevara, C.,Munoz, D.,Olascoaga, J.,Pato, A.,Ramio, L.,Meca-Lallana, V.,Hernandez, M. A.,Marzo, M. E.,Alvarez-Cermeno, J. C.,et al., (2016). Spanish registry of patients with multiple sclerosis treated with fingolimod (GILENYA registry): safety and effectiveness after four years of registry Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 609-610	Not relevant publication type
Meinl, I.,Havla, J.,Hohlfeld, R.,Kumpfel, T. (2018). Recurrence of disease activity during pregnancy after cessation of fingolimod in multiple sclerosis Multiple Sclerosis, 24(7), 991-994	Not sample size of interest (< 1,000 for NRS)
Meissner, A.,Limmroth, V. (2016). Update on the cardiovascular profile of fingolimod in the therapy of relapsing-remitting multiple sclerosis (MS) Multiple Sclerosis and Related Disorders, 8, 19-26	Not a sister publication of interest
Mekies, C.,Heinzlef, O.,Jenny, B.,Ramelli, A. L.,Clavelou, P. (2018). Treatment satisfaction and quality of life in patients treated with fingolimod 1, 899-907	Not sample size of interest (< 1,000 for NRS)
Mellion, M.,Naismith, R.,Arnold, D. L.,Boyko, A.,Evangelou, N.,Valis, M.,Evans, K. C.,Fisher, E.,Richert, N.,Li, J.,et al., (2016). MRI biomarkers of opicinumab (Anti-LINGO-1) repair in relapsing MS: results from the Phase 2b SYNERGY trial Multiple sclerosis (houndmills, basingstoke, england), 22, 269-	Not relevant publication type
Mendes D, Alves C, Batel-Marques F. Benefit-Risk of Therapies for Relapsing-Remitting Multiple Sclerosis: Testing the Number Needed to Treat to Benefit (NNTB), Number Needed to Treat to Harm (NNTH) and the Likelihood to be Helped or Harmed (LHH): A Systematic Review and Meta-Analysis. *CNS Drugs*. 2016;30(10):909-929. doi: https://dx.doi.org/10.1007/s40263-016-0377-9.	Systematic review (not checked)
Mesaros, S.,Stojsavljevic, N.,Dujmovic-Basuroski, I.,Dejanovic, I.,Pekmezovic, T.,Drulovic, J.. Long-term adherence to interferon-beta treatment in a cohort of RRMS patients in Belgrade, Serbia. Clin Neurol Neurosurg. 2012. 114:1145-8	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
Michiels, Y.,Tilleul, P.,Mechin, H.,Hammes, F. (2017). Impact of a community pharmacy-based information protocol on multiple sclerosis patients' adherence to treatment with dimethyl fumarate: tECPHIE, a randomized study vs usual practice Multiple sclerosis journal, 23(3), 922-	Not relevant publication type
Miclea, A.,Leussink, V. I.,Hartung, H. P.,Gold, R.,Hoepner, R. (2016). Safety and efficacy of dimethyl fumarate in multiple sclerosis: a multi-center observational study Journal of Neurology, 263(8), 1626-32	Not sample size of interest (< 1,000 for NRS)
Midaglia, L.,Gratacos, M.,Caronna, E.,Raguer, N.,Sastre-Garriga, J.,Montalban, X.,Tintore, M. (2018). Myasthenia gravis following alemtuzumab therapy for multiple sclerosis Neurology, 91(13), 622-624	Not relevant publication type
Milanese, C.,Beghi, E.,Giordano, L.,La Mantia, L.,Mascoli, N.,Confalonieri, P.. A post-marketing study on immunomodulating treatments for relapsing-remitting multiple sclerosis in Lombardia: preliminary results. Neurol Sci. 2005. 26 Suppl 4:S171-3	Not sample size of interest (< 1,000 for NRS)
Milanese, C.,La Mantia, L.,Palumbo, R.,and the Multiple Sclerosis Centers of Lombardia, Italy. Interferon beta treatment in relapsing-remitting multiple sclerosis: a post-marketing study in Lombardia, Italy. The Italian Journal of Neurological Sciences. 1999. 20:297-302	Not sample size of interest (< 1,000 for NRS)
Millefiorini, E.,Gasperini, C.,Pozzilli, C.,D'Andrea, F.,Bastianello, S.,Trojano, M.,Morino, S.,Morra, V. B.,Bozzao, A.,Calo, A.,Bernini, M. L.,Gambi, D.,Prencipe, M.. Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. J Neurol. 1997. 244:153-9	Not intervention of interest
Miller, A. E. (2017). Oral teriflunomide in the treatment of relapsing forms of multiple sclerosis: clinical evidence and long-term experience. [Review] 1(12), 381-396	Not relevant publication type
Miller, A. E.,Xu, X.,Macdonell, R.,Vucic, S.,Truffinet, P.,Benamor, M.,Thangavelu, K.,Freedman, M. S. (2019). Efficacy and safety of teriflunomide in Asian patients with relapsing forms of multiple sclerosis: A subgroup analysis of the phase 3 TOWER study Journal of Clinical Neuroscience, 59, 229-231	Not a sister publication of interest
Miller, A.,Spada, V.,Beerkircher, D.,Kreitman, R. R.. Long-term (up to 22 years), open-label, compassionate-use study of glatiramer acetate in relapsing-remitting multiple sclerosis. Mult Scler. 2008. 14:494-9	Not sample size of interest (< 1,000 for NRS)
Miller, D. H.,Khan, O. A.,Sheremata, W. A.,Blumhardt, L. D.,Rice, G. P.,Libonati, M. A.,Willmer-Hulme, A. J.,Dalton, C. M.,Miszkiel, K. A.,O'Connor, P. W.,International Natalizumab Multiple Sclerosis Trial, Group. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2003. 348:15-23	Not intervention of interest
Minagara, A.,Murray, T. J.,Proof Study Investigators. Efficacy and tolerability of intramuscular interferon beta-1a compared with subcutaneous interferon beta-1a in relapsing MS: results from PROOF. Curr Med Res Opin. 2008. 24:1049-55	Not sample size of interest (< 1,000 for NRS)
Mitsikostas, D. D.,Goodin, D. S. (2017). Comparing the efficacy of disease-modifying therapies in multiple sclerosis Multiple Sclerosis and Related Disorders, 18, 109-116	Not relevant publication type
Moccia, M.,Palladino, R.,Carotenuto, A.,Russo, C. V.,Triassi, M.,Lanzillo, R.,Brescia Morra, V. (2016). Predictors of long-term interferon discontinuation in newly diagnosed relapsing multiple sclerosis Multiple Sclerosis and Related Disorders, 10, 90-96	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
Moccia, M.,Palladino, R.,Carotenuto, A.,Sacca, F.,Russo, C. V.,Lanzillo, R.,Brescia Morra, V. (2018). A 8-year retrospective cohort study comparing Interferon-beta formulations for relapsing-remitting multiple sclerosis Multiple Sclerosis and Related Disorders, 19, 50-54	Not sample size of interest (< 1,000 for NRS)
Moiola, L.,Ferreira, J.,Robotti, M.,Romeo, M.,Sangalli, F.,Guerrieri, S.,Pisa, M.,Esposito, F.,Martinelli, V.,Comi, G. (2017). "real-life" outcomes in a monocentric cohort of highly active multiple sclerosis patients treated with alemtuzumab Multiple sclerosis journal, 23(3), 339-340	Not relevant publication type
Montalban X, Arnold DL, Weber MS, et al. Placebo-Controlled Trial of an Oral BTK Inhibitor in Multiple Sclerosis. New England Journal of Medicine. 2019;380(25):2406-2417. doi: https://dx.doi.org/10.1056/NEJMoa1901981.	Other Not placebo-controlled trial of interest
Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. New England Journal of Medicine. 2017;376(3):209-220. doi: https://dx.doi.org/10.1056/NEJMoa1606468.	Other Not placebo-controlled trial of interest
Montalban X. Overview of European pilot study of interferon beta-Ib in primary progressive multiple sclerosis. *Mult Scler*. 2004;10 Suppl 1:S62; discussion 62-64. https://www.ncbi.nlm.nih.gov/pubmed/15218812.	Other Not placebo-controlled trial of interest
Montalban, X.,Arnold, D. L.,Bar-Or, A.,De Seze, J.,Giovannoni, G.,Hemmer, B.,Rammohan, K.,Masterman, D.,Bernasconi, C.,Wei, W.,et al., (2016). Evaluation of no evidence of progression using composite disability outcome measures, in patients with primary progressive multiple sclerosis in the ORATORIO trial Multiple sclerosis (houndmills, basingstoke, england), 22, 50-51	Not relevant publication type
Montalban, X.,Arnold, D. L.,Weber, M.,Staikov, I.,Piasecka-Strycznska, K.,Willmer, J.,Martin, E.,Dangond, F.,Wolinsky, J. S.,Phase, E. (2019). Primary analysis of a randomized phase II study to evaluate the efficacy and safety of evobrutinib, a BTK inhibitor, in patients with relapsing MS Multiple sclerosis journal, 25, 52-53	Not relevant publication type
Montalban, X.,Arnold, D. L.,Weber, M.,Staikov, I.,Piasecka-Strycznska, K.,Willmer, J.,Martin, E.,Dangond, F.,Wolinsky, J. S.,Phase, E. (2019). Primary analysis of a randomized, placebo-controlled, phase ii study of the Bruton's tyrosine kinase inhibitor evobrutinib (M2951) in patients with relapsing multiple sclerosis Multiple sclerosis journal, 25, 10-11	Not relevant publication type
Montalban, X.,Cohen, B.,Leist, T.,Moses, H.,Hamlett, A.,Scaramozza, M.,Lachenal, N.. Oral cladribine as add on to IFN beta therapy in patients with active multiple sclerosis: results from the phase II onward study. Neurology. 2013. 80:	Not relevant publication type
Montalban, X.,Fernandez, O.,Butzkueven, H.,Barnett, M.,Nelson, M.,Garcia, E. (2016). Results of a non-randomised, parallel-group clinical trial to assess efficacy and safety of fingolimod in treatment-naïve and previously treated patients with relapsing-remitting multiple sclerosis. The EARLIMS Study Multiple sclerosis (houndmills, basingstoke, england), 22, 280-281	Not relevant publication type
Montalban, X.,Hemmer, B.,Rammohan, K.. Efficacy and safety of ocrelizumab in primary progressive multiple sclerosis - results of the Phase III, double-blind, placebo-controlled ORATORIO study. 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis. 2015. :	Not relevant publication type

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Montalban, X.,Reder, A. T.,Cohen, J.,Ritter, S.,Tomic, D.,Piani Meier, D.,Kappos, L. (2016). Effect of fingolimod on multiple sclerosis severity score (MSSS) in patients with relapsing multiple sclerosis Multiple sclerosis. Conference: 32nd congress of the european committee for treatment and research in multiple sclerosis, ECTRIMS 2016. United kingdom. Conference start: 20160914. Conference end: 20160917, 22, 645	Not relevant publication type
Montes Diaz, G.,Fraussen, J.,Van Wijmeersch, B.,Hupperts, R.,Somers, V. (2018). Dimethyl fumarate induces a persistent change in the composition of the innate and adaptive immune system in multiple sclerosis patients 1(1), 8194	Not sample size of interest (< 1,000 for NRS)
Montgomery, S. M.,Kusel, J.,Nicholas, R.,Adlard, N. (2017). Costs and effectiveness of fingolimod versus alemtuzumab in the treatment of highly active relapsing-remitting multiple sclerosis in the UK: re-treatment, discount, and disutility Journal of Medical Economics, 20(9), 962-973	Not relevant publication type
Monzani, F.,Caraccio, N.,Meucci, G.,Lombardo, F.,Moscato, G.,Casolaro, A.,Ferdeghini, M.,Murri, L.,Ferrannini, E.. Effect of 1-year treatment with interferon-beta1b on thyroid function and autoimmunity in patients with multiple sclerosis. Eur J Endocrinol. 1999. 141:325-31	Not sample size of interest (< 1,000 for NRS)
Mori, M.,Ohashi, T.,Onizuka, Y.,Hiramatsu, K.,Hase, M.,Yun, J.,Ling, Y.,Torii, S. (2017). Efficacy and safety of delayed-release dimethyl fumarate in treatment-naïve Japanese patients with relapsing-remitting multiple sclerosis: a post-hoc subgroup analysis of the apex study Journal of the neurological sciences, 381, 795-796	Not relevant publication type
Mori, M.,Ohashi, T.,Onizuka, Y.,Hiramatsu, K.,Hase, M.,Yun, J.,Matta, A.,Torii, S. (2019). Efficacy and safety of dimethyl fumarate in treatment-naive Japanese patients with multiple sclerosis: Interim analysis of the randomized placebo-controlled study 1(2), 2055217319852727	Not a sister publication of interest
Moss, B. P.,Utigard, E.,Baldassari, L. E.,Cohen, J. A.,Ontaneda, D. D. (2019). Real-world experience with ocrelizumab Multiple sclerosis journal, 25, 69-70	Not relevant publication type
Motamed M. R., N. Najimi, S. M. Fereshtehnejad (2007). The effect of interferon-beta1a on relapses and progression of disability in patients with clinically isolated syndromes (CIS) suggestive of multiple sclerosis Clinical neurology and neurosurgery, 109(4), 344-349	Other Older study not included in prior report
Muris, A. H.,Smolders, J.,Rolf, L.,Thewissen, M.,Hupperts, R.,Damoiseaux, J.,Solarium study group (2016). Immune regulatory effects of high dose vitamin D$_3$ supplementation in a randomized controlled trial in relapsing remitting multiple sclerosis patients receiving IFNbeta; the SOLARIUM study Journal of Neuroimmunology, 300, 47-56	Not intervention of interest
Naismith R. T., A. Wundes, T. Ziemssen, E. Jasinska, M. S. Freedman, A. J. Lembo, K. Selmaj, I. Bidollari, H. Chen, J. Hanna, R. Leigh-Pemberton, M. Lopez-Bresnahan, J. Lyons, C. Miller, D. Rezendes, J. S. Wolinsky, Evolve-Ms- Study Group (2020). Diroximel Fumarate Demonstrates an Improved Gastrointestinal Tolerability Profile Compared with Dimethyl Fumarate in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III EVOLVE-MS-2 Study CNS Drugs, 34(2), 185-196	Other Duration too short (< 12 weeks for RCT)

Reference	Reason for Exclusion
Naismith R. T., J. S. Wolinsky, A. Wundes, C. LaGanke, D. L. Arnold, D. Obradovic, M. S. Freedman, M. Gudesblatt, T. Ziemssen, B. Kandinov, I. Bidollari, M. Lopez-Bresnahan, N. Nangia, D. Rezendes, L. Yang, H. Chen, S. Liu, J. Hanna, C. Miller, R. Leigh-Pemberton (2019). Diroximel fumarate (DRF) in patients with relapsing-remitting multiple sclerosis: Interim safety and efficacy results from the phase 3 EVOLVE-MS-1 study Mult Scler, 1352458519881761	Not relevant publication type
Naismith, R. T.,Claxton, A. E.,Leigh-Pemberton, R. A.,Du, Y.,Hard, M. L.,Von Moltke, L.,Wolinsky, J. S. (2016). Safety and tolerability of ALKS 8700 in relapsing-remitting multiple sclerosis: phase 3 open-label study design (EVOLVE-MS-1) Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 372	Not relevant publication type
Naismith, R. T.,Hendin, B.,Wray, S.,Huang, D.,Gaudenzi, F.,Dong, Q.,Sperling, B.,Mann, M.,Werneburg, B. (2019). Patients transitioning from non-pegylated to pegylated interferon beta-1a have a low risk of new flu-like symptoms: ALLOW phase 3b trial results 1(1), 2055217318822148	Not intervention of interest
Naismith, R. T.,Leigh-Pemberton, R. A.,Rezendes, D.,Ge, T.,Von Moltke, L.,Lembo, A. J.,Wolinsky, J. S. (2017). EVOLVE-MS-2: a randomized, double-blind, phase 3 study of the gastrointestinal tolerability of ALKS 8700 versus dimethyl fumarate in relapsing-remitting multiple sclerosis Multiple sclerosis journal, 23(3), 345-346	Not relevant publication type
Naismith, R. T.,Wolinsky, J. S.,Wundes, A.,LaGanke, C.,Arnold, D. L.,Obradovic, D.,Freedman, M. S.,Gudesblatt, M.,Ziemssen, T.,Kandinov, B.,Bidollari, I.,Lopez-Bresnahan, M.,Nangia, N.,Rezendes, D.,Yang, L.,Chen, H.,Liu, S.,Hanna, J.,Miller, C.,Leigh-Pemberton, R. (2019). Diroximel fumarate (DRF) in patients with relapsing-remitting multiple sclerosis: Interim safety and efficacy results from the phase 3 EVOLVE-MS-1 study Mult Scler, 1352458519881761	Not sample size of interest (< 1,000 for NRS)
Namaka M, Pollitt-Smith M, Gupta A, et al. The clinical importance of neutralizing antibodies in relapsing-remitting multiple sclerosis. *Current Medical Research & Opinion.* 2006;22(2):223-239.	Other Systematic review (not checked)
Nandoskar, A.,Raffel, J.,Scalfari, A. S.,Friede, T.,Nicholas, R. S. (2017). Pharmacological Approaches to the Management of Secondary Progressive Multiple Sclerosis Drugs, 77(8), 885-910	Not relevant publication type
Napier, J.,Rose, L.,Adeoye, O.,Hooker, E.,Walsh, K. B. (2019). Modulating acute neuroinflammation in intracerebral hemorrhage: the potential promise of currently approved medications for multiple sclerosis 1(1), 7-15	Not relevant publication type
Neilley, L. K.,Goodin, D. S.,Goodkin, D. E.,Hauser, S. L.. Side effect profile of interferon beta-1b in MS: results of an open label trial. Neurology. 1996. 46:552-4	Not sample size of interest (< 1,000 for NRS)
Newsome S. D., O. Mokliatchouk, C. Castrillo-Viguera, M. L. Naylor (2020). Matching-adjusted comparisons demonstrate better clinical outcomes in patients with relapsing multiple sclerosis treated with peginterferon beta-1a than with teriflunomide Multiple Sclerosis and Related Disorders, 40, 101954	Not a sister publication of interest
Newsome, S. D.,Arnold, D. L.,Yun, J.,Meergans, M.,Naylor, M. L. (2017). Peginterferon beta-1a improves clinical and radiological disease outcomes in patients who are newly diagnosed with relapsing multiple sclerosis: subgroup analysis of ADVANCE Multiple sclerosis journal, 23(3), 314-	Not relevant publication type

Reference	Reason for Exclusion
Nicholas, J.,Boster, A.,Wu, N.,Yeh, W. S.,Fay, M.,Kendter, J.,Huang, M. Y.,Lee, A. (2018). Comparison of Disease-Modifying Therapies for the Management of Multiple Sclerosis: Analysis of Healthcare Resource Utilization and Relapse Rates from US Insurance Claims Data 1(1), 31-41	Not outcomes of interest
Nicoletti C. G., D. Landi, F. Monteleone, G. Mataluni, M. Albanese, B. Lauretti, C. Rocchi, I. Simonelli, L. Boffa, F. Buttari, N. B. Mercuri, D. Centonze, G. A. Marfia (2019). Treatment with Dimethyl Fumarate Enhances Cholinergic Transmission in Multiple Sclerosis CNS Drugs, 33(11), 1133-1139	Not relevant publication type
Niino, M.,Ohashi, T.,Ochi, H.,Nakashima, I.,Shimizu, Y.,Matsui, M. (2018). Japanese guidelines for dimethyl fumarate Clinical and experimental neuroimmunology, 9(4), 235-243	Not relevant publication type
Noseworthy, J. H.,Hopkins, M. B.,Vandervoort, M. K.,Karlik, S. J.,Lee, D. H.,Penman, M.,Rice, G. P.,Grinwich, K. D.,Cauvier, H.,Harris, B. J.,et al.,. An open-trial evaluation of mitoxantrone in the treatment of progressive MS. Neurology. 1993. 43:1401-6	Not intervention of interest
Novakovic, A. M.,Thorsted, A.,Schindler, E.,Jonsson, S.,Munafo, A.,Karlsson, M. O. (2018). Pharmacometric Analysis of the Relationship Between Absolute Lymphocyte Count and Expanded Disability Status Scale and Relapse Rate, Efficacy End Points, in Multiple Sclerosis Trials 1(10), 1284-1294	Not outcomes of interest
Nowinski, C. J.,Miller, D. M.,Cella, D. (2017). Evolution of Patient-Reported Outcomes and Their Role in Multiple Sclerosis Clinical Trials Neurotherapeutics, 14(4), 934-944	Not relevant publication type
Ochi, H.,Niino, M.,Onizuka, Y.,Hiramatsu, K.,Hase, M.,Yun, J.,Ling, Y.,Torii, S. (2017). Safety of delayed-release dimetyl fumarate in Japanese patients with relapsing multiple sclerosis: subgroup analysis of the apex Part 1 study Journal of the neurological sciences, 381, 791-792	Not relevant publication type
O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis. *New England Journal of Medicine.* 2011;365(14):1293-1303. doi: 10.1056/NEJMoa1014656.	Other Not placebo-controlled trial of interest
O'Connor PW, Li D, Freedman MS, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology.* 2006;66(6):894-900.	Other Not placebo-controlled trial of interest
O'Connor, P. W.,Goodman, A.,Willmer-Hulme, A. J.,Libonati, M. A.,Metz, L.,Murray, R. S.,Sheremata, W. A.,Vollmer, T. L.,Stone, L. A.. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. Neurology. 2004. 62:2038-43	Not intervention of interest
O'Connor, P.,Comi, G.,Freedman, M. S.,Miller, A. E.,Kappos, L.,Bouchard, J. P.,Lebrun-Frenay, C.,Mares, J.,Benamor, M.,Thangavelu, K.,Liang, J.,Truffinet, P.,Lawson, V. J.,Wolinsky, J. S.,Teriflunomide Multiple Sclerosis Oral Trial, Group,the Mri-Ac in Houston, Texas (2016). Long-term safety and efficacy of teriflunomide: Nine-year follow-up of the randomized TEMSO study Neurology, 86(10), 920-30	Not a sister publication of interest
Ohtani, R.,Mori, M.,Uchida, T.,Uzawa, A.,Masuda, H.,Liu, J.,Kuwabara, S. (2018). Risk factors for fingolimod-induced lymphopenia in multiple sclerosis 1(1), 2055217318759692	Not sample size of interest (< 1,000 for NRS)
Olberg, H. K.,Eide, G. E.,Cox, R. J.,Jul-Larsen, A.,Lartey, S. L.,Vedeler, C. A.,Myhr, K. M. (2018). Antibody response to seasonal influenza vaccination in patients with multiple sclerosis receiving immunomodulatory therapy European Journal of Neurology, 25(3), 527-534	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
Onesti, E.,Bagnato, F.,Tomassini, V.,Volante, G.,Denaro, F.,Frontoni, M.,Millefiorini, E.,Pozzilli, C.,Fieschi, C.. Interferon beta treatment of MS in the daily clinical setting: a 3-year post-marketing study. Neurol Sci. 2003. 24:340-5	Not sample size of interest (< 1,000 for NRS)
Ontaneda, D.,Nicholas, J.,Carraro, M.,Zhou, J.,Hou, Q.,Babb, J.,Riester, K.,Mendoza, J. P.,Livingston, T.,Jhaveri, M. (2019). Comparative effectiveness of dimethyl fumarate versus fingolimod and teriflunomide among MS patients switching from first-generation platform therapies in the US Multiple Sclerosis and Related Disorders, 27, 101-111	Not outcomes of interest
Ontaneda, D.,Singer, B.,Meng, X.,Hawker, K. (2016). Early clinical efficacy of fingolimod compared with interferon beta-1a in relapsing multiple sclerosis Multiple sclerosis. Conference: 2nd MENACTRIMS congress 2016. Amman jordan. Conference start: 20160317. Conference end: 20160319. Conference publication: (var.pagings), 22(6), NP20-NP21	Not relevant publication type
Oommen, V. V.,Tauhid, S.,Healy, B. C.,Chua, A. S.,Malik, M. T.,Diaz-Cruz, C.,Dupuy, S. L.,Weiner, H. L.,Chitnis, T.,Bakshi, R. (2016). The Effect of Fingolimod on Conversion of Acute Gadolinium-Enhancing Lesions to Chronic T1 Hypointensities in Multiple Sclerosis 1(2), 184-7	Not sample size of interest (< 1,000 for NRS)
Oreja-Guevara C., J. A. Garcia-Merino, A. Saiz, A. Rodriguez-Antiguedad, J. C. Alvarez-Cermeno, V. Estrada-Perez, G. Izquierdo, O. Fernandez (2019). [Recommendations for the use of cladribine tablets in recurring multiple sclerosis] Rev Neurol, 69(s02), 1-9	Not in English
Ostberg, A.,Pittas, F.,Taylor, B.. Use of low-dose mitozantrone to treat aggressive multiple sclerosis: a single-centre open-label study using patient self-assessment and clinical measures of multiple sclerosis status. Intern Med J. 2005. 35:382-7	Not intervention of interest
Oturai, A. B.,Koch-Henriksen, N.,Petersen, T.,Jensen, P. E.,Sellebjerg, F.,Sorensen, P. S.. Efficacy of natalizumab in multiple sclerosis patients with high disease activity: a Danish nationwide study. Eur J Neurol. 2009. 16:420-3	Not intervention of interest
Ozel O., C. B. Vaughn, S. P. Eckert, D. Jakimovski, A. A. Lizarraga, B. Weinstock-Guttman (2019). Dimethyl Fumarate in the Treatment of Relapsing-Remitting Multiple Sclerosis: Patient Reported Outcomes and Perspectives Patient Related Outcome Measures, 10, 373-384	Not relevant publication type
Palace, J.,Duddy, M.,Lawton, M.,Bregenzer, T.,Zhu, F.,Boggild, M.,Piske, B.,Robertson, N. P.,Oger, J.,Tremlett, H.,Tilling, K.,Ben-Shlomo, Y.,Lilford, R.,Dobson, C. (2019). Assessing the long-term effectiveness of interferon-beta and glatiramer acetate in multiple sclerosis: final 10-year results from the UK multiple sclerosis risk-sharing scheme Journal of Neurology, Neurosurgery & Psychiatry., 90(3), 251-260	Not relevant publication type
Palte MJ, Wehr A, Tawa M, et al. Improving the gastrointestinal tolerability of fumaric acid esters: Early findings on gastrointestinal events with diroximel fumarate in patients with relapsing-remitting multiple sclerosis from the phase 3, open-label EVOLVE-MS-1 study. Adv Ther. 2019;36(11):3154-3165. doi: 10.1007/s12325-019-01085-3.	Not sister publication of interest
Palte, M. J.,Wehr, A.,Tawa, M.,Perkin, K.,Leigh-Pemberton, R.,Hanna, J.,Miller, C.,Penner, N. (2019). Improving the Gastrointestinal Tolerability of Fumaric Acid Esters: Early Findings on Gastrointestinal Events with Diroximel Fumarate in Patients with Relapsing-Remitting Multiple Sclerosis from the Phase 3, Open-Label EVOLVE-MS-1 Study Advances in Therapy, 36(11), 3154-3165	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
Panitch H, Goodin D, Francis G, et al. Benefits of high-dose, high-frequency interferon beta-1a in relapsing-remitting multiple sclerosis are sustained to 16 months: final comparative results of the EVIDENCE trial. *Journal of the neurological sciences.* 2005;239(1):67-74. doi: 10.1016/j.jns.2005.08.003.	Not sister publication of interest
Panitch H, Miller A, Paty D, Weinshenker B. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology.* 2004;63(10):1788-1795. doi: 10.1212/01.wnl.0000146958.77317.3e.	Other Not placebo-controlled trial of interest
Paolicelli D, Manni A, Iaffaldano A, Trojano M. Efficacy and Safety of Oral Therapies for Relapsing-Remitting Multiple Sclerosis. *CNS Drugs.* 2020;34(1):65-92.	Other
Paolicelli, D.,Lucisano, G.,Manni, A.,Avolio, C.,Bonavita, S.,Brescia Morra, V.,Capobianco, M.,Cocco, E.,Conte, A.,De Luca, G.,De Robertis, F.,Gasperini, C.,Gatto, M.,Gazzola, P.,Lus, G.,Iaffaldano, A.,Iaffaldano, P.,Maimone, D.,Mallucci, G.,Maniscalco, G. T.,Marfia, G. A.,Patti, F.,Pesci, I.,Pozzilli, C.,Rovaris, M.,Salemi, G.,Salvetti, M.,Spitaleri, D.,Totaro, R.,Zaffaroni, M.,Comi, G.,Amato, M. P.,Trojano, M.,Italian, M. S. Register (2019). Retrospectively acquired cohort study to evaluate the long-term impact of two different treatment strategies on disability outcomes in patients with relapsing multiple sclerosis (RE.LO.DI.MS): data from the Italian MS Register Journal of Neurology, 18, 18	Not outcomes of interest
Paolicelli, D.,Manni, A.,Iaffaldano, A.,Di Lecce, V.,D'Onghia, M.,Iaffaldano, P.,Trojano, M. (2016). The role of neutralizing antibodies to interferon-beta as a biomarker of persistent MRI activity in multiple sclerosis: a 7-year observational study European Journal of Clinical Pharmacology, 72(8), 1025-9	Not sample size of interest (< 1,000 for NRS)
Papadopoulos, D.,Mitsikostas, D. D. (2018). Oral Disease-Modifying Treatments for Relapsing Multiple Sclerosis: A Likelihood to Achieve No Evidence of Disease Activity or Harm Analysis CNS Drugs, 32(11), 1069-1078	Not a sister publication of interest
Patten SB, Metz LM. Interferon beta-1 a and depression in relapsing-remitting multiple sclerosis: an analysis of depression data from the PRISMS clinical trial. *Multiple sclerosis (houndmills, basingstoke, england).* 2001;7(4):243-248. doi: 10.1177/135245850100700406.	Not sister publication of interest
Patten, S. B.,Fridhandler, S.,Beck, C. A.,Metz, L. M.. Depressive symptoms in a treated multiple sclerosis cohort. Mult Scler. 2003. 9:616-20	Not sample size of interest (< 1,000 for NRS)
Perlman, B.,Heller, D.,Cracchiolo, B. (2016). Interferon beta-1b-induced postmenopausal bleeding in a patient with multiple sclerosis Climacteric, 19(6), 599-600	Not relevant publication type
Peroni, S.,Sorosina, M.,Malhotra, S.,Clarelli, F.,Osiceanu, A. M.,Ferre, L.,Roostaei, T.,Rio, J.,Midaglia, L.,Villar, L. M.,Alvarez-Cermeno, J. C.,Guaschino, C.,Radaelli, M.,Citterio, L.,Lechner-Scott, J.,Spataro, N.,Navarro, A.,Martinelli, V.,Montalban, X.,Weiner, H. L.,de Jager, P.,Comi, G.,Esposito, F.,Comabella, M.,Martinelli-Boneschi, F. (2019). A pharmacogenetic study implicates NINJ2 in the response to Interferon-beta in multiple sclerosis Multiple Sclerosis, 1352458519851428	Not outcomes of interest
Petersen, E. R.,Oturai, A. B.,Koch-Henriksen, N.,Magyari, M.,Sorensen, P. S.,Sellebjerg, F.,Sondergaard, H. B. (2018). Smoking affects the interferon beta treatment response in multiple sclerosis Neurology, 90(7), e593-e600	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
Petkau AJ, White RA, Ebers GC, et al. Longitudinal analyses of the effects of neutralizing antibodies on interferon beta-1b in relapsing-remitting multiple sclerosis. *Multiple Sclerosis.* 2004;10(2):126-138.	Not sister publication of interest
Petruzzo M., R. Palladino, A. Nardone, A. Nozzolillo, G. Servillo, V. Orlando, M. De Angelis, R. Lanzillo, V. Brescia Morra, M. Moccia (2019). The impact of diagnostic criteria and treatments on the 20-year costs for treating relapsing-remitting multiple sclerosis Multiple Sclerosis and Related Disorders, 38, 101514	Not outcomes of interest
Pfeuffer, S.,Schmidt, R.,Straeten, F. A.,Pul, R.,Kleinschnitz, C.,Wieshuber, M.,Lee, D. H.,Linker, R. A.,Doerck, S.,Straeten, V.,Windhagen, S.,Pawlitzki, M.,Aufenberg, C.,Lang, M.,Eienbroeker, C.,Tackenberg, B.,Limmroth, V.,Wildemann, B.,Haas, J.,Klotz, L.,Wiendl, H.,Ruck, T.,Meuth, S. G. (2019). Efficacy and safety of alemtuzumab versus fingolimod in RRMS after natalizumab cessation Journal of Neurology, 266(1), 165-173	Not sample size of interest (< 1,000 for NRS)
Phillips, J. T.,Bar-Or, A.,Gold, R.,Giovannoni, G.,Fox, R. J.,Potts, J.,Marantz, J. L. (2016). Efficacy of delayed-release dimethyl fumarate in newly diagnosed patients with relapsing- remitting multiple sclerosis using a composite measure of disability-Integrated analysis of the phase 3 define and confirm studies Multiple sclerosis. Conference: 2nd MENACTRIMS congress 2016. Amman jordan. Conference start: 20160317. Conference end: 20160319. Conference publication: (var.pagings), 22(6), NP3-NP4	Not relevant publication type
Phillips, J. T.,Rice, G.,Frohman, E.,Vande Gaer, L.,Scott, T.,Haas, J.,Eggenberger, E.,Freedman, M. S.,Stuart, W.,Cunha, L.,Jacobs, L.,Oger, J.,Arnold, D.,Murray, T. J.,DiBiase, M.,Jethwa, V.,Goelz, S.. A multicenter, open-label, phase II study of the immunogenicity and safety of a new prefilled syringe (liquid) formulation of Avonex in patients with multiple sclerosis. Clin Ther. 2004. 26:511-21	Not sample size of interest (< 1,000 for NRS)
Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. *Lancet (london, england).* 1998;352(9139):1491-1497. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00156980/full.	Other Not placebo-controlled trial of interest
Pollmann, W.,Erasmus, L. P.,Feneberg, W.,Then Bergh, F.,Straube, A.. Interferon beta but not glatiramer acetate therapy aggravates headaches in MS. Neurology. 2002. 59:636-9	Not sample size of interest (< 1,000 for NRS)
Polman, C. H.,O'Connor, P. W.,Havrdova, E.,Hutchinson, M.,Kappos, L.,Miller, D. H.,Phillips, J. T.,Lublin, F. D.,Giovannoni, G.,Wajgt, A.,Toal, M.,Lynn, F.,Panzara, M. A.,Sandrock, A. W.,Affirm Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006. 354:899-910	Not intervention of interest
Portaccio, E.,Zipoli, V.,Siracusa, G.,Sorbi, S.,Amato, M. P.. Long-term adherence to interferon beta therapy in relapsing-remitting multiple sclerosis. Eur Neurol. 2008. 59:131-5	Not sample size of interest (< 1,000 for NRS)
Porter, B. (2018). Commentary on "Localized pigmentation disorder after subcutaneous pegylated interferon beta 1a injection" by Coghe et al Multiple Sclerosis, 24(2), 233-235	Not relevant publication type

Reference	Reason for Exclusion
Prasinou, M.,Smith, R.,Gopaluni, S.,Jayne, D. (2019). Alemtuzumab for the treatment of refractory behÃ‡et's disease: a subgroup analysis from a randomized, prospective, open label, dose ranging clinical trial (nct01405807). a trial of efficacy and safety (aleviate) Rheumatology (united kingdom), 58,	Not relevant publication type
Probstel, A. K.,Radu, E. W.,Mueller-Lenke, N.,Zhang-Auberson, L.,Bischof, D.,Merschhemke, M.,Kuhle, J.,Kappos, L.,Derfuss, T.,Decard, B. (2016). Tumefactive multiple sclerosis lesions under fingolimod: case series from an MS centre and review of phase 2 and 3 clinical trial data Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 778-779	Not relevant publication type
Prosperini L., C. Mancinelli, S. Haggiag, C. Cordioli, L. De Giglio, N. De Rossi, S. Galgani, S. Rasia, S. Ruggieri, C. Tortorella, C. Pozzilli, C. Gasperini (2020). Minimal evidence of disease activity (MEDA) in relapsing-remitting multiple sclerosis J Neurol Neurosurg Psychiatry, 91(3), 271-277	Not outcomes of interest
Prosperini, L.,Annovazzi, P.,Boffa, L.,Buscarinu, M. C.,Gallo, A.,Matta, M.,Moiola, L.,Musu, L.,Perini, P.,Avolio, C.,Barcella, V.,Bianco, A.,Farina, D.,Ferraro, E.,Pontecorvo, S.,Granella, F.,Grimaldi, L. M. E.,Laroni, A.,Lus, G.,Patti, F.,Pucci, E.,Pasca, M.,Sarchielli, P.,Italian Alemtuzumab Study, Group (2018). No evidence of disease activity (NEDA-3) and disability improvement after alemtuzumab treatment for multiple sclerosis: a 36-month real-world study Journal of Neurology, 265(12), 2851-2860	Not sample size of interest (< 1,000 for NRS)
Prosperini, L.,Lucchini, M.,Bellantonio, P.,Bianco, A.,Buttari, F.,Centonze, D.,Cortese, A.,De Giglio, L.,Fantozzi, R.,Ferraro, E.,et al., (2017). Dimethyl fumarate vs. fingolimod in multiple sclerosis: an independent, multi-centre, real world, quasi-randomized study Multiple sclerosis journal, 23(3), 316-317	Not relevant publication type
Prosperini, L.,Lucchini, M.,Haggiag, S.,Bellantonio, P.,Bianco, A.,Buscarinu, M. C.,Buttari, F.,Centonze, D.,Cortese, A.,De Giglio, L.,Fantozzi, R.,Ferraro, E.,Fornasiero, A.,Francia, A.,Galgani, S.,Gasperini, C.,Marfia, G. A.,Millefiorini, E.,Nociti, V.,Pontecorvo, S.,Pozzilli, C.,Ruggieri, S.,Salvetti, M.,Sgarlata, E.,Mirabella, M. (2018). Fingolimod vs dimethyl fumarate in multiple sclerosis: A real-world propensity score-matched study Neurology, 91(2), e153-e161	Not sample size of interest (< 1,000 for NRS)
Prosperini, L.,Pontecorvo, S. (2016). Dimethyl fumarate in the management of multiple sclerosis: appropriate patient selection and special considerations. [Review] 1, 339-50	Not relevant publication type
Prosperini, L.,Sacca, F.,Cordioli, C.,Cortese, A.,Buttari, F.,Pontecorvo, S.,Bianco, A.,Ruggieri, S.,Haggiag, S.,Brescia Morra, V.,Capra, R.,Centonze, D.,Di Battista, G.,Ferraro, E.,Francia, A.,Galgani, S.,Gasperini, C.,Millefiorini, E.,Mirabella, M.,Pozzilli, C. (2017). Real-world effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment-naive patients with multiple sclerosis Journal of Neurology, 264(2), 284-294	Not sample size of interest (< 1,000 for NRS)
Prosperini, L.,Sacca, F.,Cordioli, C.,Cortese, A.,Buttari, F.,Pontecorvo, S.,Bianco, A.,Ruggieri, S.,Haggiag, S.,Brescia Morra, V.,et al., (2017). Real-world effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment-naive patients with multiple sclerosis Journal of neurology, 264(2), 284-294	Not sample size of interest (< 1,000 for NRS)

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Pul, R.,Saadat, M.,Morbiducci, F.,Skripuletz, T.,Pul, U.,Brockmann, D.,Suhs, K. W.,Schwenkenbecher, P.,Kahl, K. G.,Pars, K.,Stangel, M.,Trebst, C. (2016). Longitudinal time-domain optic coherence study of retinal nerve fiber layer in IFNbeta-treated and untreated multiple sclerosis patients Experimental & Therapeutic Medicine, 12(1), 190-200	Not sample size of interest (< 1,000 for NRS)
Puz, P.,Lasek-Bal, A. (2016). Safety and Efficacy of Fingolimod and Natalizumab in Multiple Sclerosis After the Failure of First-Line Therapy: Single Center Experience Based on the Treatment of Forty-Four Patients Medical Science Monitor, 22, 4277-4282	Not intervention of interest
Qiu, W.,Huang, D. H.,Hou, S. F.,Zhang, M. N.,Jin, T.,Dong, H. Q.,Peng, H.,Zhang, C. D.,Zhao, G.,Huang, Y. N.,Zhou, D.,Wu, W. P.,Wang, B. J.,Li, J. M.,Zhang, X. H.,Cheng, Y.,Li, H. F.,Li, L.,Lu, C. Z.,Zhang, X.,Bu, B. T.,Dong, W. L.,Fan, D. S.,Hu, X. Q.,Xu, X. H.,Tower Trial Chinese Group (2018). Efficacy and Safety of Teriflunomide in Chinese Patients with Relapsing Forms of Multiple Sclerosis: A Subgroup Analysis of the Phase 3 TOWER Study Chinese Medical Journal, 131(23), 2776-2784	Not a sister publication of interest
Quirant-Sanchez, B.,Presas-Rodriguez, S.,Mansilla, M. J.,Teniente-Serra, A.,Hervas-Garcia, J. V.,Brieva, L.,Moral-Torres, E.,Cano, A.,Munteis, E.,Navarro-Barriuso, J.,Martinez-Caceres, E. M.,Ramo-Tello, C. (2019). Th1Th17$_{CM}$ Lymphocyte Subpopulation as a Predictive Biomarker of Disease Activity in Multiple Sclerosis Patients under Dimethyl Fumarate or Fingolimod Treatment 1, 8147803	Not sample size of interest (< 1,000 for NRS)
Racca, V.,Di Rienzo, M.,Cavarretta, R.,Toccafondi, A.,Vaini, E.,Ferratini, M.,Rovaris, M. (2016). Fingolimod effects on left ventricular function in multiple sclerosis 1(2), 201-11	Not sample size of interest (< 1,000 for NRS)
Rae-Grant, A.,Day, G. S.,Marrie, R. A.,Rabinstein, A.,Cree, B. A. C.,Gronseth, G. S.,Haboubi, M.,Halper, J.,Hosey, J. P.,Jones, D. E.,Lisak, R.,Pelletier, D.,Potrebic, S.,Sitcov, C.,Sommers, R.,Stachowiak, J.,Getchius, T. S. D.,Merillat, S. A.,Pringsheim, T. (2018). Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology Neurology, 90(17), 777-788	Not relevant publication type
Rafiee Zadeh, A.,Askari, M.,Azadani, N. N.,Ataei, A.,Ghadimi, K.,Tavoosi, N.,Falahatian, M. (2019). Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 1. [Review] 1(4), 95-104	Not relevant publication type
Rammohan, K. W.,Hartung, H. P.,Arnold, D. L.,Bar-Or, A.,Comi, G.,De Seze, J.,Giovannoni, G.,Hauser, S. L.,Hemmer, B.,Kappos, L.,et al., (2017). Infections and serious infections with ocrelizumab in relapsing multiple sclerosis and primary progressive multiple sclerosis Multiple sclerosis (houndmills, basingstoke, england), 23, 31-32	Not relevant publication type
Ranganathan, U.,Kaunzner, U.,Foster, S.,Vartanian, T.,Perumal, J. S. (2018). Immediate transient thrombocytopenia at the time of alemtuzumab infusion in multiple sclerosis Multiple Sclerosis, 24(4), 540-542	Not sample size of interest (< 1,000 for NRS)
Repovic, P.,Boster, A.,Ritter, S.,Tomic, D.,Meng, X.,Piani Meier, D.,Sprenger, T.,Barkhof, F. (2017). Long-term predictors of disability worsening in patients with multiple sclerosis in the phase 3 TRANSFORMS study Multiple sclerosis journal, 23(3), 736-737	Not relevant publication type

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Rice, G. P. A.,Filippi, M.,Comi, G.. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Neurology. 2000. 54:1145-1155	Not intervention of interest
Rice, G. P. A.,Froste, L.,Ebers, G. C.. Treatment of progressive multiple sclerosis with cladribine: observations from patient retreatment after a phase III trial. Multiple sclerosis (houndmills, basingstoke, england). 1998. 4:386	Not relevant publication type
Rice, G. P.,Oger, J.,Duquette, P.,Francis, G. S.,Belanger, M.,Laplante, S.,Grenier, J. F.. Treatment with interferon beta-1b improves quality of life in multiple sclerosis. Can J Neurol Sci. 1999. 26:276-82	Not sample size of interest (< 1,000 for NRS)
Rice, G.. Effect of cladribine on magnetic resonance imaging findings in progressive multiple sclerosis: final results of a placebo-controlled trial. Annals of neurology. 1998. 44:504	Not relevant publication type
Riechmann, P.,Comi, G.,Cook, S.. Consistent efficacy of cladribine tablets across multiple sclerosis and patient characteristics, in the double-blind, 96-week CLARITY study. Jornal of neurology. 2010. 257:S142-3, Abstract	Not relevant publication type
Riera R, Porfirio GJ, Torloni MR. Alemtuzumab for multiple sclerosis. *Cochrane Database Syst Rev.* 2016;4(4):CD011203. doi: 10.1002/14651858.CD011203.pub2.	Systematic review (not checked)
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Rio, J.,Tintore, M.,Nos, C.,Tellez, N.,Galan, I.,Montalban, X.. Interferon beta in relapsing-remitting multiple sclerosis. An eight years experience in a specialist multiple sclerosis centre. J Neurol. 2005. 252:795-800	Not sample size of interest (< 1,000 for NRS)
Rio, J.,Tintore, M.,Nos, C.,Tellez, N.,Galan, I.,Pelayo, R.,Montalban, X.. Interferon beta in secondary progressive multiple sclerosis : daily clinical practice. J Neurol. 2007. 254:849-53	Not sample size of interest (< 1,000 for NRS)
Rivera, V. M. (2018). Multiple Sclerosis: A Global Concern with Multiple Challenges in an Era of Advanced Therapeutic Complex Molecules and Biological Medicines 1(4),	Not relevant publication type
Rojas J. I., A. Pappolla, L. Patrucco, E. Cristiano, F. Sanchez (2020). Do clinical trials for new disease modifying treatments include real world patients with multiple sclerosis? Multiple Sclerosis and Related Disorders, 39, 101931	Not comparator of interest
Romano, S.,Ferraldeschi, M.,Bagnato, F.,Mechelli, R.,Morena, E.,Caldano, M.,Buscarinu, M. C.,Fornasiero, A.,Frontoni, M.,Nociti, V.,Mirabella, M.,Mayer, F.,Bertolotto, A.,Pozzilli, C.,Vanacore, N.,Salvetti, M.,Ristori, G. (2019). Drug Holiday of Interferon Beta 1b in Multiple Sclerosis: A Pilot, Randomized, Single Blind Study of Non-inferiority 1, 695	Not intervention of interest

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Roos, J. C. P.,Moran, C.,Chatterjee, V. K.,Jones, J.,Coles, A.,Murthy, R. (2019). Immune reconstitution after alemtuzumab therapy for multiple sclerosis triggering Graves' orbitopathy: a case series Eye, 33(2), 223-229	Not sample size of interest (< 1,000 for NRS)
Rose, J. W.,Giovannoni, G.,Wiendl, H.,Gold, R.,Havrdova, E.,Kappos, L.,Selmaj, K. W.,Zhao, J.,Riester, K.,Tsao, L. C.,et al., (2017). Consistent efficacy of daclizumab beta across patient demographic and disease activity subgroups in patients with relapsing-remitting multiple sclerosis Multiple sclerosis and related disorders, 17, 32-40	Not a sister publication of interest
Roskell NS, Zimovetz EA, Rycroft CE, Eckert BJ, Tyas DA. Annualized relapse rate of first-line treatments for multiple sclerosis: a meta-analysis, including indirect comparisons versus fingolimod. *Current Medical Research & Opinion.* 2012;28(5):767-780. doi: https://dx.doi.org/10.1185/03007995.2012.681637.	Other Systematic review (not checked)
Rouhi F., Z. Mohammadpour, S. K. Noureini, H. Abbastabar, M. H. Harirchian, S. Bitarafan (2020). The effects and side effects of laquinimod for the treatment of multiple sclerosis patients: a systematic review and meta-analysis of clinical trials Eur J Clin Pharmacol, 04, 04	Not intervention of interest
Roux, T.,Maillart, E.,Vidal, J. S.,Tezenas du Montcel, S.,Lubetzki, C.,Papeix, C. (2017). Efficacy and Safety of Fingolimod in Daily Practice: Experience of an Academic MS French Center 1, 183	Not sample size of interest (< 1,000 for NRS)
Rudick, R. A.,Stuart, W. H.,Calabresi, P. A.,Confavreux, C.,Galetta, S. L.,Radue, E. W.,Lublin, F. D.,Weinstock-Guttman, B.,Wynn, D. R.,Lynn, F.,Panzara, M. A.,Sandrock, A. W.,Sentinel Investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006. 354:911-23	Not intervention of interest
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Sabido-Espin, M.,Munschauer, R. (2017). Reasons for discontinuation of subcutaneous interferon beta-1a three times a week among patients with multiple sclerosis: a real-world cohort study BMC Neurology, 17(1), 57	Not comparator of interest
Said Inshasi, J.,Jumah, M. A.,Alroughani, R.,Compston, D. A. S.,Filippi, M.,Giovannoni, G.,Havrdova, E.,Yamout, B.,Margolin, D. H.,Thangavelu, K. (2016). Alemtuzumab-treated patients with active relapsingremitting multiple sclerosis demonstrate durable slowing of brain volume loss over 5 years with most not receiving treatment for 4 years-CARE-MS I and II extension study Multiple sclerosis. Conference: 2nd MENACTRIMS congress 2016. Amman jordan. Conference start: 20160317. Conference end: 20160319. Conference publication: (var.pagings), 22(6), NP7	Not relevant publication type
Saida T, Yamamura T, Kondo T, et al. A randomized placebo-controlled trial of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis from East Asia and other countries. BMC Neurol. 2019;19(1):5. doi: 10.1186/s12883-018-1220-3.	Other Not placebo-controlled trial of interest

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Saida, T.,Yamamura, T.,Kondo, T.,Yun, J.,Yang, M.,Li, J.,Mahadavan, L.,Zhu, B.,Sheikh, S. I. (2016). Placebo-controlled Phase 3 study of delayed-release dimethyl fumarate in patients with relapsing multiple sclerosis from Asia-Pacific and other countries Multiple sclerosis (houndmills, basingstoke, england), 22, 280-	Not relevant publication type
Saidu, N. E. B.,Kavian, N.,Leroy, K.,Jacob, C.,Nicco, C.,Batteux, F.,Alexandre, J. (2019). Dimethyl fumarate, a two-edged drug: Current status and future directions. [Review] 1(5), 1923-1952	Not relevant publication type
Saleem, S.,Anwar, A.,Fayyaz, M.,Anwer, F.,Anwar, F. (2019). An Overview of Therapeutic Options in Relapsing-remitting Multiple Sclerosis. [Review] 1(7), e5246	Not relevant publication type
Sandberg-Wollheim, M.,Frank, D.,Goodwin, T. M.,Giesser, B.,Lopez-Bresnahan, M.,Stam-Moraga, M.,Chang, P.,Francis, G. S.. Pregnancy outcomes during treatment with interferon beta-1a in patients with multiple sclerosis. Neurology. 2005. 65:802-6	Not sample size of interest (< 1,000 for NRS)
Sandberg-Wollheim, M.,Neudorfer, O.,Grinspan, A.,Weinstock-Guttman, B.,Haas, J.,Izquierdo, G.,Riley, C.,Ross, A. P.,Baruch, P.,Drillman, T.,Coyle, P. K. (2018). Pregnancy Outcomes from the Branded Glatiramer Acetate Pregnancy Database 1(1), 9-14	Not comparator of interest
Sangurdekar D., C. Sun, H. McLaughlin, K. Ayling-Rouse, N. E. Allaire, M. A. Penny, P. G. Bronson (2019). Genetic Study of Severe Prolonged Lymphopenia in Multiple Sclerosis Patients Treated With Dimethyl Fumarate Frontiers in Genetics, 10, 1039	Not outcomes of interest
Sanofi Aventus Pharmaceuticals,. A Multi-center Double-blind Parallel-group Placebo-controlled Study of the Efficacy and Safety of Teriflunomide in Patients With Relapsing Multiple Sclerosis.	Not relevant publication type
Sanofi Aventus Pharmaceuticals,. A Randomized, Multinational, Double-blind, Placebo-controlled, Parallel-group Design Pilot Study to Estimate the Tolerability, Safety, Pharmacokinetics, and Pharmacodynamic Effects of Teriflunomide for 24 Weeks When Added to Treatment With Glatiramer Acetate in Subjects With Multiple Sclerosis NCT00475865.	Not relevant publication type
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Sato, K.,Niino, M.,Kawashima, A.,Yamada, M.,Miyazaki, Y.,Fukazawa, T. (2018). Disease Exacerbation after the Cessation of Fingolimod Treatment in Japanese Patients with Multiple Sclerosis Internal Medicine, 57(18), 2647-2655	Not sample size of interest (< 1,000 for NRS)
Savelieva, M.,Wallstrom, E.. Modeling concentration-efficacy relationship for MRI lesion counts under siponimod treatment and its dependence on the effect on lymphocyte reduction. Multiple sclerosis.. 2014. 20:116	Not relevant publication type
Sbardella, E.,Tomassini, V.,Gasperini, C.,Bellomi, F.,Cefaro, L. A.,Morra, V. B.,Antonelli, G.,Pozzilli, C.. Neutralizing antibodies explain the poor clinical response to interferon beta in a small proportion of patients with multiple sclerosis: a retrospective study. BMC Neurol. 2009. 9:54	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
Scappaticcio L, Castellana M, Virili C, et al. Alemtuzumab-induced thyroid events in multiple sclerosis: a systematic review and meta-analysis. *Journal of Endocrinological Investigation*. 2019;26:26. doi: https://dx.doi.org/10.1007/s40618-019-01105-7.	Systematic review (not checked)
Schiffmann, I.,Scheiderbauer, J.,Riemann-Lorenz, K.,Heesen, C. (2018). Does cladribine have an impact on brain atrophy in people with relapsing remitting multiple sclerosis? Multiple Sclerosis, 24(10), 1387-1388	Not relevant publication type
Schippling, S.,O'Connor, P.,Knappertz, V.,Pohl, C.,Bogumil, T.,Suarez, G.,Cook, S.,Filippi, M.,Hartung, H. P.,Comi, G.,Jeffery, D. R.,Kappos, L.,Goodin, D. S.,Arnason, B. (2016). Incidence and course of depression in multiple sclerosis in the multinational BEYOND trial Journal of Neurology, 263(7), 1418-26	Not a sister publication of interest
Schwehr N. A., K. M. Kuntz, E. A. Enns, N. D. Shippee, E. Kingwell, H. Tremlett, A. F. Carpenter, M. Butler, A. M. S. Study group Be (2020). Informing Medication Discontinuation Decisions among Older Adults with Relapsing-Onset Multiple Sclerosis Drugs Aging, 37(3), 225-235	Not relevant publication type
Schwid SR, Panitch HS. Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis. *Clinical therapeutics*. 2007;29(9):2031-2048. doi: 10.1016/j.clinthera.2007.09.025.	Not sister publication of interest
Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MSSG. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. *Neurology*. 2001;56(11):1496-1504.	Other. Not placebo-controlled trial of interest
Selmaj, K. W.,Habek, M.,Bass, A. D.,Brassat, D.,Brinar, V.,Coles, A. J.,Vladic, A.,Wray, S.,Margolin, D. H.,Thangavelu, K.,et al., (2016). Efficacy and safety of alemtuzumab in patients with RRMS is durable over 10 years: follow-up from the CAMMS223 study Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 325-326	Not relevant publication type
Selmaj, K.,Arnold, D.,Comi, G.,Bar-Or, A.,Gujrathi, S.,Hartung, J.,Olson, A.,Cravets, M.,Frohna, P.,Cohen, J.. Safety and tolerability results of the phase 2 portion of the radiance trial: a randomized, double-blind, placebo-controlled trial of oral RPC1063 in relapsing multiple sclerosis. Neurology. 2015. 84:	Not relevant publication type
Selmaj, K.,Barkhof, F.,Belova, A. N.,Wolf, C.,van den Tweel, E. R.,Oberyé, J. J.,Mulder, R.,Egging, D. F.,Koper, N. P.,Cohen, J. A. (2017). Switching from branded to generic glatiramer acetate: 15-month GATE trial extension results Multiple sclerosis (houndmills, basingstoke, england), 23(14), 1909-1917	Not comparator of interest
Setayeshgar, S.,Kingwell, E.,Zhu, F.,Zhang, T.,Carruthers, R.,Marrie, R. A.,Evans, C.,Tremlett, H. (2019). Persistence and adherence to the new oral disease-modifying therapies for multiple sclerosis: A population-based study Multiple Sclerosis and Related Disorders, 27, 364-369	Not sample size of interest (< 1,000 for NRS)

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Sheremata, W. A.,Vollmer, T. L.,Stone, L. A.,Willmer-Hulme, A. J.,Koller, M.. A safety and pharmacokinetic study of intravenous natalizumab in patients with MS. Neurology. 1999. 52:1072-4	Not intervention of interest
Shirani, A.,Okuda, D. T.,Stuve, O. (2016). Therapeutic Advances and Future Prospects in Progressive Forms of Multiple Sclerosis Neurotherapeutics, 13(1), 58-69	Not relevant publication type
Shokrollahi Barough, M.,Ashtari, F.,Sadat Akhavi, M.,Asghari, N.,Mosayebi, G.,Mirmohammadkhani, M.,Kokhaei, N.,Bahraminia, F.,Ajami, A.,Kokhaei, P. (2018). Neutralizing antibody production against Rebif® and ReciGen® in Relapsing-Remitting Multiple Sclerosis (RRMS) patients and its association with patient's disability International immunopharmacology, 62, 109-113	Not sample size of interest (< 1,000 for NRS)
Signori A, Gallo F, Bovis F, Di Tullio N, Maietta I, Sormani MP. Long-term impact of interferon or Glatiramer acetate in multiple sclerosis: A systematic review and meta-analysis. *Multiple Sclerosis and Related Disorders*. 2016;6:57-63. doi: https://dx.doi.org/10.1016/j.msard.2016.01.007.	Systematic review (not checked)
Signoriello, E.,Landi, D.,Monteleone, F.,Sacca, F.,Nicoletti, C. G.,Buttari, F.,Sica, F.,Marfia, G. A.,Di Iorio, G.,Lus, G.,Centonze, D. (2018). Fingolimod reduces the clinical expression of active demyelinating lesions in MS Multiple Sclerosis and Related Disorders, 20, 215-219	Not sample size of interest (< 1,000 for NRS)
Singer, B.,Dunn, J.,Izquierdo, G.,Thangavelu, K.,Mittal, A.,Pozzilli, C. (2016). Alemtuzumab significantly improves disability in patients with active relapsing-remitting MS and an inadequate response to prior therapy as assessed using a novel, composite measure: confirmed disability improvement-plus: results from CARE-MS II Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 281-282	Not relevant publication type
Sipe, J. C.,Romine, J. S.,Koziol, J.,Zyroff, J.,McMillan, R.,Beutler, E.. Cladribine improves relapsing-remitting MS: a double blind, placebo-controlled study. Neurology. 1997. 48 Suppl 2:A340	Not relevant publication type
Sipe, J. C.,Romine, J.,Koziol, J.,Zyroff, J.,McMillan, R.,Beutler, E.,La Jolla, C. A.. Cladribine treatment of chronic progressive (C/P) MS: a double-blind, crossover study with 2+ years' observation. Neurology. 1995. 45 Suppl 4:A418	Not relevant publication type
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Wajgt, A.,Strzyzewska, S.,Ochudlo, S.. The treatment of chronic progressive multiple sclerosis with cladribine. Journal of the neurological sciences. 1997. Suppl:S116	Not relevant publication type
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Wolinsky, J. S.,Montalban, X.,Hauser, S. L.,Giovannoni, G.,Vermersch, P.,Bernasconi, C.,Deol-Bhullar, G.,Garren, H.,Chin, P.,Belachew, S.,Kappos, L. (2018). Evaluation of no evidence of progression or active disease (NEPAD) in patients with primary progressive multiple sclerosis in the ORATORIO trial Annals of Neurology, 84(4), 527-536	Not a sister publication of interest

| Reference	Reason for Exclusion
Wolinsky, J. S.,Montalban, X.,Hauser, S. L.,Model, F.,Deol-Bhullar, G.,Garren, H.,Kappos, L. (2017). Sustained and durable reduction in confirmed disability progression in patients with primary progressive multiple sclerosis receiving ocrelizumab: findings from the phase III ORATORIO study extended control period Multiple sclerosis journal, 23(3), 656-657	Not relevant publication type
Wolinsky, J.,McDougall, F.,Lentz, E.,Deol-Bhullar, G.,Montalban, X. (2016). Baseline assessment of fatigue and health-related quality of life in patients with primary progressive multiple sclerosis in the ORATORIO study Multiple sclerosis (houndmills, basingstoke, england), 22, 676-677	Not relevant publication type
Wolinsky, J.,Montalban, X.,Arnold, D. L.,Bar-Or, A.,De Seze, J.,Giovannoni, G.,Hemmer, B.,Rammohan, K. W.,Deol-Bhullar, G.,Masterman, D.,et al., (2017). Evaluation of no evidence of progression (NEP) in patients with primary progressive multiple sclerosis in the ORATORIO trial Multiple sclerosis (houndmills, basingstoke, england), 23, 17-	Not relevant publication type
Wong, J.,Gomes, T.,Mamdani, M.,Manno, M.,O'Connor, P. W.. Adherence to multiple sclerosis disease-modifying therapies in Ontario is low. Can J Neurol Sci. 2011. 38:429-33	Not sample size of interest (< 1,000 for NRS)
Wong, S. L.,Aldrige, J.,Hettle, R.,Khurana, I. S.,Siddiqui, M. K. (2018). Analysis of 6-month confirmed disability progression in RRMS patients treated with subcutaneous interferon beta-1a Multiple sclerosis journal, 24(1), 32-	Not relevant publication type
Wong, S. L.,Elmor, R.,Barr, P.,Ernst, F. (2017). Persistence, adverse events, and relapse in patients with relapsing remitting multiple sclerosis and initiated on IFN Beta-1a or dimethyl fumarate Multiple sclerosis (houndmills, basingstoke, england), 23, 103-104	Not relevant publication type
Wray, S.,Cha, C.,Hayward, B.,Dangond, F.,Singer, B. (2016). Results of redefine: ease of use of two autoinjectors in patients with multiple sclerosis treated with interferon ß-1a subcutaneously three times weekly Multiple sclerosis (houndmills, basingstoke, england), 22, 811-812	Not relevant publication type
Wray, S.,Hayward, B.,Dangond, F.,Singer, B. (2017). Ease of use of two autoinjectors in patients with multiple sclerosis treated with interferon beta-1a subcutaneously three times weekly: results of the randomized, crossover REDEFINE study Expert opinion on drug delivery, 1-9	Not intervention of interest
Wu Q., E. A. Mills, Q. Wang, C. A. Dowling, C. Fisher, B. Kirch, S. K. Lundy, D. A. Fox, Y. Mao-Draayer, A. M. S. Study Group (2020). Siponimod enriches regulatory T and B lymphocytes in secondary progressive multiple sclerosis JCI Insight, 5(3), 13	Not outcomes of interest
Wynn, D. R. (2019). Enduring Clinical Value of Copaxone (Glatiramer Acetate) in Multiple Sclerosis after 20 Years of Use. [Review] 1, 7151685	Not relevant publication type
Wynn, D.,Kaufman, M.,Montalban, X.,Vollmer, T.,Simon, J.,Elkins, J.,O'Neill, G.,Neyer, L.,Sheridan, J.,Wang, C.,Fong, A.,Rose, J. W.,Choice investigators. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. Lancet Neurol. 2010. 9:381-90	Not intervention of interest
Xu M, Lu X, Fang J, Zhu X, Wang J. The efficacy and safety of teriflunomide based therapy in patients with relapsing multiple sclerosis: A meta-analysis of randomized controlled trials. *Journal of Clinical Neuroscience*. 2016;33:28-31. doi: https://dx.doi.org/10.1016/j.jocn.2016.02.041.	Other
Xu, Y.,Han, J.,Ma, X.,Pei, J.,Engmann, N. J.,Pradhan, A.,Bergvall, N.,Julian, L. (2018). AN EXPLORATORY ANALYSIS OF EFFICACY OF OCRELIZUMAB FOR MULTIPLE SCLEROSIS PATIENTS WITH INCREASED DISABILITY Value in health, 21, S330-	Not relevant publication type

Reference	Reason for Exclusion
Yadav, S. K.,Soin, D.,Ito, K.,Dhib-Jalbut, S. (2019). Insight into the mechanism of action of dimethyl fumarate in multiple sclerosis. [Review] 1(4), 463-472	Not relevant publication type
Yang T, Tian X, Chen CY, et al. The efficacy and safety of fingolimod in patients with relapsing multiple sclerosis: A meta-analysis. *Br J Clin Pharmacol*. 2019;23:23. doi: 10.1111/bcp.14198.	Systematic review (not checked)
Yang, H.,Duchesneau, E. D.,Guerin, A.,Ma, E.,Thomas, N. P. (2017). Impact of ocrelizumab vs. interferon beta-1a in delaying the deterioration of patients' daily functions and associated costs in relapsing-remitting multiple sclerosis Value in health, 20(9), A721-	Not relevant publication type
Yoshida, E. M.,Rasmussen, S. L.,Steinbrecher, U. P.,Erb, S. R.,Scudamore, C. H.,Chung, S. W.,Oger, J. J.,Hashimoto, S. A.. Fulminant liver failure during interferon beta treatment of multiple sclerosis. Neurology. 2001. 56:1416	Not relevant publication type
You, X.,Scott, T.,Shang, S.,Evilevitch, V.,Sabetella, G.,Werneburg, B. (2016). A matching-adjusted indirect comparison of clinical effectiveness of subcutaneous peginterferon beta-1a and intramuscular interferon beta-1a for the treatment of relapsing multiple sclerosis Multiple sclerosis (Houndmills, Basingstoke, England), 22(3), 415-	Not relevant publication type
Young C, Grobelna A. *Dosing strategies for Copaxone for multiple sclerosis: comparative clinical effectiveness and guidelines.* August 2017 2017.	Other Systematic review (not checked)
Young, C.,Grobelna, A. (2017). Dosing strategies for Copaxone for multiple sclerosis: comparative clinical effectiveness and guidelines CADTH rapid response report: summary of abstracts,	Not publication type of interest
Yousry, T. A.,Major, E. O.,Ryschkewitsch, C.,Fahle, G.,Fischer, S.,Hou, J.,Curfman, B.,Miszkiel, K.,Mueller-Lenke, N.,Sanchez, E.,Barkhof, F.,Radue, E. W.,Jager, H. R.,Clifford, D. B.. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. 2006. 354:924-33	Not intervention of interest
Zecca, C.,Disanto, G.,Muhl, S.,Gobbi, C. (2017). Subjective patient-reported versus objective adherence to subcutaneous interferon beta-1a in multiple sclerosis using RebiSmart: the CORE study BMC Neurology, 17(1), 171	Not sample size of interest (< 1,000 for NRS)
Zecca, C.,Merlini, A.,Disanto, G.,Rodegher, M.,Panicari, L.,Romeo, M. A. L.,Candrian, U.,Messina, M. J.,Pravata, E.,Moiola, L.,Stefanin, C.,Ghezzi, A.,Perrone, P.,Patti, F.,Comi, G.,Gobbi, C.,Martinelli, V. (2018). Half-dose fingolimod for treating relapsing-remitting multiple sclerosis: Observational study Multiple Sclerosis, 24(2), 167-174	Not sample size of interest (< 1,000 for NRS)
Zecca, C.,Pavelek, Z.,Prikrylova, K.,Ghielmetti, M.,Beeler, A.,Gobbi, C. (2019). Tolerability, treatment satisfaction and quality of life outcomes in stable multiple sclerosis patients switched from injectable therapies to auto injected intramuscular interferon beta 1a: The SFERA study Multiple Sclerosis and Related Disorders, 30, 104-109	Not sample size of interest (< 1,000 for NRS)
Zecca, C.,Roth, S.,Findling, O.,Perriard, G.,Bachmann, V.,Pless, M. L.,Baumann, A.,Kamm, C. P.,Lalive, P. H.,Czaplinski, A. (2018). Real-life long-term effectiveness of fingolimod in Swiss patients with relapsing-remitting multiple sclerosis European Journal of Neurology, 25(5), 762-767	Not sample size of interest (< 1,000 for NRS)
Zephir, H.,De Seze, J.,Stojkovic, T.,Delisse, B.,Ferriby, D.,Cabaret, M.,Vermersch, P.. Multiple sclerosis and depression: influence of interferon beta therapy. Mult Scler. 2003. 9:284-8	Not sample size of interest (< 1,000 for NRS)

Reference	Reason for Exclusion
Zhang J, Shi S, Zhang Y, et al. Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev.* 2017;11(11):CD010968. doi: 10.1002/14651858.CD010968.pub2.	Other
Zhang, T.,Tremlett, H.,Leung, S.,Zhu, F.,Kingwell, E.,Fisk, J. D.,Bhan, V.,Campbell, T. L.,Stadnyk, K.,Yu, B. N.,Marrie, R. A.,Cihr Team in the Epidemiology,Impact of Comorbidity on Multiple, Sclerosis (2016). Examining the effects of comorbidities on disease-modifying therapy use in multiple sclerosis Neurology, 86(14), 1287-1295	Not comparator of interest
Ziemssen T., M. Lang, B. Tackenberg, S. Schmidt, H. Albrecht, L. Klotz, J. Haas, C. Lassek, C. Cornelissen, B. Ettle, Pangaea Study Group (2019). Long-term real-world evidence for sustained clinical benefits of fingolimod following switch from natalizumab Multiple Sclerosis and Related Disorders, 39, 101893	Not comparator of interest
Ziemssen, T.,Engelmann, U.,Jahn, S.,Leptich, A.,Kern, R.,Hassoun, L.,Thomas, K. (2016). Rationale, design, and methods of a non-interventional study to establish safety, effectiveness, quality of life, cognition, health-related and work capacity data on Alemtuzumab in multiple sclerosis patients in Germany (TREAT-MS) BMC Neurology, 16, 109	Not relevant publication type
Ziemssen, T.,Kern, R.,Cornelissen, C. (2016). Study design of PANGAEA 2.0, a non-interventional study on RRMS patients to be switched to fingolimod BMC Neurology, 16, 129	Not relevant publication type
Ziemssen, T.,Lang, M.,Tackenberg, B.,Schmidt, S.,Albrecht, H.,Klotz, L.,Haas, J.,Lassek, C.,Medin, J.,Cornelissen, C.,Pangaea study group (2018). Clinical and Demographic Profile of Patients Receiving Fingolimod in Clinical Practice in Germany and the Benefit-Risk Profile of Fingolimod After 1 Year of Treatment: Initial Results From the Observational, Noninterventional Study PANGAEA Neurotherapeutics, 15(1), 190-199	Not comparator of interest
Ziemssen, T.,Thomas, K. (2017). Alemtuzumab in the long-term treatment of relapsing-remitting multiple sclerosis: an update on the clinical trial evidence and data from the real world 1(10), 343-359	Not relevant publication type
Ziemssen, T.,Wang, H.,Zhang, W.,Thangavelu, K.,Melanson, M.,Hashemi, L.,Guo, J. (2017). Impact of alemtuzumab on work capacity based upon evidence from the CARE-MS II study Multiple sclerosis journal, 23(3), 902-	Not relevant publication type
Zintzaras E, Doxani C, Mprotsis T, Schmid CH, Hadjigeorgiou GM. Network analysis of randomized controlled trials in multiple sclerosis. *Clinical Therapeutics.* 2012;34(4):857-869.e859. doi: https://dx.doi.org/10.1016/j.clinthera.2012.02.018.	Other Systematic review (not checked)
Zipoli, V.,Portaccio, E.,Hakiki, B.,Siracusa, G.,Sorbi, S.,Amato, M. P.. Intravenous mitoxantrone and cyclophosphamide as second-line therapy in multiple sclerosis: an open-label comparative study of efficacy and safety. J Neurol Sci. 2008. 266:25-30	Not sample size of interest (< 1,000 for NRS)
Zivadinov, R.,Bergsland, N.,Carl, E.,Ramasamy, D. P.,Hagemeier, J.,Dwyer, M. G.,Lizarraga, A. A.,Kolb, C.,Hojnacki, D.,Weinstock-Guttman, B. (2019). Effect of Teriflunomide and Dimethyl Fumarate on Cortical Atrophy and Leptomeningeal Inflammation in Multiple Sclerosis: A Retrospective, Observational, Case-Control Pilot Study 1(3),	Not sample size of interest (< 1,000 for NRS)

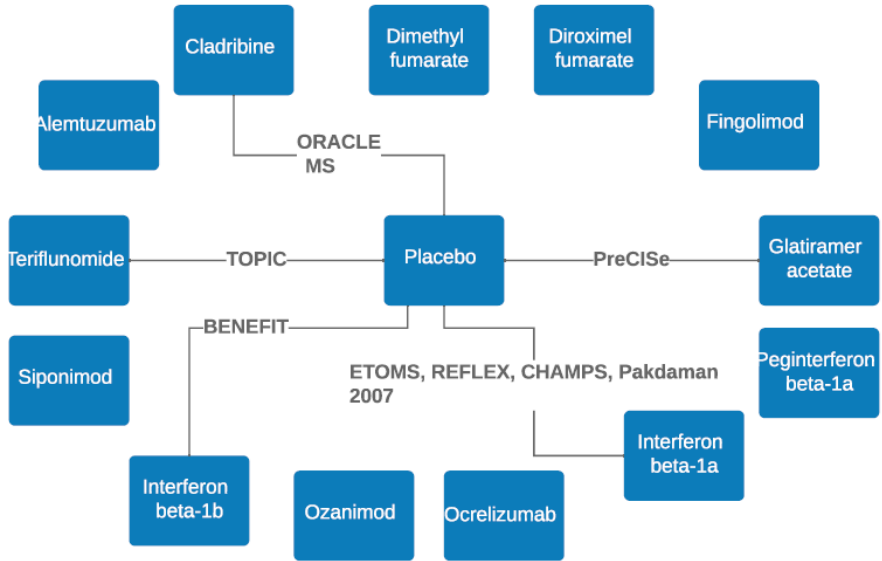| Reference	Reason for Exclusion
Zivadinov, R.,Cha, C.,Buckle, G.,Aldridge, J.,Haas, G.,Reed, J.,Hughes, B. (2016). Patient real-world clinical, neurological, tolerability, and safety outcomes for dimethyl fumarate and interferon beta-1a 44 mug subcutaneously three times weekly: a retrospective study using propensity score stratification and matching (PROTRACT) Multiple sclerosis (Houndmills, Basingstoke, England), Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2016. United Kingdom. Conference Start: 20160914. Conference End: 20160917. 22, 618-619	Not relevant publication type
Zivadinov, R.,Kresa-Reahl, K.,Weinstock-Guttman, B.,Edwards, K.,Burudpakdee, C.,Bergsland, N.,Dwyer, M. G.,Khatri, B.,Thangavelu, K.,Chavin, J.,Mandel, M.,Cohan, S. (2019). Comparative effectiveness of teriflunomide and dimethyl fumarate in patients with relapsing forms of MS in the retrospective real-world Teri-RADAR study 1(5), 305-316	Not sample size of interest (< 1,000 for NRS)
Zivadinov, R.,Medin, J.,Khan, N.,Korn, J. R.,Chitnis, T.,Naismith, R. T.,Alvarez, E.,Dwyer, M. G.,Bergsland, N.,Carl, E.,Silva, D.,Weinstock-Guttman, B.,Ms-Mrius Study Group (2019). Impact of fingolimod on clinical and magnetic resonance imaging outcomes in routine clinical practice: A retrospective analysis of the multiple sclerosis, clinical and MRI outcomes in the USA (MS-MRIUS) study Multiple Sclerosis and Related Disorders, 27, 65-73	Not sample size of interest (< 1,000 for NRS)
Zörner, B.,Filli, L.,Reuter, K.,Kapitza, S.,Lörincz, L.,Sutter, T.,Weller, D.,Farkas, M.,Easthope, C. S.,Czaplinski, A.,et al., (2016). Prolonged-release fampridine in multiple sclerosis: improved ambulation effected by changes in walking pattern Multiple sclerosis (houndmills, basingstoke, england), 22(11), 1463-1475	Not intervention of interest
Zwibel, H. L.,Copolymer-1 Treatment Study Principal, Investigators. Glatiramer acetate in treatment-naive and prior interferon-beta-1b-treated multiple sclerosis patients. Acta Neurol Scand. 2006. 113:378-86	Not sample size of interest (< 1,000 for NRS)

Appendix E. Evidence Maps

Randomized Controlled Trials for Multiple Sclerosis
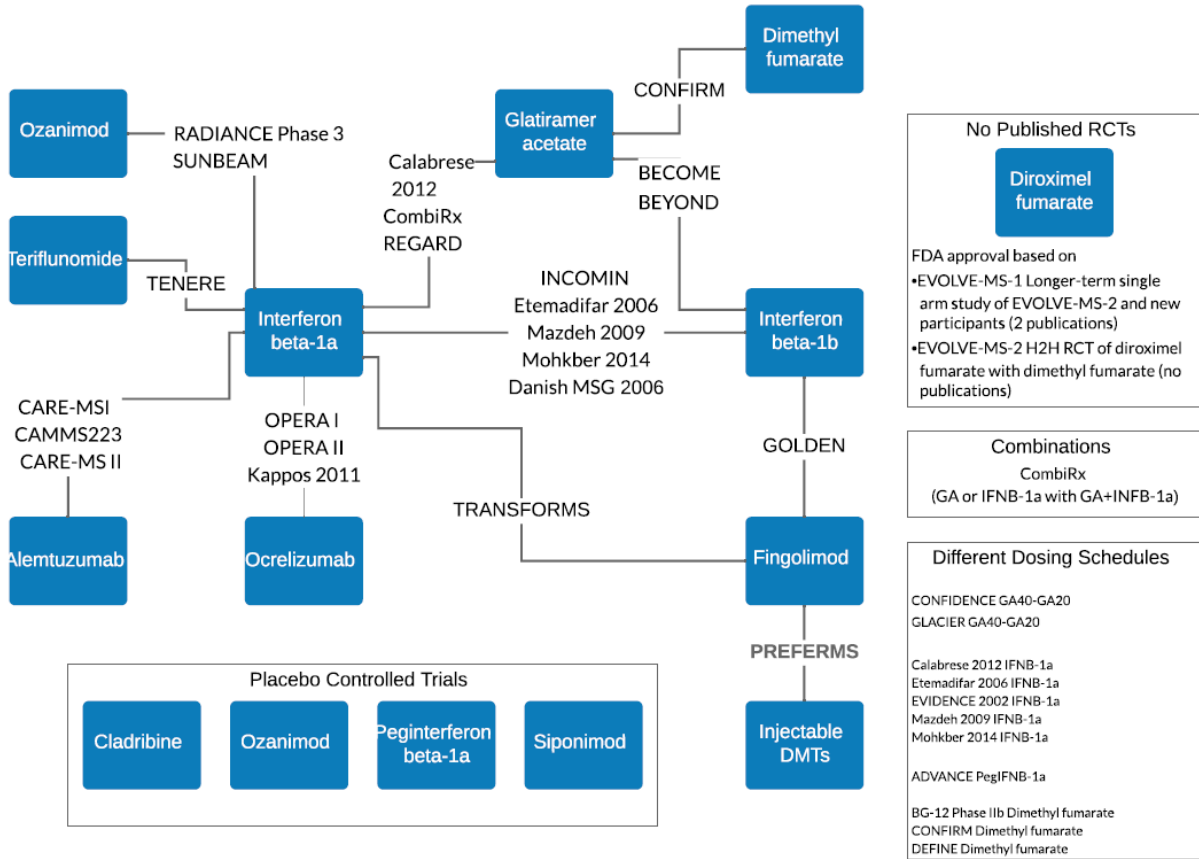
Randomized Controlled Trials for Clinically Isolated Syndrome