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Alemtuzumab, Cladribine, Fingolimod, Natalizumab, and Rituximab as First-Line Treatments in Adults With Highly Active Relapsing-Remitting Multiple Sclerosis

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Health Technology Assessment

Key Messages

What Is the Problem?

- Relapsing-remitting multiple sclerosis (RRMS), the most common disease course of multiple sclerosis (MS), is a chronic immune-mediated disease with clearly defined episodes of new or increasing neurologic symptoms followed by periods of relative stability. In contrast, the highly active, aggressive disease course leads to rapid disability, and these patients face an unmet need.
- The principal goal of MS treatment is to delay and prevent the accumulation of disability by reducing the frequency of relapses.
- Currently reimbursed first-line drugs fail to prevent the consequences of irreversible damage to the nervous system.
- There has been a paradigm shift in clinical practice toward the use of a high-efficacy treatment strategy as early as possible during the inflammatory process to provide optimal clinical benefits in preserving neurologic function in patients with highly active RRMS.

What Did We Do?

- A systematic review of the clinical effectiveness and safety of alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab relative to current first-line drugs in adults with highly active RRMS was conducted; it identified post hoc subgroup analyses from 5 randomized controlled trials (RCTs) and 1 prospective comparative cohort study.

What Did We Find?

- Evidence was uncertain and conclusions were limited by risk of bias and small sample sizes; conclusions for some outcome comparisons were also limited by imprecision and incomplete reporting.
- Compared to placebo, cladribine and natalizumab may result in a clinically important reduction in relapses, disability, and key MRI lesions. Alemtuzumab may result in a clinically important reduction in relapses compared to interferon, while fingolimod may result in a clinically important reduction in relapses compared to placebo. The clinical evidence was insufficient to determine the effect of fingolimod on relapses when compared with interferon. Harms outcomes, when reported, appeared consistent with the known harms profile of the drugs.
- Assessment of the effectiveness and safety of rituximab could not be performed due to the lack of evidence.

Key Messages

- Evidence was also lacking for many important outcomes such as health-related quality of life (HRQoL), instrumental activities of daily living, symptoms, and cognitive outcomes. No evidence could be identified to inform on treatment sequencing.
- Two pragmatic RCTs (the TREAT-MS and DELIVER-MS trials) are currently ongoing, aiming to compare an early, high-efficacy treatment strategy versus a traditional escalation treatment strategy, which may inform treatment sequencing.
- Further research is needed to compensate for clinical data gaps to inform an appropriate and relevant economic evaluation.

What Does This Mean?

- Jurisdictions may reconsider the current reimbursement criteria for drugs used in the first-line setting specifically for adults demonstrating highly active RRMS; however, caution should be taken given the gaps and uncertainty in evidence.
- Upon request from public drug plans, this review may inform a future implementation advice panel or expert committee recommendation.

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Abbreviations

AE	adverse event
ARR	annualized relapse rate
CI	confidence interval
CNS	central nervous system
DMT	disease-modifying therapies
EDSS	Expanded Disability Status Scale
Gd	gadolinium
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
ITC	indirect treatment comparison
MCID	minimal clinically important difference
MS	multiple sclerosis
NEDA	no evidence of disease activity
nRCT	nonrandomized controlled trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RRMS	relapsing-remitting multiple sclerosis
RRR	relative risk reduction
SAE	serious adverse event
SD	standard deviation
WDAE	withdrawal due to adverse event

Executive Summary

Background and Policy Context

MS is a chronic, immune-mediated disease associated with inflammation, demyelination, and neurodegeneration.[1] Distortion or interruption in nerve impulses results in symptoms that vary between individuals.[1] Symptoms may include muscle weakness, spasticity, dizziness, tingling or reduced sensations, visual disturbances, bladder and bowel dysfunction, mental and physical fatigue, and cognitive impairment.[2] RRMS is the most common disease course, with clearly defined episodes of new or increasing neurologic symptoms followed by periods of relative stability.[3] Some patients will, however, have a highly active, aggressive disease with rapid disability.[4] Highly active or aggressive MS is identified based on 4 domains: relapse frequency, relapse severity, relapse recovery, and key lesions on brain scan.[4]

The principal goal of MS treatment is to delay or prevent the accumulation of disability by reducing the frequency of relapses.[4] There is an unmet need in the relatively small proportion of patients who have highly active RRMS, as they experience relapses and irreversible damage to the nervous system despite treatment with currently reimbursed traditional first-line drugs, which fail to prevent the devastating consequences of early accumulation of disability.[4,5] Traditional first-line treatments for RRMS include injectable drugs (glatiramer acetate, interferon beta-1a, and interferon beta-1b), as well as oral drugs (teriflunomide and dimethyl fumarate).[4] Higher efficacy treatments include fingolimod, cladribine, natalizumab, alemtuzumab, ofatumumab, and ocrelizumab.[4,6] To preserve neurologic function, there has been a paradigm shift in clinical practice toward the use of high-efficacy treatment strategies early in the inflammatory process in patients with highly active RRMS. The Canadian MS Working Group now considers high-efficacy treatments as first-line options for patients with high disease activity, aggressive disease presentation, or rapidly evolving symptoms at onset, to prevent early disability worsening.[4] However, most public reimbursement in Canada requires being refractory or experiencing intolerance to a prior disease-modifying therapy (DMT) with a traditional first-line drug. In some jurisdictions, ocrelizumab and ofatumumab are high-efficacy treatments currently reimbursed in the first-line setting.

The objective of this health technology assessment (HTA) is to review the clinical effectiveness and safety of alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab relative to current first-line drugs in adults with highly active RRMS.

Clinical Evidence

A systematic review of published RCTs and prospective comparative cohort studies comparing high-efficacy treatments with current first-line treatments or placebo was conducted. Seven publications met the final inclusion criteria, reporting findings from post hoc subgroup analyses of 5 RCTs and 1 prospective comparative cohort study.

When compared to placebo, cladribine and natalizumab, which clinical experts identified as the most frequently prescribed drugs in clinical practice, may result in a clinically important reduction in relapses, disability, and key MRI lesions; however, there is uncertainty in the evidence identified. Evidence suggests

that alemtuzumab may result in a clinically important reduction in relapses compared to interferon, while fingolimod may result in a clinically important reduction in relapses compared to placebo; again, there is uncertainty in the evidence. The evidence was, however, insufficient to determine the effect of fingolimod on relapses when compared with interferon. Harms outcomes, when reported, appeared consistent with the known harms profiles of the drugs. Assessment of the effectiveness and safety of rituximab could not be performed due to the lack of evidence. Evidence was also lacking for many outcomes that were considered important to patients and clinicians, such as HRQoL, instrumental activities of daily living, symptoms, and cognitive outcomes. An economic evaluation could not be conducted due to significant clinical data gaps, including the methodological limitations precluding assessment of comparative treatment efficacy in an indirect comparison. Therefore, the comparative cost-effectiveness of first-line treatments for highly active relapsing MS is unknown.

Limitations

Conclusions are limited by risk of bias, incomplete reporting, small sample sizes, and imprecision (wide confidence intervals [CIs] included the possibility that either of the treatments compared could be favoured).

Conclusions and Implications for Decision- or Policy-Making

No clinical trial has been designed to assess the relative benefits and harms of an early high-efficacy treatment strategy versus a traditional escalation treatment strategy in patients with highly active RRMS. The rationale to use higher efficacy treatments upon disease presentation in these patients is supported by major guidelines[4] and by observational real-world evidence, such as studies of MS registries. Of note, 2 pragmatic RCTs (the TREAT-MS[7] and DELIVER-MS[8] trials) are currently ongoing, aiming to compare an early high-efficacy treatment strategy versus a traditional escalation treatment strategy in RRMS and in a prespecified subgroup of patients with high risk.

Evidence suggests that natalizumab, cladribine, alemtuzumab, and fingolimod may be effective for first-line treatment of adults with highly active RRMS. Considering the gaps and uncertainty in evidence outlined in this report, jurisdictions may consider requesting an implementation advice panel or expert committee recommendation.

Introduction and Rationale

Background and Rationale

Disease Background

MS is a chronic immune-mediated disease of the central nervous system (CNS).[1] Symptoms of MS are thought to be due to demyelination, a process in which the immune system recognizes self-cells and tissues within the CNS and orchestrates an inflammatory response that damages or destroys them. These cells and tissues include myelin, which is the insulating substance wrapped around the axons, the nerve fibres in the white matter of the CNS. The immune reaction may also damage the axons themselves and the

oligodendrocytes, the CNS cells responsible for myelin-making. Damaged myelin, or demyelination, forms scar tissue that is called sclerosis, giving the disease its name.[1] The inflammation, demyelination, and neurodegeneration associated with MS distort or interrupt nerve impulses transmitted to and from the brain and spinal cord, resulting in several possible symptoms that vary from 1 individual to another, as well as over time for any given individual.[1] The different symptoms associated with different areas of CNS inflammation may include muscle weakness, spasticity, dizziness, tingling or reduced sensations, visual disturbances, bladder and bowel dysfunction, mental and physical fatigue, and cognitive impairment.[2]

MS diagnosis relies on clinical, imaging, and laboratory findings.[4,9] There are no symptoms, physical findings, or laboratory tests that can, by themselves, determine if a person has MS. The long-standing McDonald criteria[9] are used for diagnosing MS; the current version of MS diagnostic criteria requires evidence of damage in at least 2 separate areas of the CNS to confirm dissemination in space; evidence that confirms dissemination in time (which can be done at a single time point of onset); and ruling out other possible causes. In addition, imaging evidence and cerebrospinal fluid findings should be consistent with demyelinating disease.[4,9]

Relapsing MS is the most common disease course, being the phenotype identified in approximately 85% of patients upon diagnosis.[3] It is characterized by clearly defined episodes of new or increasing neurologic symptoms, followed by periods of relative stability and partial or complete recovery. The natural course of RRMS includes periods during which all symptoms may disappear or only some symptoms will continue and become permanent, but despite clinical inactivity the disease unfortunately remains. Subclinical new inflammatory activity can be detected with routine MRI during periods of remission as evidence of inadequate treatment response and/or risk of future disability.

Among patients with RRMS, a subgroup of patients who have an active, aggressive disease course and rapid disability accumulation remains difficult to define.[10] One observational study conducted in British Columbia, using 3 different sets of definitions, found that 4% to 14% of patients had what was described as aggressive MS.[11] This type of disease presentation is associated with poor prognosis and outcomes over relatively short periods of time.[4,10] Previous efforts described severe or aggressive MS in patients with highly active relapsing disease who experience frequent and severe relapses, rapid worsening, and high inflammatory and neurodegenerative activity.[10] More specifically, the Canadian MS Working Group proposed a list of factors to identify highly active or aggressive MS that is based on 4 domains (relapse frequency, relapse severity, relapse recovery, and MRI).[4] The Canadian MS Working Group suggests intensifying treatment if a major level of concern is present in any domain, or if a minor level of concern is present in any 2 domains.[4] Of note, "highly active MS" is a term used relatively recently among the MS community as the understanding of MS evolves. Therefore, "highly active" may have not traditionally been assessed or presented as a selection criterion in earlier study designs and clinical trials.

Standards of Therapy

There is no curative treatment available for MS, and the current therapeutic strategy is aimed at reducing the risk of relapses and disability progression.[4,5] The Canadian MS Working Group recommends early treatment (i.e., during the inflammatory phase of the disease) to provide optimal clinical benefit and alter the rate of

progression.[4] Various DMTs with different mechanisms of action have been approved by Health Canada to treat RRMS by suppressing and/or modulating the dysregulated immune system, limiting CNS inflammation, and preventing relapses and new lesions. They include various beta interferon products, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, alemtuzumab, fingolimod, natalizumab, ocrelizumab, ofatumumab, and ozanimod. Rituximab — although not approved for treatment of MS by Health Canada — is used in clinical practice, according to the clinical experts consulted, and is supported by the Institute for Clinical and Economic Review (ICER) in its 2023 MS Final Evidence Report.[12]

Table 1: Drugs Indicated in RMS

Drug	Mechanism of action	Indication[a]	Route of administration	Recommended dose	Serious side effects or safety issues
Ozanimod (Zeposia)[13]	S1P receptor modulator; the mechanism by which ozanimod and its active metabolites exert their therapeutic effects on MS is unknown but may involve reduction of lymphocyte migration into the CNS.	RRMS to decrease the frequency of clinical exacerbations	Oral capsule	Initial dosing: days 1 to 4 (0.23 mg once daily), days 5 to 7 (0.46 mg once daily) The maintenance dosage is 0.92 mg once daily taken orally starting on day 8.	May result in transient reductions in heart rate and atrioventricular delays. Elevations of aminotransferases may occur in patients receiving it. May increase susceptibility to infections; causes a reduction in circulating lymphocyte counts to approximately 43% to 47% of baseline values.
Teriflunomide (Aubagio)[14]	Not completely understood; may reduce numbers of activated lymphocytes available for migration into the CNS.	RRMS[b]	Oral tablet	14 mg once daily	Hepatotoxicity and risk of teratogenicity. Contraindicated in patients who are hypersensitive to this drug or to leflunomide; patients currently treated with leflunomide; severe hepatic impairment; individuals who are pregnant and individuals with childbearing potential who are not using contraception; immunodeficiency states, such as AIDS; serious active infection; impaired bone marrow function or significant anemia, leucopenia, neutropenia, or thrombocytopenia.
Dimethyl fumarate (Tecfidera)[15]	Not completely understood; activates the NRF2 pathway, which is involved in cellular response to oxidative stress.	RRMS[b]	Oral capsule	240 mg twice daily (total of 480 mg daily)	PML, reduced lymphocyte counts. Contraindicated in patients who are hypersensitive to this drug or to any ingredient in the

Drug	Mechanism of action	Indication[a]	Route of administration	Recommended dose	Serious side effects or safety issues
					formulation or component of the container.
Interferon beta-1a (Avonex; Rebif)[16,17]	Effects on MS not completely understood. It exerts its biological effects by binding to specific receptors on the surface of human cells, and inducing the expression of numerous IFN-induced gene products.	RMS (RRMS, SPMS with relapses) and patients with a single demyelinating event, accompanied by abnormal MRI scans, with lesions typical of MS	IM injection (Avonex) SC injection (Rebif)	IM: 30 mcg/ week (increase up to 60 mcg/ week if needed) SC: 22 mcg or 44 mcg 3 times/ week	Hepatic injury, thrombotic microangiopathy, hematologic side effects (abnormal blood cell counts), injection site reactions, depression or suicide. Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease (Rebif only), pregnant individuals (Rebif only).
Interferon beta-1b (Betaseron; Extavia)[18,19]	Effects on MS not completely understood. It exerts its biological effects by binding to specific receptors on the surface of human cells, and inducing the expression of numerous IFN-induced gene products.	RRMS, SPMS, single demyelinating event accompanied by at least 2 clinically silent lesions typical of MS	SC injection (Betaseron, Extavia)	0.25 mg every other day	Hepatic injury, thrombotic microangiopathy, hematologic side effects (abnormal blood cell counts), injection site reactions, depression or suicidal ideation. Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, pregnant individuals, and patients with current severe depression and/or suicidal ideation (Extavia only).
Pegylated IFN beta-1a (Plegridy)[20]	Effects on MS not completely understood. It exerts its biological effects by binding to type I IFN receptors on the surface of human cells.	RRMS	SC injection	125 mcg every 2 weeks	Hepatic injury, thrombotic microangiopathy, hematologic side effects (abnormal blood cell counts), injection site reactions, depression or suicidal ideation. Contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation or the container; pregnant patients; patients with current severe depression and/ or suicidal ideation.
Glatiramer acetate (Copaxone)[21]	Likely modifies the immune processes responsible for pathogenesis of MS.	RRMS; single demyelinating event accompanied by abnormal	SC injection	20 mg/day	Contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

Drug	Mechanism of action	Indication[a]	Route of administration	Recommended dose	Serious side effects or safety issues
		MRI scans and patients considered to be at risk of developing CDMS			
Ocrelizumab (Ocrevus)[22]	Reduction in CD20.	RRMS, PPMS	IV infusion	600 mg Q6M	Infusion reactions, infections (herpes, respiratory tract). Contraindicated in patients with active or severe infection or with PML.
Cladribine (Mavenclad)[23]	Inhibits lymphocyte proliferation.	Monotherapy for the treatment of adult patients with RRMS	Oral	3.5 mg/kg over 2 years	Lymphopenia, infections (herpes zoster, TB or LTB reactivation, PML), malignancies, teratogenic effects.
Fingolimod (Gilenya)[24]	S1P receptor modulator; its effects on MS are not fully known; its active metabolite binds to receptors on lymphocytes, blocks lymphocytes from leaving lymph nodes, reduces the number of lymphocytes in peripheral blood, and reduces lymphocyte migration into CNS.	RRMS;[b] generally recommended in MS patients who have had inadequate response to or are unable to tolerate 1 or more therapies for MS	Oral capsule	0.5 mg/day	PML, skin cancer, infections (varicella; VZV vaccination recommended), heart block. Contraindicated in patients who are hypersensitive to fingolimod, who are at increased risk for opportunistic infection, have hepatic insufficiency, active severe infections, known active malignancies, major cardiovascular issues, severe arrhythmias, and pregnancy.
Natalizumab (Tysabri)[25]	Binds to the alpha-4 subunit of human integrin: blocks interaction of alpha-4 beta-1 integrin with VCAM-1; and blocks the interaction of alpha-4 beta-7 integrin with MadCAM-1.	RRMS;[b] generally recommended in MS patients who have had an inadequate response to or are unable to tolerate other therapies for MS	IV infusion	300 mg every 4 weeks	PML, herpes. Contraindicated in patients who have or have had PML, or are at risk for PML; hypersensitive to this drug or to any ingredient in the formulation or any component of the drug; immunocompromised, including those immunocompromised due to immunosuppressant or antineoplastic therapies, or immunodeficiencies.
Alemtuzumab (Lemtrada)[26]	Not fully understood. Binds to CD52; may involve immunomodulation through the depletion	RRMS with highly active disease despite an adequate course of	IV infusion	Initial treatment cycle: 12 mg/day for 5 consecutive days.	Autoimmune and immune-mediated conditions, infections, infusion reactions, stroke, malignancies. Contraindicated in patients

Drug	Mechanism of action	Indication[a]	Route of administration	Recommended dose	Serious side effects or safety issues
	and repopulation of lymphocytes.	treatment with ≥ 2 other DMTs		Second treatment cycle: 12 mg/day for 3 consecutive days administered 12 months after the initial treatment course.	who are hypersensitive to alemtuzumab or to any ingredient in the formulation or component of the container; are infected with HIV; have active or latent TB, active severe infections, or active malignancies; are on antineoplastic or immunosuppressive therapies; or have a history of PML.
Ofatumumab (Kesimpta)[27]	Reduction in CD20.	RRMS with active disease defined by clinical and imaging features	SC injection	Initial dosing of 20 mg at weeks 0, 1, and 2, followed by 20 mg monthly starting at week 4.	Contraindicated in patients with active HBV infection; severe, active infections; history of PML; severely immunocompromised patients, and those with known active malignancies.

CNS = central nervous system; DMT = disease-modifying therapies; GPCR = G-protein–coupled receptor; HBV = hepatitis B virus; IFN = interferon; IL = interleukin; IM = intramuscular; MAdCAM-1 = mucosal addressin cell adhesion molecule-1; MS = multiple sclerosis; NRF2 = nuclear factor (erythroid-derived 2)-like-2; PML = progressive multifocal leukoencephalopathy; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; S1P = sphingosine-1-phosphate; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; VCAM-1 = vascular cell adhesion molecule-1; VSV = varicella zoster virus.

[a]Health Canada–approved indication.

[b]Indicated as monotherapy.

Source: Product monographs for: cladribine,[23] ocrelizumab,[22] Plegridy,[20] alemtuzumab,[26] dimethyl fumarate,[15] fingolimod,[24] glatiramer acetate,[21] Avonex;[16] Rebif,[17] Betaseron,[18] Extavia,[19] natalizumab,[25] teriflunomide,[14] and ofatumumab.[27]

Among the treatment options, recommendations from the Canadian MS Working Group identify the following first-line treatments approved for relapsing MS: 5 injectable drugs (glatiramer acetate, 3 formulations of interferon beta-1a, and interferon beta-1b) and 2 oral drugs (teriflunomide and dimethyl fumarate).[4] Six additional DMTs available in Canada are considered to be of high efficacy by the Canadian MS Working Group:[4] fingolimod, cladribine, natalizumab, alemtuzumab, ofatumumab,[6] and ocrelizumab.

Historically, high-efficacy DMTs were reserved for patients with poor response or tolerability with a traditional first-line drug which is called the escalation treatment strategy.[4] However, there has been a paradigm shift in the treatment of MS. The MS Working Group now considers high-efficacy DMTs as initial treatment options for patients with high disease activity, aggressive disease presentation, or rapidly evolving symptoms at onset, as these patients are at significant risk of early disability worsening.[4] This is referred to as the early high-efficacy treatment strategy. Several observational studies from MS registries around the world concluded that an early high-efficacy treatment strategy was superior to an escalation treatment strategy at preventing disability progression over time.[28-32] A number of recent peer-reviewed publications, including studies, reviews, and opinion pieces, recommend the use of the early high-efficacy treatment strategy, especially in patients with high disease activity.[33-38] In clinical practice, an increasing number of neurologists prefer the treatment strategy of initiating high-efficacy therapies early for the appropriate patients, according to the 2 clinical experts consulted, instead of following the traditional escalation treatment strategy.

The clinical experts highlighted that the traditional strategy of initiating lower-efficacy treatments first, with the possibility of switching to another DMT afterward if necessary, is still typically used for many patients due to reimbursement criteria. Of note, besides the traditional first-line agents, 2 B-cell high-efficacy treatments (ofatumumab and ocrelizumab) are currently listed by some of the provincial drug plans as first-line treatments for patients with RRMS, and have been reviewed by CADTH.[39,40] Clinician groups with expertise in treating MS noted that earlier use of higher efficacy treatments for patients presenting with high disease activity, more aggressive disease, or rapidly evolving MS at onset could prevent irreversible damage to the nervous system that may result from the current traditional sequential escalation approach that requires trial, failure, or intolerance to other options.

Given the aforementioned changes in how MS is treated, public drug programs requested an HTA to inform their formulary management of first-line drugs in adults with highly active RRMS. Public drug programs identified alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab as drugs of interest.

Clinical Review Methods

Project Scope

Public drug programs and clinical experts informed the scope of the review. A proposed project scope document was posted for stakeholder feedback. Feedback was received from industry, clinicians, and patient groups, which was considered when developing the protocol.

Objective

The objective was to systematically review the clinical effectiveness and safety of alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab relative to current first-line drugs in adults with highly active RRMS. This report does not provide a reimbursement recommendation.

Jurisdictions expressed interest in an economic evaluation assessing the cost-effectiveness of alemtuzumab, natalizumab, cladribine, fingolimod, or rituximab as first-line treatments in adults with highly active RRMS. However, this was dependent upon the findings of the clinical review to populate an economic model. We may explore the feasibility of a budget impact assessment tool in consultation with public drug plans.

Policy Question

Should alemtuzumab, natalizumab, cladribine, fingolimod, or rituximab be used as first-line treatments in adults with highly active RRMS?

Research Question

What is the clinical efficacy and safety of alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab as first-line treatments in patients with highly active RRMS when compared to drugs currently used as first-line treatments in adult patients with highly active RRMS?

Review Conduct

The methods for the systematic review were planned a priori and the protocol was registered in the PROSPERO International Prospective Registry of Systematic Reviews on March 31, 2023 (registration number: CRD42023409691). Changes to the protocol that occurred during the review process are described briefly, with reasons:

- Patient engagement activities were not performed for this review. However, industry, clinicians, and patient groups, were invited to provide input and feedback on the study protocol and draft report. Feedback received was used to ensure the completeness and relevance of the final published report.
- Considering the limited amount of evidence meeting the selection criteria, it was decided, once the article selection process was performed, to include all relevant treatment comparisons, including versus placebo.

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement.[41]

All review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The input was provided by 2 clinical specialists with expertise in the diagnosis and management of RRMS.

Eligibility Criteria

Prespecified selection criteria for inclusion of studies in this systematic review are presented in Table 2. To be included, studies had to meet all of the eligibility criteria.

Table 2: Selection Criteria

Criteria	Description
Population	Patients who are DMT-naive, with highly active relapsing MS Subgroups according to: • age at diagnosis (e.g., 18 years to < 50 years; ≥ 50 years) • time since diagnosis (to account for disease duration) • EDSS score (e.g., < 3; 3 to < 6; ≥ 6) • MRI activity at baseline
Interventions	• Alemtuzumab (Lemtrada) 12 mg/day IV infusion for 5 consecutive days for the first treatment course, then 12 mg/day for 3 consecutive days administered 12 months later • Cladribine (Mavenclad) 3.5 mg/kg orally over the course of 2 years, administered as 1 treatment course of 1.75 mg/kg per year • Fingolimod (Gilenya; generics) 0.5 mg orally once daily • Natalizumab (Tysabri) 300 mg IV infusion every 4 weeks • Rituximab (including biosimilars) 500 mg IV infusion every 6 months

Criteria	Description
Comparators	Relapsing MS first-line therapies:[a] • glatiramer acetate • interferon beta-1a • interferon beta-1b • teriflunomide • dimethyl fumarate • ocrelizumab • ofatumumab
Outcomes	Efficacy outcomes (any time point): • relapse (e.g., relapse rate, relapse-free rate, time to relapse) • disability progression (including time to progression) or improvement • function (e.g., MSFC score, including T25-FW or 9-HPT individual scores) • imaging outcomes (e.g., MRI brain lesions, MRI brain volume, spinal cord imaging) • cognitive outcomes (e.g., MSNQ, PASAT 3, SDMT) • symptoms (e.g., fatigue, cognition, mobility, visual disturbance) • HRQoL (e.g., MSWOL-54, MSQLI, MS-QLQ27) • instrumental activities of daily living (e.g., absenteeism, presentism, employment status) Harms outcomes (any time point): • adverse events • serious adverse events • withdrawal due to adverse events • mortality • notable harms: injection-related reactions, opportunistic infections, serious infections, PML, lymphopenia, neutropenia, malignancies
Study designs	Published phase II, phase III, and phase IV RCTs If no RCTs are available to adequately inform the research question: published nonrandomized controlled trials and comparative prospective cohort studies

9-HPT = 9-Hole Peg Test; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; HRQoL = health-related quality of life; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSNQ = Multiple Sclerosis Neuropsychological Questionnaire; MSQLI = Multiple Sclerosis Quality of Life Inventory; MS-QLQ27 = 27-item Multiple Sclerosis Quality of Life Questionnaire; MSWOL-54 = Multiple Sclerosis Quality of Life-54; PASAT 3 = 3-second Paced Auditory Serial Addition Task; PML = progressive multifocal leukoencephalopathy; RCT = randomized controlled trial; SDMT = Symbol Digit Modality Test; T25-FW = Timed 25-Foot Walk.

[a]Health Canada–recommended dosage for MS or clinically relevant dosage based on expert advice or on the Canadian MS Working Group Guidelines.

The following was considered when selecting studies for inclusion:

- The systematic review included RCTs with a head-to-head comparison between 1 of the interventions (alemtuzumab, natalizumab, cladribine, fingolimod, or rituximab) and 1 of the comparators (glatiramer acetate, interferon beta-1a, interferon beta-1b, teriflunomide, dimethyl fumarate, ocrelizumab, or ofatumumab), in the targeted population of patients who are DMT-naive with highly active RRMS. Full texts of titles or abstracts describing potentially relevant studies in a wider patient population were retrieved for assessment and included in the systematic review if appropriate subgroup results were reported. Direct evidence from RCTs was sought first, since well-designed RCTs allow for causal inferences to be drawn with greater certainty compared with nearly any other study type.

- As few head-to-head RCTs were identified for all outcome comparisons, additional relevant evidence was included. This included the following:
  - Placebo-controlled RCTs were initially identified for the purpose of performing indirect treatment comparisons (ITCs), specifically Bucher ITCs. However, it was not deemed appropriate to attempt to perform ITCs due to the limited overall body of evidence that could be identified in the literature in the specific patient population, and to the lack of reporting of patients' characteristics. Therefore, placebo-controlled RCTs were considered for inclusion if they evaluated 1 of the interventions under review (alemtuzumab, natalizumab, cladribine, fingolimod, or rituximab) compared to placebo, in the targeted population of patients with highly active RRMS who are DMT-naive.
  - Nonrandomized controlled trials (nRCTs) and comparative prospective cohort studies were considered for inclusion if they evaluated 1 of the interventions (alemtuzumab, natalizumab, cladribine, fingolimod, or rituximab) versus 1 of the comparators (glatiramer acetate, interferon beta-1a, interferon beta-1b, teriflunomide, dimethyl fumarate, ocrelizumab, or ofatumumab) in the targeted population of patients who are DMT-naive with highly active RRMS for any given outcome comparison that lacked RCT evidence. To be considered prospective, comparative cohort studies must have clearly defined a hypothesis before the enrolment of patients and collection of outcomes data (i.e., registry studies were excluded).
- There was no prespecified definition for highly active RRMS, to avoid excluding potentially relevant evidence. Disease definitions from the studies were assessed individually for relevance to the RRMS clinical setting in Canada. According to the clinical experts consulted for this review, highly active (also called aggressive) disease is associated with features that put a patient at high risk of disability; these include a high number or frequent relapses, an MRI indicative of high activity, as well as situations where another relapse may be devastating (e.g., in patients who did not recover well from a prior relapse). Studies of wider populations were only included if findings could be isolated for patients who are treatment-naive with highly active RRMS (e.g., in subgroup analyses). The clinical experts were consulted when there was uncertainty about whether the population investigated in any study would qualify as having highly active disease.
- This review was limited to studies reported in English or French. Studies reported in other languages were excluded.
- When multiple reports were identified for the same study, they were all included and cited; however, only unique data were extracted without duplication and the reports were considered as 1 single study in the analysis. The first complete report of a study was identified as the primary report, while subsequent reports were referred to as associated reports. Abstracts, conference proceedings, or results posted on clinicaltrials.gov were not considered to be complete reports, as they typically do not provide sufficient information to properly assess risk of bias or generalizability; therefore, studies reporting findings only through these means of publication were not included in the systematic review. However, abstracts of previously published studies were included if they contained data that were relevant to the review.

Literature Search Methods

An information specialist developed and conducted a literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's PRESS Peer Review of Electronic Search Strategies checklist.[42] The complete search strategy is presented in Appendix 1.

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid, Embase via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. The main search concepts were relapsing multiple sclerosis and alemtuzumab, natalizumab, cladribine, fingolimod, or rituximab. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register and the European Union Clinical Trials Information System (CTIS).

CADTH-developed search filters were applied to limit retrieval to HTAs, systematic reviews, meta-analyses or network meta-analyses, and RCTs. The RCT study design filter was used in the search for included studies, while additional filters (HTAs, systematic reviews, meta-analyses, and network meta-analyses) were used to retrieve background or supplementary information. A secondary search was conducted to identify nonrandomized studies for inclusion using filters to limit retrieval to any types of clinical trials or observational studies. Retrieval was not limited by publication date but was limited to the English or French language. Conference abstracts were excluded from the search results.

The initial search was completed on March 27, 2023. A secondary search was completed on August 15, 2023. Regular alerts updated the database literature searches until November 27, 2024.

Grey literature (literature that is not commercially published) was identified by searching sources listed in relevant sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist,[43] which included the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google was used to search for additional internet-based materials. The grey literature search was updated before completion of the stakeholder feedback period. Refer to Appendix 1 for more information on the grey literature search strategy.

Study Selection Process

We undertook a staged approach to screening, whereby all records from the first literature search were screened for eligible RCTs, including placebo-controlled RCTs. Next, we screened the second literature search for nRCTs and prospective comparative cohort studies to fill the gaps in the RCT evidence, considering the limited evidence for all comparison outcomes.

Before screening, 2 reviewers conducted a pilot testing round by independently screening 100 randomly selected articles in duplicate, after which they met to resolve disagreements and confirm a mutual understanding of the selection criteria. No additional pilot testing rounds were needed.

Once the reviewers were satisfied with their understanding of the selection criteria, the 2 reviewers independently screened the titles and abstracts of all of the citations retrieved from the literature searches for relevance to the clinical research question in Microsoft Excel workbooks. Full texts of titles or abstracts that were judged to be potentially relevant by at least 1 reviewer were retrieved and independently assessed by 2 reviewers for possible inclusion; disagreements at the full-text level were discussed until consensus was reached. If consensus could not be reached, a third reviewer was consulted. Reference lists of included studies and relevant systematic reviews identified during screening were screened by title, then by full text. Reviewers did not attempt to retrieve further information from study investigators in cases where a study's eligibility for inclusion could not be ascertained from the report.

A list of studies selected for inclusion in the systematic review was posted to the website for stakeholder review for 10 business days. Feedback and any additional studies identified for potential inclusion were reviewed following the outlined process.

Data Extraction

All relevant data were extracted directly into a standardized data abstraction form, which was part of a review-specific Microsoft Excel workbook. The form was pilot tested with 2 studies before beginning full data extraction to ensure that it was usable and that it completely and reliably captured the items of interest, while avoiding redundancies.

Formal data extraction was performed by 1 reviewer and independently checked for accuracy and completeness by a second reviewer. Any disagreement in the assessment of these data was resolved through discussion until consensus was reached, or through involvement of a third reviewer if required.

Relevant information to be extracted included details of the study characteristics, methodology, population, intervention, and comparator, as well as relevant results and conclusions regarding the outcomes and the subgroups of interest. All numerical data, including data presented in text or in figures, were extracted. We chose to extract and use the harms data for the overall population in the included RCTs, as harms results in the subgroup population of interest were either not reported, or were reported inconsistently, across publications. This was deemed appropriate, the rationale being that harms outcomes are not expected to differ based on disease activity. In addition, the data would then include a substantially larger sample size. If data were not reported for an outcome, no assumption was made about its presence or absence. Reviewers did not contact the authors of included studies to clarify any information or retrieve missing information.

Risk of Bias Assessments

The reviewers used the following risk of bias assessments, according to the study design of the included studies:

- Outcome-level risk of bias of relevant RCTs, based on the effect of assignment to the intervention (i.e., intention-to-treat effect), was assessed using the Cochrane Risk of Bias tool, version 2 (RoB 2).[44] This assessment tool facilitates the evaluation of potential biases across 5 domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. A judgment of low risk of bias, some concerns regarding the risk of bias, or high risk of bias was assigned for each domain.
- Outcome-level risk of bias in nonrandomized studies was assessed using the Risk Of Bias In Nonrandomized Studies – Interventions (ROBINS-I) tool.[45] ROBINS-I facilitates the assessment of the risk of bias across 7 domains: confounding, selection bias, measurement of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Risk of bias per domain per study result was assessed and used to assign an overall judgment to each study result (low, moderate, serious, or critical risk of bias, or no information).

For each tool, the overall risk of bias of each study was rated and designated based on the domain-level assessments. Where possible, attempts were made to predict the direction of the potential bias. A rationale is provided for decisions about the risk of bias for both the domain-level and overall assessments.

The risk of bias was evaluated in duplicate by 2 independent reviewers. Any disagreement in the risk of bias for the domain-level and overall assessments was resolved through discussion, with the involvement of a third reviewer when consensus could not be reached. Information necessary to evaluate the risk of bias was obtained from the published reports of each study.

Critical appraisal included the generalizability assessment of the findings (i.e., patient population, choice of outcomes, treatment regimen, and length of follow-up). Throughout the critical appraisal process, reviewers included clinical input from experts consulted for this review.

Studies were not excluded from the systematic review based on the results of the risk of bias assessment or critical appraisal. However, the critical appraisal results and how they affect study findings were used to inform conclusions about the body of evidence for each outcome comparison.

Data Analysis and Synthesis

Before synthesis, we tabulated the characteristics of the included studies — using standardized terminology and similar summary measures when possible — and presented these in a table with an accompanying textual summary. We then charted the available studies and considered which were similar enough in their population, interventions, comparators, and outcomes (PICO) elements (including time point of outcome measurement) to be grouped in the synthesis. Since there was no more than 1 study per outcome comparison evaluated, no synthesis was undertaken.

Interpretation and Drawing Conclusions

Conclusions were drawn for each outcome comparison based on informal appraisals of the certainty of evidence. The following criteria were considered: the risk of bias of the contributing studies, the precision of the effect estimates, and the generalizability (or applicability) of the findings to Canadian clinical practice.

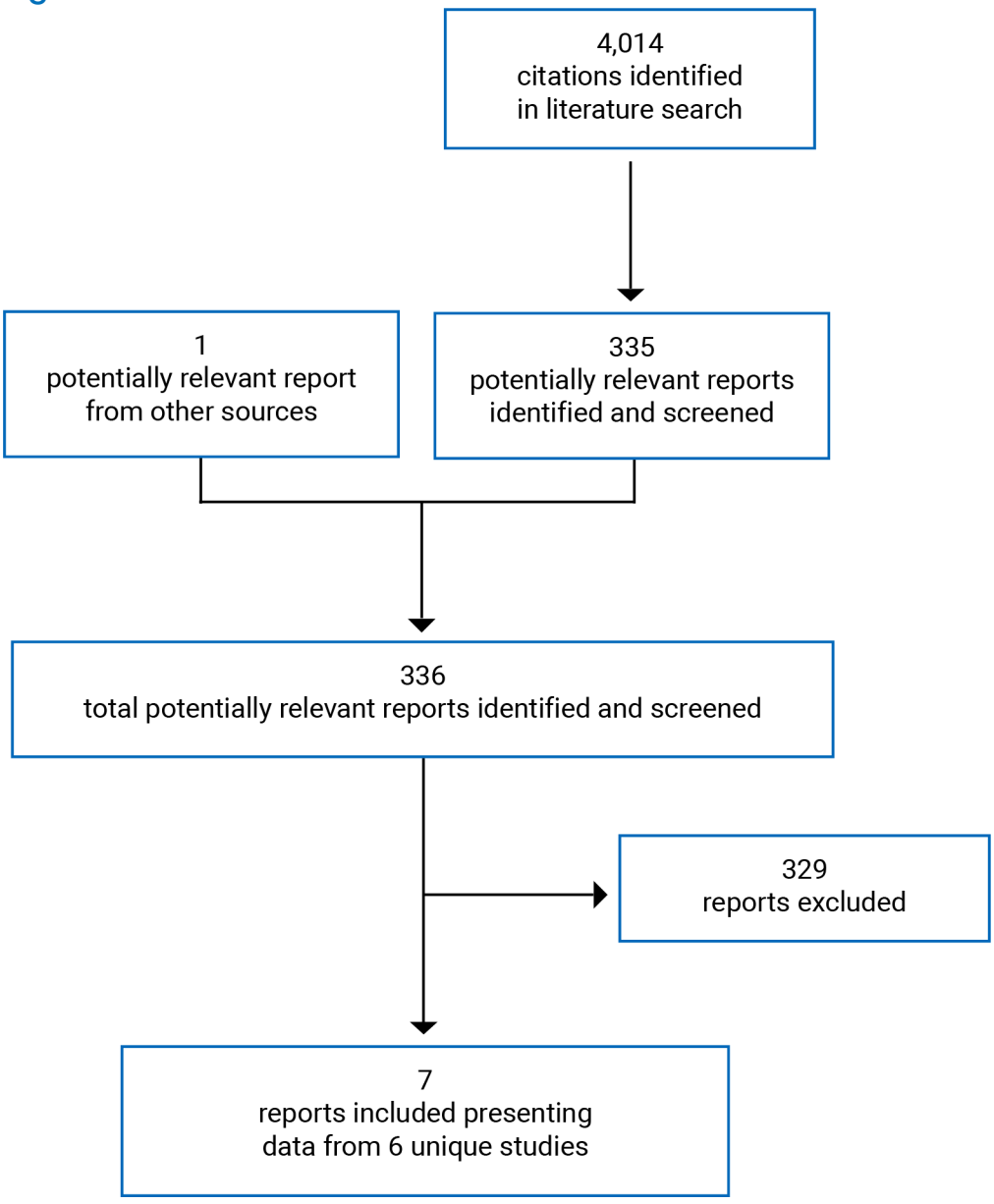
Results of Clinical Evaluation

Selection of Primary Studies

A total of 4,014 citations were identified in the literature searches. Following screening of titles and abstracts, 335 studies were identified as potentially relevant and retrieved for full-text review. One report was retrieved from a total of 37 publications from other sources and was included as potentially relevant (i.e., input from clinical experts on the included studies list). Of these, 7 reports were included in the systematic review, reporting results from 6 individual studies: 5 subgroup analyses from active-controlled or placebo-controlled RCTs[46-51] and 1 observational study.[52]

The report selection process is outlined in Figure 1. Lists of the included and excluded reports, with details describing the rationale for those excluded, are presented in Appendix 2 and 3, respectively.

Figure 1: Flow Chart of the Selection Process



Study and Patient Characteristics

A total of 7 reports were included in the systematic review, reporting results from 6 individual studies: 5 post hoc subgroup analyses from RCTs[46-51] and 1 prospective comparative cohort study.[52] Study characteristics are shown in Appendix 4 and outlined in Table 3.

Population

The population of interest was patients who are treatment-naive with highly active RRMS, which was defined in the studies as at least 2 relapses within the previous year, and at least 1 gadolinium (Gd)-enhancing

lesion. Baseline characteristics were not reported specifically for the subgroup populations in the RCTs.[46-51] Randomization in these studies was not stratified by the presence of highly active disease; therefore, there is uncertainty as to whether the randomization was maintained in the subgroups. In the prospective comparative cohort study,[52] the mean age of patients ranged between 30 years and 32 years across treatment groups at baseline. For disease characteristics, the mean time since the first onset of symptoms was approximately 2 years, with a mean Expanded Disability Status Scale (EDSS) score of 2 and a mean of 2 relapses in the previous year.[52]

Interventions and Comparators

The RCTs included in the systematic review[46-51] evaluated the efficacy and safety of alemtuzumab, fingolimod, cladribine, and natalizumab compared to interferon or a matching placebo over the course of 1 year to 2.5 years. The included prospective comparative cohort study[52] compared natalizumab, fingolimod, and interferon against each other over the course of 2 years.

Outcomes

The RCTs assessed relapses as the primary outcome using the annualized relapse rate (ARR), which is the number of MS relapses experienced in a year. Definitions of relapses are described in Table 3 and were consistent across most studies,[46-49,51] with the exception of the FREEDOMS study,[50] which was reported to be based mainly on disability. The prospective comparative cohort study[52] included relapses as part of its primary outcome, no evidence of disease activity (NEDA), which was defined as the absence of clinical relapses, disability worsening, and radiological activity. A minimally clinically important difference (MCID) has not been estimated for ARR; therefore, assessment of clinical relevance of the results relied on input from the clinical experts consulted for this review.

Disability assessments relied on the EDSS,[46-52] which is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death) in half-point increments starting from 1.0 (i.e., no EDSS of 0.5), and which is widely known and used in clinical practice. The EDSS quantifies disability in the 7 Kurtzke functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral); in conjunction with ambulation, they are rated in the context of a standard neurologic examination, and then these ratings are used together with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign a score. Validity of this tool has been established and it is usually used as a gold standard for evaluating new scales.[53] A clinically meaningful change for patients with MS has been proposed as a change of at least 1.0 if the EDSS score at baseline was 0 to 5.5, and a change of at least 0.5 for higher baseline EDSS scores.[54] This was similar to 2 other studies, which considered "clinically meaningful" to be an increase of at least 1.5 points when the baseline was 0; an increase of at least 1 point from a baseline of 1 to 5.5; and an increase of at least 0.5 points from a baseline score greater than or equal to 6.[55,56]

MRI outcomes were used in the studies[46-52] as secondary end point measurements. Key MRI outcomes included Gd-enhanced T1 brain MRI lesions, which are useful for identifying active inflammation (Gd enhancement represents leakage into the perivascular space as a result of local breakdown of the blood brain barrier due to inflammation).[57] Another key MRI outcome would be an increase in hyperintense T2-weighted brain MRI lesions, which are associated with brain atrophy and reflective of accumulation of

disease burden.[57] Finally, T1-hypointense lesions are considered representative of axonal loss and matrix destruction.[58] An MCID was not estimated for MRI outcomes; therefore, the assessment of clinical relevance of the results relied on input from the clinical experts consulted for this review. MRI outcomes may be considered a good surrogate for clinical disease activity.[59,60]

Harms results in the subgroup population of interest were either not reported, or were reported inconsistently, across publications; therefore, we chose to extract harms data for the overall population in the included RCTs. This was deemed appropriate, the rationale being that harms outcomes are not expected to differ based on disease activity.

Table 3: High-Level Study Characteristics[a]

Criteria	CARE-MS I trial Krieger et al. 2014[46] (Abstract)	TRANSFORMS trial Cohen et al. 2013[47]	CLARITY trial Vermersch et al. 2021[49]	FREEDOMS trial Devonshire et al. 2012[50]	AFFIRM trial Hutchinson et al. 2009[51]	Prosperini et al. 2017[52]
Design	Subgroup analysis from head-to-head RCT		Subgroup analysis from placebo-controlled RCT			Prospective comparative cohort study
Blinding	Rater-blinded	Double-blinded				Open-label
Population	Highly active relapsing MS, with no previous MS therapy: • ≥ 2 relapses within the prior year • ≥ 1 Gd-enhancing lesion at baseline.	Highly active disease: • treatment-naive • ≥ 2 relapses within the prior year • ≥ 1 Gd-enhancing T1 lesion at baseline.	Highly active disease: • treatment-naive • ≥ 2 relapses within the prior year • ≥ 1 Gd-enhancing T1 or ≥ 9 T2 lesions.	Treatment-naive, rapidly evolving, severe relapsing MS: • ≥ 2 relapses within the prior year • ≥ 1 Gd-enhancing lesion.	Highly active relapsing MS: • ≥ 2 relapses within the prior year • ≥ 1 Gd+ lesion on T1-weighted MRI.	Highly active treatment-naive: • no prior DMT • ≥ 2 relapses within the prior year • ≥ 1 Gd-enhancing lesion.
N	N = 166	N = 57	N = 187	N = 85	N = 209	N = 120
Interventions	Alemtuzumab 12 mg IV daily for 5 days, then daily for 3 days at 12 months	Fingolimod 0.5 mg orally daily for 12 months	Cladribine 3.5 mg/kg orally over a 2-year administration	Fingolimod 0.5 mg orally daily for 24 months	Natalizumab 300 mg IV infusion every 4 weeks	Natalizumab Fingolimod Interferon beta-1b or beta-1a
Comparators	Interferon beta-1a 44 mcg SC 3 times per week	Interferon beta-1a 30 mcg IM weekly for 12 months	Matching placebo			Interventions compared against one another
Primary outcome	Relapse rate at 2 years	Relapse rate at 1 year	Relapse rate at 2 years	Relapse rate at 2 years	Relapse rate at 2.5 years	NEDA at 2 years
Primary outcome definition	• New or worsening neurologic symptoms attributable to MS • Lasting ≥ 48 hours	• New, worsening, or recurrent neurologic symptoms • After ≥ 30 days of the onset of prior relapse	• Meeting predefined increase in EDSS • No fever • Lasting ≥ 24 hours	• Presence of symptoms assessed by neurologist and meeting predefined change in EDSS	• New or recurrent neurologic symptoms • No fever or infection • Lasting ≥ 24 hours	• New or worsening neurologic symptoms attributable to MS • Lasting ≥ 48 hours • No pyrexia

Criteria	CARE-MS I trial Krieger et al. 2014[46] (Abstract)	TRANSFORMS trial Cohen et al. 2013[47]	CLARITY trial Vermersch et al. 2021[49]	FREEDOMS trial Devonshire et al. 2012[50]	AFFIRM trial Hutchinson et al. 2009[51]	Prosperini et al. 2017[52]
	• No pyrexia • After ≥ 30 days of clinical stability • Meeting predefined change in EDSS	• Lasting ≥ 24 hours • No fever or infection • Meeting predefined increase in EDSS	• Preceded by ≥ 30 days of clinical stability		• With neurologic signs identified by neurologist	• After ≥ 30 days of clinical stability • Meeting predefined change in EDSS
Other key outcomes	• Sustained accumulation of disease activity (EDSS) • Radiological activity • Harms	• Radiological activity • Harms	• Sustained accumulation of disease activity (EDSS) • MRI outcomes • Harms	• Disability progression (EDSS) • Harms	• Sustained progression of disability (EDSS) • MRI outcomes • Harms	• Relapse • Disability • Radiological activity

DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; Gd = gadolinium; IM = intramuscular; MS = multiple sclerosis; NA = not applicable; NEDA = no evidence of disease activity; RCT = randomized controlled trial; SC = subcutaneous.

[a]Abstracts identified via the searches or other means that included relevant data were included in the review, given the paucity of published research.

Summary of Risk of Bias Assessment

The risk of bias appraisal of all of the included studies is outlined in Table 4 and Table 5 and described in detail in Appendix 5. The key limitations (i.e., those having an impact on the interpretation of the findings) are summarized in this section. A separate section reports the risk of bias assessment for the prospective comparative cohort study.[52]

There is a risk of bias in the systematic review due to missing evidence. Frequently, the included publications would only report P values for results. As such, this indicates that the results are available (and were analyzed), although we were unable to comprehensively include them in our report or use them to inform conclusions.

Subgroup Analyses From RCTs

The post hoc subgroup analyses from 5 RCTs that were included in the review were rated as having a high risk of bias for all outcomes.[46-51] Among the key issues was the fact that, in all RCTs, subgroups were analyzed post hoc. Therefore, randomization was not stratified for the subgroup, raising concerns about whether the groups being compared were similar in important prognostic factors. Characteristics of patients assigned to each intervention group were not reported for the subgroup of interest in any RCT, precluding confirmation of whether prognostic balance was achieved, at least for measured factors. In addition, no information was reported as to how patients with missing outcome data were handled. Discontinuations were reported in the overall population, but were not reported for the relevant subgroup. Therefore, the proportion of patients with missing outcome data in each intervention group in the subgroup is not known, and it is unclear whether bias may have been introduced. Finally, the harms profiles of the interventions and comparators differed enough that assessors may have guessed which study drug patients were receiving, based on the specific harms outcomes reported, despite being blinded to treatment assignment. This may introduce bias in the subjectively measured AEs, but not in the efficacy assessments, as all of the studies had different assessors for efficacy and for harms outcomes. As such, efficacy assessors were not aware of any information pertaining to the harms assessment.

Observational Evidence

The prospective comparative cohort study by Prosperini et al. (2017) was rated as having a serious risk of bias for all outcomes assessed.

More specifically, the study was considered at risk of bias due to confounding. Propensity score matching was performed using the nearest neighbour procedure; however, the publication did not report the potential confounding factors that were identified by the authors. No sensitivity analysis was performed to control for potentially unidentified confounding domains in the relevant cohort. Various methods could have been used to adjust for the differences between treatment groups in uncaptured known confounders and unknown potential confounders, which can affect the validity of the comparison and introduce bias for which the direction is unknown. The outcomes of relapse and disability were subject to additional bias, considering that these require evaluations by assessors who were aware of the intervention received.

Table 4: Risk of Bias Assessment per Outcome Within Each RCT Using RoB2[44]

Study	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Relapse						
CARE-MS I[46,61]	Some concern	High	High	Low	Some concern	High
TRANSFORMS[47,62]	Some concern	High	High	Low	Some concern	High
CLARITY[49,63]	Some concern	High	High	Low	Some concern	High
FREEDOMS[50,64]	Some concern	High	High	Low	Some concern	High
AFFIRM[51,65]	Some concern	High	High	Low	Some concern	High
Disability progression						
CLARITY[49,63]	Some concern	High	High	Low	Some concern	High
FREEDOMS[50,64]	Some concern	High	High	Low	Some concern	High
AFFIRM[51,65]	Some concern	High	High	Low	Some concern	High
Imaging outcomes						
TRANSFORMS[47,62]	Some concern	High	High	Low	Some concern	High
CLARITY[49,63]	Some concern	High	High	Low	Some concern	High
AFFIRM[51,65]	Some concern	High	High	Low	Some concern	High
Harms						
CARE-MS I[46,61]	Some concern	High	Low	Some concern	Some concern	High
TRANSFORMS[47,62]	Some concern	High	Low	Some concern	Some concern	High
CLARITY[49,63]	Some concern	High	Low	Some concern	Some concern	High
FREEDOMS[50,64]	Some concern	High	Low	Some concern	Some concern	High
AFFIRM[51,65]	Some concern	High	Low	Some concern	Some concern	High

RoB2 = Cochrane Risk of Bias tool, version 2.

Table 5: Risk of Bias Assessment per Outcome for the Study by Prosperini et al. Using ROBINS-I[45]

Prosperini et al. 2017[52]	Confounding	Patient selection	Classification of interventions	Deviations from intended interventions	Missing data	Outcome measurement	Selection of reported results	Overall
Relapse	Serious	Low	Low	Low	Low	Moderate	Moderate	Serious
Disability	Serious	Low	Low	Low	Low	Moderate	Moderate	Serious
Imaging outcomes	Serious	Low	Low	Low	Low	Low	Moderate	Serious

ROBINS-I = Risk Of Bias In Nonrandomized Studies – Interventions.

Data Analysis and Synthesis

Results

Alemtuzumab Versus Interferon Beta-1a

The relevant results presented in this section are based on information from an abstract.

Relapses

After 2 years of follow-up in the CARE-MS I trial (N = 105 patients in the alemtuzumab arm and N = 61 patients in the interferon arm),[46] the ARR was 0.20 relapses per year in the alemtuzumab arm and 0.41 relapses per year in the interferon arm (no measures of precision were reported) (P = 0.0068). The use of alemtuzumab was therefore associated with a relative rate reduction of 51% versus interferon (no measure of precision reported).

The proportions of patients who were relapse-free at 2 years were 76% in those receiving alemtuzumab and 50% in those receiving interferon (no measures of precision were reported). The use of alemtuzumab was associated with a hazard ratio (HR) of 0.40 (95% CI, 0.24 to 0.68; P = 0.0007) versus interferon.

The magnitude of the between-group differences in relapse outcomes may be considered clinically meaningful, according to the clinical experts consulted for this review.

Although no numeric result was reported, the report indicated that alemtuzumab was statistically superior to interferon with regard to freedom from clinical, MRI, and disease activity (P = 0.0025).

Disability

No numeric result was reported; however, the report indicated that there was no statistical difference between groups with regard to the mean change in EDSS scores.

Function

No data were reported for the outcome of function.

Imaging Outcomes

No numeric result was reported; however, the report indicated that alemtuzumab was superior to interferon to prevent an increase in the mean number of Gd-enhancing lesions, new or enlarging T2 lesions, and new T1-hypointense lesions (P < 0.05).

Cognitive Outcomes

No data were reported for cognitive outcomes.

Symptoms

No data were reported for the symptoms of RRMS.

Health-Related Quality of Life

No data were reported for the outcome of HRQoL.

Instrumental Activities of Daily Living

No data were reported for the instrumental activities of daily living.

Harms – Overall Study Population

High proportions of patients experienced adverse events (AEs) throughout the 2-year follow-up of the CARE-MS study,[61] and proportions were similar between the alemtuzumab and interferon treatment groups (96% and 92%, respectively). The proportions of patients who experienced serious adverse events (SAEs) were 18% in the alemtuzumab arm and 14% in the interferon arm. Withdrawals due to adverse events (WDAEs) were low in both groups, but numerically higher in patients receiving interferon (1% and 6%, respectively). One death (< 1%) was reported in the alemtuzumab group (automobile accident).

Regarding harms of special interest, infections were reported as AEs in 67% of patients receiving alemtuzumab and in 45% of patients receiving interferon. The proportions of patients with SAEs of infections (2% and 1%, respectively) and malignancies (1% and 0%, respectively) were low in both groups.

Fingolimod Versus Interferon Beta-1a

Relapses

After 1 year of follow-up in the TRANSFORMS study (N = 27 patients in the fingolimod arm and N = 30 patients in the interferon arm),[47] the use of fingolimod was associated with an ARR reduction of 25% (P = 0.614) versus interferon (no measure of precision reported). The ARR within each treatment group was not reported in the publication; as the absolute difference in relapses between fingolimod and interferon cannot be assessed, it is not possible to determine the clinical relevance of these results.

Disability

No data were reported for the outcome of disability.

Function

No data were reported for the outcome of function.

Imaging Outcomes

The mean number of Gd-enhancing T1 lesions was 0.26 in the fingolimod arm and 0.43 in the interferon arm (no measures of precision were reported). The use of fingolimod was associated with an RRR of 40% (P = 0.620) versus interferon (no measure of precision reported). The mean number of new or newly enlarging T2 lesions was 1.87 in the fingolimod arm and 5.24 in the interferon arm, yielding an RRR of 64% (no measure of precision reported) (P = 0.038).

Cognitive Outcomes

No data were reported in for cognitive outcomes.

Symptoms

No data were reported in for the symptoms of relapsing MS.

Health-Related Quality of Life
No data were reported for the outcome of HRQoL.

Instrumental Activities of Daily Living
No data were reported for the instrumental activities of daily living.

Harms – Overall Study Population
High proportions of patients experienced AEs throughout the 1-year follow-up duration of the TRANSFORMS study,[62] and proportions were similar between the fingolimod and interferon treatment groups (86% and 92%, respectively). The proportions of patients who experienced SAEs were 7% in the fingolimod arm and 6% in the interferon arm. WDAEs were low in both groups, but numerically higher in patients receiving fingolimod (6% in the fingolimod arm versus 4% in the interferon arm). No deaths were reported throughout the study.

There was limited reporting of harms of special interest in the publication; those reported were experienced by similar proportions of patients in both the fingolimod and interferon treatment groups, except for malignancies, which were numerically more frequent in patients receiving fingolimod (2% and < 1%, respectively).

Cladribine Versus Placebo

Relapses
After 2 years of follow-up in the CLARITY study (N = 94 patients in the cladribine arm and N = 93 patients in the placebo arm),[49] the mean number of relapses was 0.21 (standard deviation [SD] = 0.44) in the cladribine arm and 0.80 (SD = 1.14) in the placebo arm. This resulted in an ARR of 0.12 (95% CI, 0.08 to 0.19) in the cladribine arm and 0.47 (95% CI, 0.37 to 0.59) in the placebo arm. The use of cladribine was associated with a rate ratio of 0.26 (95% CI, 0.16 to 0.42; P < 0.0001) versus placebo according to a Poisson regression model, corresponding to a relative rate reduction of 74% (95% CI not reported).

The proportions of patients who experienced a relapse throughout the study, according to Kaplan-Meier survival curves, was 21% (95% CI, 12.6 to 30.1) in patients receiving cladribine and 47% (95% CI, 36.7 to 57.7) in patients receiving placebo. The use of cladribine was associated with an HR of 0.36 (95% CI, 0.21 to 0.62; P = 0.0002) versus placebo.

The magnitude of the between-group differences in relapse outcomes may be considered clinically meaningful, according to the clinical experts consulted for this review.

Disability
The study assessed disability using the confirmed EDSS progression, defined in the study as the time to an increase of at least 1 point in the EDSS score (or 1.5 points, if the EDSS score at baseline was 0), which was sustained for at least 3 months, or at least 6 months. These selected thresholds were considered appropriate by the clinical experts, and they reflect the fact that EDSS becomes less sensitive at higher levels of disability.

The proportions of patients who experienced a 3-month confirmed EDSS progression throughout the study, according to Kaplan-Meier survival curves, were 10% (95% CI, 4 to 16) in patients receiving cladribine and 30% (95% CI, 20 to 40) in patients receiving placebo. The use of cladribine was associated with an HR of 0.29 (95% CI, 0.14 to 0.63; P = 0.0016) versus placebo, and with an RRR of 71% (95% CI not reported).

Similarly, the proportion of patients who experienced a 6-month confirmed EDSS progression was 4% (95% CI, 0.2 to 9) in patients receiving cladribine and 23% (95% CI, 14 to 32) in patients receiving placebo. The use of cladribine was associated with an HR of 0.17 (95% CI, 0.06 to 0.51; P = 0.0015) versus placebo, and with an RRR of 83% (95% CI not reported).

The magnitude of the between-group differences in progression of disability may be considered clinically meaningful, according to the clinical experts consulted for this review.

Function

No data were reported for the outcome of function.

Imaging Outcomes

The mean number of new Gd-enhancing T1 lesions per scan was 0.13 (95% CI, 0.08 to 0.21) in the cladribine arm and 1.19 (95% CI, 0.83 to 1.71) in the placebo arm. The magnitude of the between-group differences in imaging outcomes may be considered clinically meaningful, according to the clinical experts consulted for this review. The use of cladribine was associated with a rate ratio of 0.11 (95% CI, 0.06 to 0.20; P < 0.0001) versus placebo, according to a negative binomial regression model, corresponding to a relative rate reduction of 89% (95% CI not reported).

Similarly, the mean number of active T2 lesions per scan was 0.40 (95% CI, 0.28 to 0.56) in the cladribine arm and 1.84 (95% CI, 1.36 to 2.50) in the placebo arm. The use of cladribine was associated with a rate ratio of 0.22 (95% CI, 0.14 to 0.34; P < 0.0001) versus placebo.

Finally, the mean number of new T1-hypointense lesions per scan was 0.15 (95% CI, 0.10 to 0.22) in the cladribine arm and 0.70 (95% CI, 0.52 to 0.95) in the placebo arm. The use of cladribine was associated with a rate ratio of 0.21 (95% CI, 0.12 to 0.35; P < 0.0001) versus placebo.

Cognitive Outcomes

No data were reported for cognitive outcomes.

Symptoms

No data were reported for the symptoms of relapsing MS.

Health-Related Quality of Life

No data were reported for the outcome of HRQoL.

Instrumental Activities of Daily Living

No data were reported for the instrumental activities of daily living.

Harms – Overall Study Population

High proportions of patients experienced AEs throughout the 2-year follow-up duration of the CLARITY study,[63] and proportions were similar between the cladribine and placebo treatment groups (81% and 73%, respectively). The proportions of patients who experienced SAEs were 8% in the cladribine arm and 6% in the placebo arm. WDAEs were low in both groups (4% and 2%, respectively). Two deaths (< 1%) were reported in both the cladribine arm (due to myocardial infarction and metastatic pancreatic carcinoma) and the placebo arm (due to suicide and hemorrhagic stroke).

As for harms of special interest, infections were reported as AEs in 48% of patients receiving cladribine and in 43% of patients receiving placebo. The proportions of patients with SAEs of infections (2.3% and 1.6%, respectively) and malignancies (1.4% and 0%, respectively) were low in both groups, but numerically higher in patients receiving cladribine. However, the proportion of patients experiencing lymphopenia or lymphocytopenia was higher with cladribine (22%) compared to placebo (2%).

Fingolimod Versus Placebo

Relapses

After 2 years of follow-up in the FREEDOMS study (N = 48 patients in the fingolimod arm and N = 37 patients in the placebo arm),[50] the ARR was 0.24 relapses per year (95% CI, 0.15 to 0.40) in the fingolimod arm and 0.74 relapses per year (95% CI, 0.49 to 1.11) in the placebo arm. The use of fingolimod was associated with a rate ratio of 0.33 (95% CI, 0.18 to 0.62; P = 0.0006) versus placebo according to a negative binomial regression model, corresponding to a relative rate reduction of 67% (95% CI not reported). The magnitude of the between-group difference in relapse may be considered clinically meaningful, according to the clinical experts consulted for this review.

Disability

In the study, disability progression was defined as an increase of at least 1 point in the EDSS score (or 0.5 points if the EDSS score at baseline was at least 5.5). A disability progression after 3 months meant that this criterion had to be met both at the onset of disability, and maintained at least up until the follow-up assessment 3 months later. These selected thresholds were considered appropriate by the clinical experts consulted, and they reflect the fact that EDSS becomes less sensitive at higher levels of disability.

The proportion of patients who experienced freedom from disability progression confirmed after 3 months throughout the study, according to Kaplan-Meier survival curves, was 85% (95% CI, 74 to 95) in patients receiving fingolimod and 79% (95% CI, 65 to 93) in patients receiving placebo. The use of fingolimod was associated with an HR of 0.73 (95% CI, 0.25 to 2.07; P = 0.55) versus placebo, and with an RRR of 27% (95% CI not reported). The magnitude of the between-group differences in progression of disability was not considered clinically meaningful, according to the clinical experts consulted.

Function

No data were reported for the outcome of function.

Imaging Outcomes
No data were reported for imaging outcomes.

Cognitive Outcomes
No data were reported for cognitive outcomes.

Symptoms
No data were reported for the symptoms of RRMS.

Health-Related Quality of Life
No data were reported for the outcome of HRQoL.

Instrumental Activities of Daily Living
No data were reported for the instrumental activities of daily living.

Harms – Overall Study Population
High proportions of patients experienced AEs throughout the 2-year follow-up duration of the FREEDOMS study,[64] and proportions were similar between the fingolimod and placebo treatment groups (94% and 93%, respectively). The proportions of patients who experienced SAEs were 10% in the fingolimod arm and 13% in the placebo arm. WDAEs averaged 8% in both groups. Two deaths (< 1%) were reported, both of which occurred in the placebo group (due to pulmonary embolism and a traffic accident).

There was limited reporting of harms of special interest in the publication; those reported were experienced by similar proportions of patients in both the fingolimod and placebo treatment groups, except for malignancies, which were numerically more frequent in patients receiving placebo (0.9% in the fingolimod group and 2.2% in the placebo group). However, the proportions of patients experiencing lymphopenia or lymphocytopenia were higher with fingolimod (3.5%) compared with placebo (0.5%).

Natalizumab Versus Placebo

Relapses
After 2.5 years of follow-up in the AFFIRM study (N = 148 patients in the natalizumab arm and N = 61 patients in the placebo arm),[51] the ARR was 0.28 relapses per year in the natalizumab arm and 1.46 relapses per year in the placebo arm (no measure of precision was reported). The use of natalizumab was therefore associated with a relative rate reduction of 81% (P < 0.001) versus placebo (no measure of precision reported).

The ARR that required treatment with corticosteroids was 0.15 relapses per year in the natalizumab arm and 0.76 relapses per year in the placebo arm, yielding a relative rate reduction of 80% (P < 0.001) (no measures of precision reported).

The cumulative probability of relapse throughout the study was 29% in patients receiving natalizumab and 76% in patients receiving placebo (no measures of precision reported). The use of natalizumab was associated with an HR of 0.25 (95% CI, 0.16 to 0.39; P < 0.001) versus placebo.

The magnitude of the between-group differences in relapse outcomes may be considered clinically meaningful, according to the clinical experts consulted for this review.

Disability

The cumulative probability of disability progression sustained for 3 months throughout the study, according to Kaplan-Meier survival curves, was 14% in patients receiving natalizumab and 29% in patients receiving placebo (95% CI not reported). The use of natalizumab was associated with an HR of 0.47 (95% CI, 0.24 to 0.93; P = 0.029) versus placebo, and with an RRR of 53% (95% CI not reported).

Similarly, the cumulative probability of disability progression sustained for 6 months was 10% in patients receiving natalizumab and 26% in patients receiving placebo (95% CI not reported). The use of natalizumab was associated with an HR of 0.36 (95% CI, 0.17 to 0.76; P = 0.008) versus placebo, and with an RRR of 65% (95% CI not reported).

The magnitude of the between-group differences in progression of disability may be considered clinically meaningful, according to the clinical experts consulted for this review.

Function

No data were reported for the outcome of function.

Imaging Outcomes

The mean number of new Gd-enhancing lesions was 0.5 (SD = 2.8) in the natalizumab arm and 3.2 (SD = 7.4) in the placebo arm. The use of natalizumab was associated with an RRR of 84% (no measure of precision reported) (P < 0.001) versus placebo.

Similarly, the mean number of new or enlarging T2-hyperintense lesions was 4.2 (SD = 17.8) in the natalizumab arm and 19.1 (SD = 23.6) in the placebo arm, yielding an RRR of 78% (no measure of precision reported) (P < 0.001).

Finally, the mean number of new T1-hypointense lesions was 2.2 (SD = 6.1) in the natalizumab arm and 7.0 (SD = 8.8) in the placebo arm, yielding an RRR of 69% (no measure of precision reported) (P < 0.001).

The magnitude of the between-group differences in imaging outcomes may be considered clinically meaningful, according to the clinical experts consulted for this review.

Cognitive Outcomes

No data were reported for cognitive outcomes.

Symptoms

No data were reported for the symptoms of RRMS.

Health-Related Quality of Life

No data were reported for the outcome of HRQoL.

Instrumental Activities of Daily Living

No data were reported for the instrumental activities of daily living.

Harms – Overall Study Population

High proportions of patients experienced AEs throughout the 2.5-year follow-up duration of the AFFIRM study,[65] and proportions were similar between the natalizumab and placebo treatment groups (95% and 96%, respectively). The proportion of patients who experienced SAEs was 19% in the natalizumab arm and 24% in the placebo arm. WDAEs were low in both groups (6% and 4%, respectively). Two deaths (< 1%) were reported, both of which occurred in the natalizumab group (due to malignant melanoma and alcohol intoxication).

Regarding harms of special interest, injection-related reactions were reported in 24% of patients receiving natalizumab and 18% of patients receiving placebo. The proportions of patients with AEs of infections were high and similar between groups (79% each); however, few patients reported SAEs of infections (3% each) or malignancies (< 1% each), and those proportions were also similar between treatment arms.

Natalizumab, Fingolimod, and Interferon Beta-1a or Beta-1b – Observational Evidence

No Evidence of Disease Activity

After 2 years of follow-up in the study by Prosperini et al.,[52] the proportions of patients reaching NEDA was 75% in the natalizumab group (n = 40), 67% in the fingolimod group, and 40% in the interferon group (n = 40) (measures of precision not reported). Statistical significance was not reached for any between-group comparison.

Relapses

The proportion of patients who experienced relapses was 12% in the natalizumab arm, 20% in the fingolimod arm, and 42% in the interferon arm (measures of precision not reported). The use of natalizumab was associated with an HR of 0.29 (95% CI, 0.11 to 0.81; P = 0.045) versus interferon, and the use of fingolimod was associated with an HR of 0.48 (95% CI, 0.20 to 1.12; P = 0.19) versus interferon.

Disability

The proportion of patients who experienced disability worsening was 5% in the natalizumab arm, 10% in the fingolimod arm, and 27% in the interferon arm (measures of precision not reported). The use of natalizumab was associated with an HR of 0.18 (95% CI, 0.04 to 0.82; P = 0.081) versus interferon; the use of fingolimod was associated with an HR of 0.39 (95% CI, 0.12 to 1.25; P = 0.22) versus interferon; and the use of natalizumab was associated with an HR of 0.40 (95% CI, 0.08 to 5.32; P = 0.37) versus fingolimod.

The proportion of patients who experienced disability reduction was 20% in the natalizumab arm, 5% in the fingolimod arm, and 0% in the interferon arm (measures of precision not reported). There was a statistically significant between-group difference in the comparison of natalizumab versus interferon (P = 0.009); the magnitude of the difference and 95% CI were not reported. Other comparisons between groups did not reach statistical significance; again, the magnitude of the differences and associated 95% CIs were not reported.

Function
No data were reported for the outcome of function.

Imaging Outcomes
The proportion of patients who experienced radiological activity was 22% in the natalizumab arm, 27% in the fingolimod arm, and 55% in the interferon arm (measures of precision not reported). The use of natalizumab was associated with an HR of 0.42 (95% CI, 0.19 to 0.93; P = 0.096) versus interferon; the use of fingolimod was associated with an HR of 0.50 (95% CI, 0.24 to 1.05; P = 0.13) versus interferon; and the use of natalizumab was associated with an HR of 0.99 (95% CI, 0.38 to 2.57; P = 0.99) versus fingolimod.

Cognitive Outcomes
No data were reported for cognitive outcomes.

Symptoms
No data were reported for the symptoms of RRMS.

Health-Related Quality of Life
No data were reported for the outcome of HRQoL.

Instrumental Activities of Daily Living
No data were reported for the instrumental activities of daily living.

Discussion

Summary of the Evidence
We conducted a systematic review of 7 reports (reporting results for post hoc subgroup analyses of 5 RCTs and 1 prospective comparative cohort study) identified through a systematic search and selection procedure. The studies reported findings on the use of alemtuzumab, natalizumab, cladribine, and fingolimod compared to first-line MS treatments or placebo;[46-52] no study was identified to evaluate the use of rituximab in the first-line treatment of patients with highly active RRMS.

In the studies contributing to the evidence, highly active RRMS was defined as having at least 2 relapses within the prior year, and at least 1 Gd-enhancing lesion.[46-52] Disability assessments relied on EDSS score, which is used in clinical practice. Definitions and assessments of relapse and progression of disability were considered fairly objective and representative of clinical practice. The principal goal of MS treatment is to delay and prevent the accumulation of disability by reducing the frequency of relapses and MRI lesions;[4] as such, the study follow-up ranged between 1 year and 2.5 years and allowed for the appropriate evaluation of relapses (assessed as a primary outcome) and disability (generally assessed as a key secondary outcome). No evidence was identified to inform the following outcomes: function, cognitive outcomes, symptoms, HRQoL, and instrumental activities of daily living.

The 5 subgroup analyses from RCTs included in the systematic review were rated as having a high risk of bias,[46-51] mainly due to the randomization process that was not stratified for the subgroups (as these were defined post hoc) and to limited reporting of patient characteristics and missing outcome data at the subgroup level. The observational study was rated as having a serious risk of bias,[52] mainly due to the risk of confounding. Our confidence in the findings from the included studies is limited by the small sample sizes. This introduces uncertainty due to imprecision, which is reflected in the wide CIs (when measures of precision were reported); in many cases, the imprecision precluded a conclusion as to which treatment may be favoured. There were also limited absolute comparative effect estimates reported in the publications, thus precluding conclusions regarding the clinical importance of the observed effects. It was not deemed appropriate to attempt to perform ITCs, due to the limited overall body of evidence that could be identified in the literature in the specific patient population, and to the lack of reporting of patients' characteristics.

Interpretation of Clinical Results From the Systematic Review

Alemtuzumab Versus Interferon Beta-1a

Evidence from post hoc subgroup analyses of a rater-blinded RCT[46] suggests that alemtuzumab may result in a clinically important reduction in the relapse rate, as well as in a clinically important increase in the proportions of patients remaining relapse-free at 2 years compared to interferon. However, the evidence to support this conclusion is uncertain. In addition to the high risk of bias and the small sample size, no measure of precision was reported for the absolute differences. This considerably limits the interpretation of the results. No data were reported for the outcome of disability, which is particularly important according to patient and clinician input, especially considering that disability can progress in patients with MS despite the absence of relapses. Therefore, the evidence available for alemtuzumab versus interferon in patients with highly active RRMS is considered limited due to insufficient reporting. The clinical experts consulted for this review highlighted that alemtuzumab is only rarely used in clinical practice at this time, due to the extent of possibly serious complications associated with its use, while there are currently other highly effective alternatives available with lower potential for complications and AEs. The harms profile of alemtuzumab appeared overall similar to that of interferon in the study[61] and did not raise new safety concerns.

Fingolimod Versus Interferon Beta-1a

Evidence from post hoc subgroup analyses of a double-blind RCT[47] was insufficient to draw any conclusion as to whether fingolimod or interferon beta-1a were favoured with respect to reduction in the relapse rate at 1 year. The reporting of the results was limited to only a relative rate reduction and P value, which was not statistically significant and suggests that there is imprecision. With respect to Gd-enhancing T1 lesions at 1 year, the evidence was insufficient to draw any conclusion as to which treatment was favoured; again, the P value suggested imprecision. For Gd-enhancing T2 lesions at 1 year, fingolimod was favoured statistically over interferon beta-1a; however, a full appraisal of the clinical relevance of the results was not possible. As was the case for all the results reported in the publication, the absence of absolute between-group differences with CIs precluded any conclusion to be drawn about the presence or absence of a clinically important effect. The evidence is uncertain, as it was associated with a high risk of bias, and the sample size was particularly small. In addition, no data were reported for the outcome of disability, or for any other

important clinical outcome. The clinical experts consulted for this review highlighted that fingolimod is now rarely being initiated in new patients in clinical practice, as other options currently available are considered at least of comparable efficacy with fewer long-term harms and requirements for monitoring. The harms profile of fingolimod appeared overall similar to that of interferon in the study[62] and did not raise new safety concerns; however, reporting of notable known harms of the drug was limited.

Cladribine Versus Placebo

Evidence from post hoc subgroup analyses of a double-blind RCT[49] suggest that cladribine may result in a clinically important reduction in relapse rate, progression of disability, and key MS-related lesions on MRI scan at 2 years compared to placebo. The evidence is uncertain, considering the high risk of bias and the relatively small sample size. The overall harms profile of cladribine appeared similar to that of placebo in the study;[63] however, patients receiving cladribine reported numerically more SAEs of infections and malignancies, and a higher proportion of patients experienced lymphopenia or lymphocytopenia, consistent with the known harms profile of the drug.

Fingolimod Versus Placebo

Evidence from post hoc subgroup analyses of a double-blind RCT[50] suggest that fingolimod may result in a clinically important reduction in the relapse rate at 2 years compared to placebo. The particularly small sample size introduced uncertainty due to imprecision and there is a possibility that the ends of the CIs may constitute a difference that would not be considered clinically meaningful. The evidence was insufficient to draw any conclusion as to whether fingolimod or placebo were favoured with respect to disability progression. The reporting of the results was limited; the absolute between-group difference with a CI was not reported. Although the absolute rates of progression were similar in each group (85% versus 79%), the CI for the relative effect was wide, suggesting important imprecision that precludes a conclusion of similarity or no difference. Disability progression was considered a particularly important outcome according to the clinical experts consulted for this HTA. Overall, the evidence is uncertain and was associated with a high risk of bias. The harms profile of fingolimod appeared similar to that of placebo in the study;[64] however, reporting of harms of special interest was limited. Among these harms, patients receiving fingolimod seemed to experience numerically more malignancies and lymphopenia or lymphocytopenia compared to placebo.

Natalizumab Versus Placebo

Evidence from subgroup analyses of a double-blind RCT[51] suggests that natalizumab may result in a clinically important reduction in the relapse rate, including those relapses requiring corticosteroids and the cumulative probability of relapse, as well as in the rate of MS-related hospitalizations at 2.5 years compared to placebo. In addition, natalizumab may result in a clinically important reduction in the progression of disability and key MS-related lesions on MRI scan compared to placebo. There is uncertainty in the evidence, due to the high risk of bias, relatively small sample size, and the absence of any measure of precision for the absolute differences, which limits the interpretation of the results. The harms profile of natalizumab appeared overall similar to that of placebo in the study[65] and did not raise new safety concerns.

Natalizumab, Fingolimod, and Interferon Beta-1a or Beta-1b – Observational Evidence

Findings from 1 comparative observational study[52] were included to inform the effectiveness and harms of natalizumab and fingolimod compared with interferon in patients who are treatment-naive with highly active relapsing disease, in the context of limited evidence from RCTs. Findings suggest that natalizumab may result in a clinically important reduction in relapses at 2 years compared with interferon, providing that the uncertainty surrounding the results is taken into account when interpreting the findings. Sources of uncertainty include the serious risk of bias, small sample size, and incomplete reporting.

For relapse reduction at 2 years, natalizumab was favoured statistically over interferon; however, a full appraisal of the clinical relevance of the results was not possible. As was the case for all the results reported in the publication, the absence of absolute between-group differences with CIs precluded any conclusion to be drawn about the presence or absence of a clinically important effect. In the comparison of fingolimod versus interferon for the same outcome, the evidence was insufficient to determine which treatment was favoured. Although there was no measure of precision reported for the between-group absolute effect estimate, the HR had a wide CI, including the possibility that either treatment could be favoured.

With respect to disability worsening, natalizumab was favoured over interferon, although — as previously mentioned — no conclusions could be drawn about the precision of the effect. In the comparison of fingolimod versus interferon for this outcome, the evidence was insufficient to determine which treatment was favoured due to the wide CI associated with the relative treatment effect estimate.

With respect to disability reduction, natalizumab was statistically favoured over interferon; however, no absolute or relative between-group effect estimates were reported. There was insufficient reporting to draw meaningful conclusions for the comparison of fingolimod versus interferon for this outcome.

With respect to radiological activity, natalizumab may be favoured over interferon; however, the absence of CIs for the absolute between-group differences again meant that no conclusion could be drawn. In the comparison of fingolimod and interferon, the result was not statistically significant.

In addition, the study did not assess harms outcomes, which constitute a significant aspect of MS treatments.

Additional Considerations

Patients who present with a highly active disease have an aggressive disease course, based on relapse frequency, relapse severity, relapse recovery, and key lesions on brain scan.[4] Canadian data suggest that these patients account for between 4% and 14% of all patients with RRMS.[11]

There is currently an unmet need in the relatively small proportion of patients who have highly active RRMS as they continue to experience relapses and to accumulate irreversible neurologic disability despite treatment with traditional first-line drugs, as described by the Canadian MS Working Group[4] and highlighted by 2 clinical experts in the treatment of patients with MS who were consulted for this HTA.

The unmet need may be met from the recent global shift in clinical practice, moving away from the historically used escalation treatment strategy toward the use of an early high-efficacy treatment strategy,

especially in patients with highly active RRMS. Clinician groups with expertise in treating MS noted that earlier use of higher efficacy treatments for patients presenting with high disease activity, more aggressive disease, or rapidly evolving MS at onset could prevent irreversible damage to the nervous system.[4] Several observational studies from MS registries around the world concluded that an early high-efficacy treatment strategy was superior to an escalation treatment strategy at preventing disability progression over time.[28-32] In the scientific literature, a number of recent peer-reviewed publications, including studies, reviews, and opinion pieces, recommend the use of the early high-efficacy treatment strategy, especially in patients with high disease activity.[33-38] In clinical practice, an increasing number of neurologists prefer the treatment strategy of initiating high-efficacy therapies early for the appropriate patients (instead of following the traditional escalation treatment strategy), according to the clinical experts consulted.

As highlighted by the clinical experts consulted for this review, that there are several barriers to performing RCTs in the specific patient population of patients with RRMS who are treatment-naive and who present with highly active disease. Definitive conclusions could not be drawn from the evidence identified throughout the systematic review process, mainly because the trials did not intend to address this specific research question a priori. Feedback received on the draft clinical report noted that the "highly active disease" terminology and the recognition of the relevance of this subgroup is relatively recent. As such, this subgroup has not traditionally been used as a selection criterion to design specific trials in this population. As a result, after an extensive search of the overall MS literature, only post hoc subgroup analyses, as well as a prospective comparative cohort study, met our eligibility criteria. It may be that further evidence exists but was not captured for this subgroup of highly active patients, because the "highly active" terminology was not in use at the time of the study being conducted. These provided uncertain evidence considering issues such as the unstratified randomization process that increased the risk of bias in subgroup analyses, the small sample sizes of the subgroups that introduced uncertainty, the limited reporting of patient characteristics and precision estimates, as well as the missing outcome data, once again at the subgroup level. When the overall study population was considered as per intended in the trials, these RCTs each appropriately informed decision-making, leading to positive reimbursement recommendations regarding the use of alemtuzumab,[66] natalizumab,[67,68] cladribine,[69] and fingolimod[70] in patients with RRMS in the second-line setting.

However, the population of patients with highly active RRMS faces an unmet need. As highlighted by clinician groups and by the clinical experts consulted throughout the HTA process, the current traditional sequential escalation approach that requires trial, failure, or intolerance to traditional first-line drugs fails to prevent irreversible damage to the nervous system, resulting in an early and rapid accumulation of disability.[4,10] As such, there is a rationale, supported by clinicians and by the Canadian MS Working Group,[4] to use higher efficacy treatments upon disease presentation in patients with high disease activity, more aggressive disease, or rapidly evolving MS, because an early effective treatment — as early as possible during the inflammatory phase of the disease — is expected to provide optimal clinical benefits and therefore prevent the devastating consequences of early disability worsening.[4,5]

Barriers to performing RCTs may be present especially in the context of a recent substantial change in clinical practice, where an increasing number of neurologists are preferring the treatment strategy of initiating high-efficacy therapies early for the appropriate patients. The clinical experts consulted indicated

that the change in paradigm was supported at this time by major treatment guidelines.[4] As such, the Canadian MS Working Group recommends early high-efficacy treatment strategy in patients with high disease activity, aggressive disease presentation, or rapidly evolving symptoms at onset, as these patients are at significant risk of early disability worsening.[4] Upon first presentation, recommendations are to perform risk stratification based on patient demographic and clinical factors known to be associated with early disease worsening, to identify patients who would be candidates for a more aggressive treatment strategy (i.e., early initiation of alemtuzumab, cladribine, fingolimod, natalizumab, or ocrelizumab).[4] Acknowledging that high-quality evidence from RCTs was lacking, the Canadian MS Working Group recommendations were issued based on the evidence available and clinical expert consensus.[4]

Although well-designed RCTs allow for causal inferences to be drawn with greater certainty than any other study type, the clinical experts consulted indicated that findings from observational real-world evidence, such as studies of MS registries, were widely recognized within the MS medical community as a motor of change toward adopting an early high-efficacy treatment paradigm. As per the HTA protocol, we have not undertaken a systematic review and process to identify registry studies; however, we were provided some of these publications through clinician input and feedback. The clinical experts consulted for this HTA highlighted 4 studies which, in their opinion, had a substantial impact on clinical practice. These include the following:

- Iaffaldano et al.[28] was a retrospective observational cohort study using propensity score matching and performed using the Italian MS Registry. A total of 363 patients who were treatment-naive received early intensive therapy (i.e., first-line natalizumab, alemtuzumab, mitoxantrone, fingolimod, cladribine, or ocrelizumab) and 363 patients who were treatment-naive received an escalation approach (i.e., interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, or azathioprine; followed escalation after at least 1 year of treatment). After at least 5 years of follow-up, the use of an early intensive therapy was associated with a slower disability progression, which was maintained over time, although all patients receiving the escalation approach had been switched to 1 of the high-efficacy treatments after a suboptimal response to first-line DMTs.[28]
- Buron et al.[29] was a retrospective nationwide cohort study using propensity score matching and performed using the Danish MS Registry. A total of 194 patients who were treatment-naive received a high-efficacy DMT (i.e., first-line natalizumab, fingolimod, alemtuzumab, cladribine, daclizumab, or ocrelizumab) and 194 patients who were treatment-naive received a moderate-efficacy DMT (i.e., interferon beta, teriflunomide, dimethyl fumarate, or glatiramer acetate). After a mean follow-up of 5 years, patients who started with a high-efficacy treatment had a reduced risk of relapse and disability progression, and the magnitude of the benefits was higher in patients with high inflammatory activity.[29]
- Simonsen et al.[31] was a retrospective observational cohort study performed using the Norwegian BOT-MS Registry. Patients were matched using a risk score to categorize disease activity. A total of 103 patients received a first-line high-efficacy drug (natalizumab, fingolimod, or alemtuzumab), while 491 patients received a first-line moderate-efficacy drug (i.e., interferon, glatiramer acetate, teriflunomide, or dimethyl fumarate). After 2 years of follow-up, the authors concluded that the use

of a first-line high-efficacy drug increased the likelihood of achieving NEDA, and that the benefit was increased in patients with a higher risk of disease activity.[31]

- Spelman et al.[32] was a retrospective cohort study comparing MS treatment strategies from 2 countries: Denmark, where most patients initiated treatment with a conventional DMT, and Sweden, where initiation of a high-efficacy DMT was increasingly used as a first-line option. A total of 2,161 patients from Denmark, and 2,700 patients from Sweden, met the inclusion criteria. After a follow-up ranging between 3 and 7 years, the early high-efficacy Swedish strategy was associated with a lower rate of disability progression.[32]

With regard to clinical trial evidence, 2 currently ongoing pragmatic RCTs may help provide clarity in the future regarding the optimal choice of treatment paradigms in patients with RRMS: the TREAT-MS[7] and DELIVER-MS trials,[8] which are expected to have results available in 2025 and 2030, respectively, aim to compare the treatment paradigms of an early high-efficacy treatment strategy versus a traditional escalation treatment strategy. Randomized trials of the relative benefits and harms of the 2 treatment strategies will contribute to evidence-informed decision-making and mitigate some of the current uncertainty in the overall population of patients with MS. In addition, the TREAT-MS trial is expected to provide information on the specific subpopulation of patients with highly active disease, as it includes a prespecified subgroup of patients deemed to be at higher risk for accumulation of disability.

Strengths and Limitations of the Systematic Review

Strengths

The systematic review was developed using robust methodology. The research protocol was developed a priori, registered with the PROSPERO database, and a detailed scoping plan was posted publicly for stakeholder input. The literature search was comprehensive and was also publicly posted for stakeholder feedback. Evidence collection and evaluation of the risk of bias of the included studies was completed independently by 2 reviewers, while data extraction was completed by a single reviewer with verification by a second. Conflicts in data collection were resolved through consensus or adjudicated by a third reviewer.

Limitations

The systematic review was based on limited availability of evidence, coming exclusively from post hoc analyses of head-to-head or placebo-controlled RCTs and 1 observational study. We discourage the use of informal naive indirect comparisons (i.e., observational comparisons across the results of separate trials or groups of trials), because they do not preserve within-trial randomization. Such comparisons are likely to be affected by bias due to confounding. No evidence could be identified to evaluate the use of rituximab in the patient population. In addition, there was no evidence to inform conclusions regarding the following outcomes: function, cognitive outcomes, symptoms, HRQoL, and instrumental activities of daily living. Most included subgroup analyses were subject to important limitations, including relatively small sample sizes, imprecision, risk of bias, and inadequate reporting, introducing uncertainty in the findings. One prospective comparative cohort study was included in the review; much like the RCTs, conclusions from this study were limited by small sample sizes, imprecision for many outcome comparisons, risk of bias, and inadequate reporting.

Conclusions and Implications for Decision- or Policy-Making

This HTA aimed to review the clinical effectiveness and safety of alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab as treatments relative to current first-line drugs in adults with highly active RRMS, a specific population experiencing early and rapid accumulation of disability.[4,10] These patients face an unmet need for aggressive treatment earlier in their disease to minimize neurologic damage, and consequently disability in the long and short term. Clinician groups, as well as the 2 clinical experts consulted, highlighted the shift toward earlier treatment with high-efficacy treatments, especially in those with highly active disease. This ensures that high-efficacy drugs are introduced as early as possible during the inflammatory process, which aims to address the unmet need and provide optimal clinical benefits in preserving neurologic function.[4,5]

A systematic review of findings from post hoc subgroup analyses of 5 RCTS and 1 prospective comparative cohort study informed the HTA. Conclusions for all outcome comparisons were limited by risk of bias and small sample sizes; conclusions for some outcome comparisons were also limited by imprecision (wide CIs included the possibility that either of the treatments compared could be favoured) and incomplete reporting. Compared to placebo, evidence suggests that cladribine and natalizumab, which were identified by the clinical experts as the most frequently prescribed in clinical practice, may result in a clinically important reduction in relapses, disability, and key MRI lesions; however, the evidence is uncertain. Evidence suggests that alemtuzumab may result in a clinically important reduction in relapses compared to interferon, while fingolimod may result in a clinically important reduction in relapses compared to placebo; again, the evidence is uncertain. The evidence was insufficient to determine the effect of fingolimod on relapses when compared with interferon. Harms outcomes, when reported, appeared consistent with the known harms profile of the drugs; follow-up times in the studies may have been insufficient for harms that take longer to occur (e.g., malignancies). Assessment of the effectiveness and safety of rituximab, or of most high-efficacy treatments relative to current first-line therapies, could not be performed due to the lack of evidence. Evidence was also lacking for many outcomes that were considered important to this review, such as HRQoL, instrumental activities of daily living, symptoms, and cognitive outcomes.

Several limitations in the evidence arose from the fact that, despite an extensive search of the overall MS literature, no clinical trial was designed to assess the relative benefits and harms of the 2 treatment strategies in patients with highly active RRMS. At this point in time, the rationale to use higher efficacy treatments upon disease presentation in these patients is supported by major Guidelines[4] and by observational real-world evidence, such as studies of MS registries, which the clinical experts indicated were widely recognized within the MS medical community as a motor of change toward adopting an early high-efficacy treatment paradigm. Clinical trial evidence is expected to become available in the future, as 2 pragmatic RCTs (the TREAT-MS[7] and DELIVER-MS[8] trials) are currently ongoing, which will provide clarity regarding the optimal choice of treatment strategy, and will contribute to inform decision-making and mitigate some of the current uncertainty.

Given the need for earlier access to high-efficacy treatments in this specific population, jurisdictions may reconsider the reimbursement criteria for natalizumab, cladribine, alemtuzumab, and/or fingolimod for use

in first-line treatment specifically for adults with highly active RRMS in light of the findings. To help manage the gaps and uncertainty in evidence outlined in this report, jurisdictions may consider requesting an implementation advice panel or expert committee recommendation.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Cochrane Central Register of Controlled Trials (CCTR)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: March 27 and August 15, 2023

Alerts: Monthly search updates until November 27, 2023

Search filters applied: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; guidelines; overview of reviews; randomized controlled trials; controlled clinical trials; observational studies

Limits:

- Language limit: English- and French-language
- Conference abstracts: excluded

Table 6: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract

Syntax	Description
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

Multidatabase Strategy

Initial Search

1. Alemtuzumab/
2. (alemtuzumab* or campath* or lemtrada* or mabcampath* or HSDB8177 or HSDB-8177 or LDP03 or LDP-03 or remnig* or bxt1523 or bxt-1523 or LDP103 or LDP-103 or qz402673 or qz-402673 or mabkampat*).ti,ab,kf,ot,hw,rn,nm.
3. Natalizumab/
4. (natalizumab* or tysabri* or antegren* or HSDB8174 or HSDB-8174 or an100226 or an-100226 or bg0002 or bg-0002 or dst356a1 or dst-356al or pb006 or pb-006).ti,ab,kf,ot,hw,rn,nm.
5. Cladribine/
6. (cladribin* or cladarabin* or biodribin* or intocel* or leustat* or litak* or litax* or mavenclad* or movectro* or mylinax* or BRN0624220 or BRN-0624220 or CCRIS9374 or CCRIS-9374 or HSDB7564 or HSDB-7564 or NSC105014* or NSC-105014* or RWJ26251 or RWJ-26251).ti,ab,kf,ot,hw,rn,nm.
7. Fingolimod Hydrochloride/
8. (fingolimod* or gilenia* or gilenya* or imusera* or inzolfi* or fty720 or fty-720 or tdi132 or tdi-132).ti,ab,kf,ot,hw,rn,nm.
9. Rituximab/
10. (rituximab* or Rituxan* or Truximab* or MabThera* or Mab Thera* or Truxima* or blitzima* or reditux* or ritemvia* or rituxin* or rituzena* or rixathon* or ritucad* or riximyo* or truxella* or halpryza* or riabni* or rituenza* or ritumax* or tuxella* or ruxience* or hycela* or acellbia* or abp 798 or abp798 or “hlx 01” or hlx01 or SAIT101 or SAIT 101 or GP2013 or GP 2013 or mk 8808 or mk8808 or rtxm83 or rxtm 83 or ibi301 or ibi 301 or HSDB 7455 or HSDB7455 or IDEC-102 or IDEC102 or IDEC-C2B8 or

IDECC2B8 or PF-05280586 or PF05280586 or PF-5280586 or PF5280586 or RO-452294 or RO452294 or RG-105 or RG105 or CT-P10 or CTP10 or 4F4X42SYQ6).ti,ab,kf,kw,ot,hw,nm,rn.

11. or/1-10
12. Multiple Sclerosis, Relapsing-Remitting/
13. (RRMS or RMS).ti,ab,kf.
14. ((ms or multiple scleros*) adj3 (relaps* or remit*)).ti,ab,kf.
15. or/12-14
16. 11 and 15
17. 16 use medall
18. 16 use cctr
19. *alemtuzumab/
20. (alemtuzumab* or campath* or lemtrada* or mabcampath* or HSDB8177 or HSDB-8177 or LDP03 or LDP-03 or remnig* or bxt1523 or bxt-1523 or LDP103 or LDP-103 or qz402673 or qz-402673 or mabkampat*).ti,ab,kf,dq.
21. *natalizumab/
22. (natalizumab* or tysabri* or antegren* or HSDB8174 or HSDB-8174 or an100226 or an-100226 or bg0002 or bg-0002 or dst356a1 or dst-356al or pb006 or pb-006).ti,ab,kf,dq.
23. *cladribine/
24. (cladribin* or cladarabin* or biodribin* or intocel* or leustat* or litak* or litax* or mavenclad* or movectro* or mylinax* or BRN0624220 or BRN-0624220 or CCRIS9374 or CCRIS-9374 or HSDB7564 or HSDB-7564 or NSC105014* or NSC-105014* or RWJ26251 or RWJ-26251).ti,ab,kf,dq.
25. *fingolimod/
26. (fingolimod* or gilenya* or imusera* or inzolfi* or fty720 or fty-720 or tdi132 or tdi-132).ti,ab,kf,dq.
27. *rituximab/
28. (rituximab* or Rituxan* or Truximab* or MabThera* or Mab Thera* or Truxima* or blitzima* or reditux* or ritemvia* or rituxin* or rituzena* or rixathon* or ritucad* or riximyo* or truxella* or halpryza* or riabni* or rituenza* or ritumax* or tuxella* or ruxience* or hycela* or acellbia* or abp 798 or abp798 or “hlx 01” or hlx01 or SAIT101 or SAIT 101 or GP2013 or GP 2013 or mk 8808 or mk8808 or rtxm83 or rxtm 83 or ibi301 or ibi 301 or HSDB 7455 or HSDB7455 or IDEC-102 or IDEC102 or IDEC-C2B8 or IDECC2B8 or PF-05280586 or PF05280586 or PF-5280586 or PF5280586 or RO-452294 or RO452294 or RG-105 or RG105 or CT-P10 or CTP10 or 4F4X42SYQ6).ti,ab,kf,dq.
29. or/19-28
30. exp Multiple sclerosis/ and (relapse/ or remission/ or (relaps* or remit*).ti,ab,kf,dq.)
31. (RRMS or RMS).ti,ab,kf.
32. ((ms or multiple scleros*) adj3 (relaps* or remit*)).ti,ab,kf.

33. or/30-32
34. 29 and 33
35. 34 use oemezd
36. (conference abstract or conference review).pt.
37. 35 not 36
38. 17 or 37
39. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
40. Randomized Controlled Trial/
41. exp Randomized Controlled Trials as Topic/
42. "Randomized Controlled Trial (topic)"/
43. Controlled Clinical Trial/
44. exp Controlled Clinical Trials as Topic/
45. "Controlled Clinical Trial (topic)"/
46. Randomization/
47. Random Allocation/
48. Double-Blind Method/
49. Double Blind Procedure/
50. Double-Blind Studies/
51. Single-Blind Method/
52. Single Blind Procedure/
53. Single-Blind Studies/
54. Placebos/
55. Placebo/
56. Control Groups/
57. Control Group/
58. (random* or sham or placebo*).ti,ab,hw,kf.
59. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
60. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
61. (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
62. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
63. allocated.ti,ab,hw.
64. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.

65. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
66. (pragmatic study or pragmatic studies).ti,ab,hw,kf.
67. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
68. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
69. (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
70. or/39-69
71. (systematic review or meta-analysis).pt.
72. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
73. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
74. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
75. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
76. (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
77. (handsearch* or hand search*).ti,ab,kf.
78. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
79. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.
80. (meta regression* or metaregression*).ti,ab,kf.
81. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
82. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
83. (cochrane or (health adj2 technology assessment) or evidence report).jw.
84. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
85. (outcomes research or relative effectiveness).ti,ab,kf.
86. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.
87. [(meta-analysis or systematic review).md.]
88. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
89. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
90. umbrella review*.ti,ab,kf.
91. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
92. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.

93. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
94. or/71-93
95. 70 or 94
96. 38 and 95
97. 18 or 96
98. remove duplicates from 97
99. limit 98 to (english or french)

Secondary Search

1. Alemtuzumab/
2. (alemtuzumab* or campath* or lemtrada* or mabcampath* or HSDB8177 or HSDB-8177 or LDP03 or LDP-03 or remnig* or bxt1523 or bxt-1523 or LDP103 or LDP-103 or qz402673 or qz-402673 or mabkampat*).ti,ab,kf,ot,hw,rn,nm.
3. Natalizumab/
4. (natalizumab* or tysabri* or antegren* or HSDB8174 or HSDB-8174 or an100226 or an-100226 or bg0002 or bg-0002 or dst356a1 or dst-356al or pb006 or pb-006).ti,ab,kf,ot,hw,rn,nm.
5. Cladribine/
6. (cladribin* or cladarabin* or biodribin* or intocel* or leustat* or litak* or litax* or mavenclad* or movectro* or mylinax* or BRN0624220 or BRN-0624220 or CCRIS9374 or CCRIS-9374 or HSDB7564 or HSDB-7564 or NSC105014* or NSC-105014* or RWJ26251 or RWJ-26251).ti,ab,kf,ot,hw,rn,nm.
7. Fingolimod Hydrochloride/
8. (fingolimod* or gilenia* or gilenya* or imusera* or inzolfi* or fty720 or fty-720 or tdi132 or tdi-132).ti,ab,kf,ot,hw,rn,nm.
9. Rituximab/
10. (rituximab* or Rituxan* or Truximab* or MabThera* or Mab Thera* or Truxima* or blitzima* or reditux* or ritemvia* or rituxin* or rituzena* or rixathon* or ritucad* or riximyo* or truxella* or halpryza* or riabni* or rituenza* or ritumax* or tuxella* or ruxience* or hycela* or acellbia* or abp 798 or abp798 or “hlx 01” or hlx01 or SAIT101 or SAIT 101 or GP2013 or GP 2013 or mk 8808 or mk8808 or rtxm83 or rxtm 83 or ibi301 or ibi 301 or HSDB 7455 or HSDB7455 or IDEC-102 or IDEC102 or IDEC-C2B8 or IDECC2B8 or PF-05280586 or PF05280586 or PF-5280586 or PF5280586 or RO-452294 or RO452294 or RG-105 or RG105 or CT-P10 or CTP10 or 4F4X42SYQ6).ti,ab,kf,kw,ot,hw,nm,rn.
11. or/1-10
12. Multiple Sclerosis, Relapsing-Remitting/
13. (RRMS or RMS).ti,ab,kf.
14. ((ms or multiple scleros*) adj3 (relaps* or remit*)).ti,ab,kf.
15. or/12-14

16. 11 and 15
17. 16 use medall
18. *alemtuzumab/
19. (alemtuzumab* or campath* or lemtrada* or mabcampath* or HSDB8177 or HSDB-8177 or LDP03 or LDP-03 or remnig* or bxt1523 or bxt-1523 or LDP103 or LDP-103 or qz402673 or qz-402673 or mabkampat*).ti,ab,kf,dq.
20. *natalizumab/
21. (natalizumab* or tysabri* or antegren* or HSDB8174 or HSDB-8174 or an100226 or an-100226 or bg0002 or bg-0002 or dst356a1 or dst-356al or pb006 or pb-006).ti,ab,kf,dq.
22. *cladribine/
23. (cladribin* or cladarabin* or biodribin* or intocel* or leustat* or litak* or litax* or mavenclad* or movectro* or mylinax* or BRN0624220 or BRN-0624220 or CCRIS9374 or CCRIS-9374 or HSDB7564 or HSDB-7564 or NSC105014* or NSC-105014* or RWJ26251 or RWJ-26251).ti,ab,kf,dq.
24. *fingolimod/
25. (fingolimod* or gilenya* or imusera* or inzolfi* or fty720 or fty-720 or tdi132 or tdi-132).ti,ab,kf,dq.
26. *rituximab/
27. (rituximab* or Rituxan* or Truximab* or MabThera* or Mab Thera* or Truxima* or blitzima* or reditux* or ritemvia* or rituxin* or rituzena* or rixathon* or ritucad* or riximyo* or truxella* or halpryza* or riabni* or rituenza* or ritumax* or tuxella* or ruxience* or hycela* or acellbia* or abp 798 or abp798 or “hlx 01” or hlx01 or SAIT101 or SAIT 101 or GP2013 or GP 2013 or mk 8808 or mk8808 or rtxm83 or rxtm 83 or ibi301 or ibi 301 or HSDB 7455 or HSDB7455 or IDEC-102 or IDEC102 or IDEC-C2B8 or IDECC2B8 or PF-05280586 or PF05280586 or PF-5280586 or PF5280586 or RO-452294 or RO452294 or RG-105 or RG105 or CT-P10 or CTP10 or 4F4X42SYQ6).ti,ab,kf,dq.
28. or/18-27
29. exp Multiple sclerosis/ and (relapse/ or remission/ or (relaps* or remit*).ti,ab,kf,dq.)
30. (RRMS or RMS).ti,ab,kf.
31. ((ms or multiple scleros*) adj3 (relaps* or remit*)).ti,ab,kf.
32. or/29-31
33. 28 and 32
34. 33 use oemezd
35. (conference abstract or conference review).pt.
36. 34 not 35
37. 17 or 36
38. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.

39. (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt.
40. Multicenter Study.pt.
41. Clinical Studies as Topic/
42. exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/
43. Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/
44. Randomization/
45. Random Allocation/
46. Double-Blind Method/
47. Double Blind Procedure/
48. Double-Blind Studies/
49. Single-Blind Method/
50. Single Blind Procedure/
51. Single-Blind Studies/
52. Placebos/
53. Placebo/
54. Control Groups/
55. Control Group/
56. Cross-Over Studies/ or Crossover Procedure/
57. (random* or sham or placebo*).ti,ab,hw,kf.
58. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
59. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
60. (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
61. (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf.
62. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
63. (phase adj3 (study or studies or trial*)).ti,ab,hw,kf.
64. ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf.
65. ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf.
66. allocated.ti,ab,hw.
67. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
68. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
69. (pragmatic study or pragmatic studies).ti,ab,hw,kf.

70. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
71. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
72. trial.ti,kf.
73. or/38-72
74. exp animals/
75. exp animal experimentation/
76. exp models animal/
77. exp animal experiment/
78. nonhuman/
79. exp vertebrate/
80. [animal.po.]
81. or/74-80
82. exp humans/
83. exp human experiment/
84. [human.po.]
85. or/82-84
86. 81 not 85
87. 73 not 86
88. 37 and 87
89. epidemiologic methods.sh.
90. epidemiologic studies.sh.
91. observational study/
92. observational studies as topic/
93. clinical studies as topic/
94. controlled before-after studies/
95. cross-sectional studies/
96. historically controlled study/
97. interrupted time series analysis/
98. exp seroepidemiologic studies/
99. national longitudinal study of adolescent health/
100. cohort studies/
101. cohort analysis/
102. longitudinal studies/

103. longitudinal study/
104. prospective studies/
105. prospective study/
106. follow-up studies/
107. follow up/
108. followup studies/
109. retrospective studies/
110. retrospective study/
111. case-control studies/
112. exp case control study/
113. cross-sectional study/
114. observational study/
115. quasi experimental methods/
116. quasi experimental study/
117. single-case studies as topic/
118. (observational study or validation studies or clinical study).pt.
119. (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
120. cohort*.ti,ab,kf.
121. (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
122. ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
123. ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.
124. (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.
125. ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.
126. (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
127. (population adj3 (study or studies or analysis or analyses)).ti,ab,kf.
128. (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
129. ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
130. (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.
131. ((natural adj experiment) or (natural adj experiments)).ti,ab,kf.
132. (quasi adj (experiment or experiments or experimental)).ti,ab,kf.

133. ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
134. (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf.
135. case series.ti,ab,kf.
136. case reports.pt.
137. case report/
138. case study/
139. (case adj3 (report or reports or study or studies or histories)).ti,ab,kf.
140. organizational case studies.sh.
141. or/89-140
142. 37 and 141
143. 88 or 142

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS]

WHO ICTRP

International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials.

[Search terms -- alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS]

Grey Literature

Search dates: Spring 2023

Keywords: alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS

Limits: none

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

The complete search archive of sites consulted for this report will be available on request.

Appendix 2: List of Included Studies

Note that this appendix has not been copy-edited.

Randomized Active-Controlled Trials

1. CARE-MS I Subgroup publication:

   Krieger S, Lubetzki C, Palmer J, Margolin DH. Alemtuzumab reduces disease activity in treatment naive patients with highly active relapsing-remitting multiple sclerosis. *Mult Scler J*. 2014;Vol.20(1 suppl):106 to 107.

   Related publication:

   Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomized controlled phase 3 trial. *Lancet*. 2012; 380: 1819 to 28.

2. TRANSFORMS Subgroup publication:

   Cohen JA, Barkhof F, Comi G, et al. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. *J Neurol*. 2013;260(8):2023 to 3.

   Related publications:

   Cohen JA, Barkhof F, Comi G et al. Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis. *N Engl J Med*. 2010;362:402 to 15.; 2010.

   Radue EW, Barkhof F, Cohen J, Holdbrook F, Francis G, Kappos L. MRI Analyses in RRMS Patients with Highly Active Disease: Results from FREEDOMS and TRANSFORMS Phase 3 Studies. *Neurology*. 2012;78(1 Suppl).

Randomized Placebo-Controlled Trials

1. CLARITY Subgroup publication:

   Vermersch P, Galazka A, Dangond F, et al. Efficacy of cladribine tablets in high disease activity patients with relapsing multiple sclerosis: post hoc analysis of subgroups with and without prior disease-modifying drug treatment. *Curr Med Res Opin*. 2021;37(3):459 to 464.

   Related publication:

   Giovannoni G, Comi G, Cook S, et al. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. *N Engl J Med*. 2010;362:416 to 26.

2. FREEDOMS Subgroup publication:

   Devonshire V, Havrdova E, Rague E-W, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomized, placebo-controlled FREEDOMS study. *Lancet Neurol*. 2012;11(5):420 to 8.

   Related publication:

Kappos L, Radue EW, O'Connor P, et al. A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis. *N Engl J Med*. 2010;362:387 to 401.

Radue EW, Barkhof F, Cohen J, Holdbrook F, Francis G, Kappos L. MRI Analyses in IIMS Patients with Highly Active Disease: Results from FREEDOMS and TRANSFORMS Phase 3 Studies. *Neurology*. 2012;78(1 Suppl).

3. AFFIRM Subgroup publications:

Hutchinson M, Kappos L, Calabresi PA, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol*. 2009;256:405 to 415.

Related publication:

Polman CH, O'Connor PW, Havrdova E, et al. A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006;354:899 to 910.

Observational Studies

1. Main publication:

Prosperini L, Sacca F, Cordioli C, et al. Real-world effectiveness of natalizumab and fingolimod compared with self-injectable drugs in non-responders and in treatment naive patients with multiple sclerosis. *J Neurol*. 2017;264:284 to 294.

Appendix 3: List of Excluded Studies

Note that this appendix has not been copy-edited.

Table 7: List and Reason of Excluded Studies

Author (year)	Reason for exclusion	References
Active-controlled RCTs		
AGIUS et al. 2014	Population	CNS Neuroscience and Therapeutics 2014 20(5):446 to 51
ALBERT et al. 2020	Population — not in MS	—
ARNOLD et al. 2016 (Mult Scler)	Design	Multiple sclerosis. Conference: 32nd congress of the European committee for treatment and research in multiple sclerosis, ECTRIMS 2016 22(329):
ARNOLD et al. 2016 (Neurol)	Population	Neurology 2016 87(14):1464 to 1472
ARNOLD et al. 2020	Population	Multiple Sclerosis Journal 2020 Vol.26(3 SUPPL):129 to 130p
ARNOLD et al. 2015	Design	Neurology 2015 84(Durable effect of alemtuzumab on MRI activity in treatment-naive active relapsing-remitting multiple sclerosis patients: 4-year follow-up of CARE-MS I
ARROYO GONZALEZ et al. 2017	Population	Multiple Sclerosis 2017 23(10):1367 to 1376
ARROYO et al. 2020	Population	Multiple Sclerosis 2020 26(8):955 to 963
BALCER et al. 2013	Population	2013 333(Alemtuzumab improves visual outcomes in treatment-naive patients with relapsing-remitting multiple sclerosis (RRMS): analysis from the phase 3 CARE-MS I study
BALCER et al. 2013	Duplicate	Journal of the Neurologic Sciences 2013 333(Alemtuzumab improves visual outcomes in treatment-naive patients with relapsing-remitting multiple sclerosis (RRMS): analysis from the phase 3 CARE-MS I study
BARKHOF et al. 2011	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2011 Vol.17(10 SUPPL. 1):S406p
BARKHOF et al. 2014	Population	Multiple Sclerosis 2014 20(13):1704 to 13
BARKHOF et al. 2015	Design	Multiple sclerosis (Houndmills, Basingstoke, England) 2015 Vol.23(11 SUPPL. 1):44 to 45p
BASS et al.	Unavailable	Multiple Sclerosis 1219 13(1219 to 1220
BASS et al. 2021	Population	Multiple Sclerosis and Related Disorders 2021 49(102717
BELL GORROD et al. 2020	Design - treatment switching	—

Author (year)	Reason for exclusion	References
BENEDICT et al. 2017	Population	Neurology Vol.88(16):2017 to 04 to 22 to 2017 to 04 to 28. 69th American Academy of Neurology Annual Meeting
BOSTER et al. 2017	Population	Multiple Sclerosis 2017 23(83 to 84
BUTZKUEVEN et al. 2017	Population	Multiple Sclerosis Journal 2017 Vol.23(3):405 to 406p
BUTZKUEVEN et al. 2018	Population	Journal of Neurology, Neurosurgery and Psychiatry 2018 Vol.89(6):e35-p
BUTZKUEVEN et al. 2020	Population	BMJ Open 2020 10(10):e038861
CHITNIS et al. 2014	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2014 Vol.20(1 SUPPL. 1):208 to 209p
COHEN et al. 2010	Population	New England Journal of Medicine 2010 362(5):402 to 15
COHEN et al. 2012	Population - Not in the specific population	Lancet 2012 380(9856):1819 to 28
COHEN et al. 2013	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2013 Vol.19(11 SUPPL. 1):268p
COHEN et al. 2009	Population	Neurology Vol.72(11 Suppl 3):A254
COLES et al. 2008	Population	New England Journal of Medicine 2008 359(17):1786 to 801
COLES et al. 2011 (Lancet Neurol)	Population	Lancet Neurology 2011 10(4):338 to 48
COLES et al. 2011 (Mult Scler)	Population - Not in the specific population	Multiple sclerosis. Conference: 32nd congress of the European committee for treatment and research in multiple sclerosis, ECTRIMS 2016 22(75 to 76
COLES et al. 2016	Design	Neurology 2017 89(11)(1117 to 1126
COLES et al. 2017	Design	Multiple sclerosis (Houndmills, Basingstoke, England) 2011 Vol.17(10 SUPPL. 1):S510p
COLES et al. 2012	Population - Not in the specific population	Neurology 2012 78(1 Meeting Abstract):
COLES et al. 2015	Design	Neurology 2015 84(Alemtuzumab slows brain volume loss over 4 years despite most relapsing-remitting multiple sclerosis patients not receiving treatment for 3 years
COMI et al. 2017	Population	Journal of Neurology 2017 264(12):2436 to 2449
COMI et al. 2017	Duplicate	Journal of Neurology 2017 Vol.264(12):2436 to 2449p
CREE et al. 2018	Population	Therapeutic Advances in Neurologic Disorders 2018 11(no pagination):
CREE et al. 2020 (JAMA Neurol 78)	Population	JAMA Neurology 2020 Vol.78(1):1 to 13p
CREE et al. 2020 (JAMA Neurol 24)	Population	JAMA Neurology 2020 24(24
CREE et al. 2019 (Eur J Neurol 78)	Design	European Journal of Neurology 2019 26(484 to 485

Author (year)	Reason for exclusion	References
CREE et al. 2019 (Eur J Neurol 24)	Design	European Journal of Neurology 2019 26(163):2019 to 06
CREE et al. 2019 (Neurol)	Design	Multiple Sclerosis 2021 27(14):2219 to 2231
CREE et al. 2021	Design	Multiple Sclerosis Journal 2017 Vol.23(3):322-p
CREE et al. 2017	Design	Neurology Vol.92(15):2019 to 05 to 04 to 2019 to 05 to 10. 71st Annual Meeting of the American Academy of Neurology
DERFUSS et al. 2015	Population	Neurology 2015 84(Relapse outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of three phase 3 fingolimod trials
DERFUSS et al. 2016	Population	Multiple Sclerosis and Related Disorders 2016 8(124 to 30
DESHMUKH et al. 2019	Design	Annals of Indian Academy of Neurology 2019 Vol.22(SUPPL 1):S11-p
DIAZ et al. 2014	Design	Lancet Neurology 2014 13(9):869 to 70
FOX et al. 2016 (Mult Scler)	Population - Not in the specific population	Multiple Sclerosis 1396 15(1396 to 1395
FOX et al. 2016 (J Neurol Sc)	Population - Not in the specific population	Journal of the Neurologic Sciences 2016 363(188 to 94
FOX et al. 2012	Population - Not in the specific population	2012 78(Relapse outcomes with alemtuzumab vs. Rebif(registered trademark) in treatment-naive relapsing-remitting multiple sclerosis (CARE-MS I): secondary and tertiary end points
FOX et al. 2017	Population	Neurology Vol.88(16):2017 to 04 to 22 to 2017 to 04 to 28. 69th American Academy of Neurology Annual Meeting
GARTNER et al. 2018	Comparison	Multiple Sclerosis Journal Experimental, Translational and Clinical 2018 4(2):
GHEZZI et al. 2020	Comparison	Neurology and Therapy 2020 9(1):193 to 195
GIOVANNONI et al. 2016	Population	Neurology 2016 87(19):1985 to 1992
GIOVANNONI et al. 2020	Design (extension)	—
GIOVANNONI et al. 2022	Design (extension)	—
GOODIN et al. 2013	Population	—
GRAVES et al. 2013	Population - Not in the specific population	Multiple Sclerosis 2013 19(10):1302 to 9
GRAVES et al. 2013	Duplicate	—
HARTUNG et al. 2013	Unavailable	—
HAVRDOVA et al. 2012	Population - Not in the specific population	Neurology 2012 78(1 Meeting Abstract):
HAVRDOVA et al. 2017	Design	Neurology 2017 89(11):1107 to 1116

Author (year)	Reason for exclusion	References
HUGHES, J. et al. 2010	Population	Annals of Internal Medicine 2010 152(10):JC5 to 6, JC5 to 7, JC5 to 8
HUGHES, J. et al. 2010	Duplicate	Annals of Internal Medicine 2010 152(10):JC5 to 6, JC5 to 7, JC5 to 8
HUGHES, J. et al. 2010	Duplicate	Annals of Internal Medicine 2010 152(10) (JC56+JC57+JC58
HUGHES, R., et al. 2018	Population – not in MS	–
HUNTER, S. F., et al. 2016	Population	Multiple Sclerosis 2016 22(782):2016 to 09
HUNTER, S. F., et al. 2019	Population	Multiple Sclerosis Journal 2019 25(35 to 36
HUNTER, S. F., et al. 2019	Duplicate	Neurology Vol.92(15):2019 to 05 to 04 to 2019 to 05 to 10. 71st Annual Meeting of the American Academy of Neurology
INVESTIGATORS, Camms Tria 2008	Duplicate	New England Journal of Medicine 2008 Vol.359(17):1786 to 1801p
KHATRI et al. 2014	Population - Not in the specific population	Multiple Sclerosis and Related Disorders 2014 3(3) (355 to 363
KHATRI et al. 2012	Population	Neurology 2012 78(1 Meeting Abstract):
KLOTZ et al. 2013	Language	–
LICATA et al. 2017	Population	Journal of the Neurologic Sciences 2017 381(246):2017 to 09
LYCKE et al. 2013	Population - Not in the specific population	Journal of the Neurologic Sciences 2013 333(e374-e375
LYCKE et al. 2013	Duplicate	2013 333(Adverse event profile of alemtuzumab over time in treatment-naive patients with early, active relapsing-remitting multiple sclerosis (RRMS; CARE-MS I study)
LYCKE et al. 2013	Duplicate	Multiple sclerosis (Houndmills, Basingstoke, England) 2013 Vol.19(11 SUPPL. 1):487 to 488p
MACDONELL et al. 2015	Design	Multiple Sclerosis 2015 Conference: 8th congress of the pan Asian committee for treatment and research in multiple sclerosis, PACTRIMS. Vol.21(6):806p
MARGOLIN et al. 2014	Design	Neurology 2014 82(10 SUPPL. 1):
MASJEDI et al. 2021	Population	American Journal of Clinical and Experimental Immunology 2021 10(3)(86 to 92
Mäurer et al. 2015	Outcome	–
MONTALBAN et al. 2014	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2014 Vol.20(1 SUPPL. 1):83 to 84p
MOREAU et al. 2014	Population - Not in the specific population	–

Author (year)	Reason for exclusion	References
MUNSCHAUER et al. 2009	Population	Journal of the Neurologic Sciences 2009 Vol.285(Suppl 1):S109p
NYGAARD et al. 2020	Population	Multiple Sclerosis Journal 2020 Vol.26(3 SUPPL):207 to 208p
ONTANEDA et al. 2015	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2015 Vol.23(11 SUPPL. 1):758p
ONTANEDA et al. 2018	Design	Multiple Sclerosis Journal 2018 Vol.24(2):470 to 471p
OVERAS et al. 2022	Population	Multiple Sclerosis Journal 2022 Vol.28(3):845 to 846p
POZZILLI et al. 2010	Design	Expert Opinion on Pharmacotherapy 2010 11(11):1957 to 60
REPOVIC et al. 2017	Population	Multiple Sclerosis Journal 2017 Vol.23(3):736 to 737p
SAIDA et al. 2017	Design - extension study	—
SELMAJ et al. 2012	Population - Not in the specific population	Neurology 2012 78(1 Meeting Abstract):
SINGER et al. 2016	Population	—
SMITH et al. 2016	Design - cost-effectiveness	—
SOLARI et al. 2022	Design	Multiple Sclerosis Journal 2022 Vol.28(3):203 to 204p
SORENSEN et al. 2014	Design	The Lancet Neurology 2014 13(6)(526 to 527
SORENSEN et al. 2013	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2013 Vol.19(11 SUPPL. 1):207 to 208p
SPANU et al. 2022	Population	Multiple Sclerosis Journal Experimental, Translational and Clinical 2022 8(3):
SPANU et al. 2022	Duplicate	Multiple Sclerosis Journal Experimental, Translational and Clinical 2022 8(3):
STEINMAN et al. 2014	Design - cost-effectiveness	—
SVENNINGSSON et al. 2022	Population - Not in the specific population	Lancet Neurology 2022 21(8):693 to 703
THOMAS et al. 2018	Population	Neurology Vol.90(15):2018 to 04 to 21 to 2018 to 04 to 27. 70th Annual Meeting of the American Academy of Neurology
THOMAS et al. 2017	Population	Neurology Vol.88(16):2017 to 04 to 22 to 2017 to 04 to 28. 69th American Academy of Neurology Annual Meeting
TREMLETT et al. 2005	Design	Neurology 2005 64(1):174 to 5; author reply 174 to 5
WIENDL et al. 2016	Unavailable	Multiple sclerosis. Conference: 32nd congress of the European committee for treatment and research in multiple sclerosis, ECTRIMS 2016 22(328):

Author (year)	Reason for exclusion	References
ZIEMSSEN et al. 2020	Design	CNS Drugs 2020 34(9):973 to 988
Placebo-controlled RCTs		
AFOLABI et al. 2017	Population	Multiple Sclerosis Journal 2017
AFOLABI et al. 2018	Population	Multiple Sclerosis 2018 24(11):1461 to 1468
ANONYMOUS 2014 (Lancet Neuro)	No additional result	The Lancet Neurology 2014 13(6)(536
ANONYMOUS 2014 (Lancet Neuro)	Errata	Neurology Vol.96(15 SUPPL 1):2021 to 04 to 17 to 2021 to 04 to 22. 73rd Annual Meeting of the American Academy of Neurology
ANONYMOUS 2010	Design (journal club)	Multiple sclerosis (Houndmills, Basingstoke, England) 2012 Vol.18(4 SUPPL. 1):205 to 206p
BATTAGLINI et al. 2021	Population	Lancet Neurology 2014 13(6):545 to 56
CALABRESI et al. 2012 (Mult Scler)	Population	2012 79(Efficacy and safety of fingolimod in patients with relapsing-remitting multiple sclerosis (RRMS): results from an additional 24-month double-blind, placebo-controlled study (freedoms II study)
CALABRESI et al. 2014	Population	Neurology 2012 Vol.79(11):e90-e91p
CALABRESI et al. 2012 (Neurology)	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2012 Vol.18(4 SUPPL. 1):187p
CALABRESI et al. 2012	Duplicate	Multiple Sclerosis 2010 16(2):197 to 207
CHIN et al. 2012	Population	Journal of Neurology 2013 260(4):1136 to 46
COMI et al. 2010	Design	—
COMI et al. 2013	Population	Journal of the Neurologic Sciences Vol.285(Suppl 1):S114
COMI et al. 2016	Unavailable	Multiple Sclerosis 2011 17(5):578 to 93
COMI et al. 2009	Population	Journal of the Neurologic Sciences Vol.285(Suppl 1):S206
COOK et al. 2011	Population	Journal of Neurology 2004 251(4):407 to 13
COOK et al. 2009	Population	Neurology 2013 80(1 MeetingAbstracts):
DALTON et al. 2004	Population	Journal of Neurology 2014 261(S18-S19
DE STEFANO et al. 2013	Population	European Journal of Neurology 2014 21(24):
DE STEFANO et al. 2014 (J Neuro)	Population	Multiple Sclerosis 2018 24(2):222 to 226
DE STEFANO et al. 2014 (Eur J Neuro)	Population	Multiple Sclerosis 2022 28(1):111 to 120
DE STEFANO et al. 2018	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2014 Vol.20(1 SUPPL. 1):118p
DE STEFANO et al. 2022	Design	Journal of the Neurologic Sciences Vol.285(Suppl 1):S114
DONG et al. 2014	Design	New England Journal of Medicine 2010 362(5):416 to 26

Author (year)	Reason for exclusion	References
GIOVANNONI et al. 2009	Population	Multiple sclerosis. Conference: 32nd congress of the European committee for treatment and research in multiple sclerosis, ECTRIMS 2016 22(304):
GIOVANNONI et al. 2010	Population	Multiple sclerosis. Conference: 32nd congress of the European committee for treatment and research in multiple sclerosis, ECTRIMS 2016 22(305):
GIOVANNONI et al. 2016	Population	European Journal of Neurology 2017 24(203 to 204
GIOVANNONI et al. 2016	Duplicate	Multiple Sclerosis Journal 2017 Vol.24(3):396-p
GIOVANNONI et al. 2017 (Eur J Neurol)	Population	*Multiple Sclerosis Journal 2017 Vol.24(3):396 to 397p*
GIOVANNONI et al. 2017 (MS J)	Design	Sinapse 2017 Vol.17(1):160-p
GIOVANNONI et al. 2017	Duplicate	Sinapse 2017 Vol.Conference: Neuro 2017. Portugal. 17(1):160p
GIOVANNONI et al. 2017 (Sin p160)	Design	Sinapse 2017 Vol.17(1):169 to 170p
GIOVANNONI et al. 2017	Duplicate	Multiple Sclerosis Journal 2017 Vol.23(3):613 to 614p
GIOVANNONI et al. 2017 (Sin p169)	Population	*Sinapse 2017 Vol.17(2):84-p*
GIOVANNONI et al. 2017 (MS J)	Population	Multiple Sclerosis Journal 2018 Vol.24(2):NP6-p
GIOVANNONI et al. 2017	Duplicate	Journal of Neurology, Neurosurgery and Psychiatry 2018 Vol.Conference: Annual Scientific Meeting of the Australian and New Zealand Association of Neurologists, ANZAN 2018. Australia. 89(6):e27-e28p
GIOVANNONI et al. 2017 (Neurol)	Population	Multiple Sclerosis 2018 24(12):1594 to 1604
GIOVANNONI et al. 2018 (MS J)	Population	Multiple Sclerosis 2019 25(6):819 to 827
GIOVANNONI et al. 2018 (J Neurol &)	Population	Multiple Sclerosis Journal 2019 Vol.26(9):NP62-NP63p
GIOVANNONI et al. 2018 (Mult Scler)	Design	Neurology and Therapy 2019 8(S7-S8
GIOVANNONI et al. 2019 (Mult Scler)	Population	European Journal of Neurology 2020 27(468):2020 to 05
GIOVANNONI et al. 2019 (MS J)	Design	Multiple Sclerosis Journal 2020 Vol.26(1 SUPPL):50 to 51p
GIOVANNONI et al. 2019 (Neurol Ther)	Population	Advances in Therapy 2021 38(9):4975 to 4985
GIOVANNONI et al. 2020 (Eur J Neurol)	Design	Frontiers in Immunology 2021 12 (no pagination) (35003076
GIOVANNONI et al. 2020 (MS J)	Design	Journal of Neurology, Neurosurgery and Psychiatry 2022 Vol.93(6):A18-p
GIOVANNONI et al. 2021 (Adv Ther)	Design	Neurology Vol.88(16):2017 to 04 to 22 to 2017 to 04 to 28. 69th American Academy of Neurology Annual Meeting

Author (year)	Reason for exclusion	References
GIOVANNONI et al. 2021 (Front Immun)	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2015 Vol.23(11 SUPPL. 1):263 to 264p
GIOVANNONI et al. 2022	Design	2013 80(Fingolimod reduces annualized relapse rate in patients with relapsing-remitting multiple sclerosis: freedoms II study subgroup analysis
GOL et al. 2015	Population - Not in the specific population	Neurology 2013 80(1 MeetingAbstracts):
GOODIN et al. 2013	Population	European Journal of Neurology 2020 27(916 to 917
GOODIN et al. 2013	Duplicate	–
GREENBERG et al. 2020	Population	New England Journal of Medicine 2008 358(7):676 to 88
HARTUNG et al. 2014	Population - not in MS	Multiple Sclerosis and Related Disorders 2018 26(236 to 237
HAUSER et al. 2008	Population	Lancet Neurology 2009 8(3):254 to 60
HAVRDOVA et al. 2018	Population	Neurology 2017 88(16 Supplement 1):
HAVRDOVA et al. 2009	Population	Multiple Sclerosis Journal 2018 Vol.Conference: 10th Pan-Asian Committee for Treatment and Research in Multiple Sclerosis Congress, PACTRIMS 2017. Vietnam. 24(3):394p
HOHLFELD et al. 2017	Population	–
HOHLFELD et al. 2018	Population	New England Journal of Medicine 2006 355(11):1124 to 40
HONCE et al. 2019	Design	New England Journal of Medicine 2010 362(5):387 to 401
KAPPOS et al. 2006	Population	Journal of neurology Vol.257(Suppl 1):S144
KAPPOS et al. 2010 (N Engl J Med)	Population	Journal of Neurology 2016 263(2):354 to 360
KAPPOS et al. 2010 (J of Neurol)	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2012 Vol.18(4 SUPPL. 1):414p
KAPPOS et al. 2016	Population	Multiple Sclerosis and Related Disorders 2014 3(3):341 to 9
KHAN et al. 2012	Design	European Journal of Neurology 2021 28(12):4135 to 4145
KREMENCHUTZKY et al. 2014	Population	European journal of neurology. Conference: 2nd congress of the European academy of neurology. Copenhagen Denmark. Conference start 2016 23(414 to 415
LANGDON et al. 2021	Population	–
LANGDON et al. 2016	Population	Neurology 2013 80(1 MeetingAbstracts):
LEIST et al. 2014	Population - not in MS	–
LEIST et al. 2013	Population	–

Author (year)	Reason for exclusion	References
LEIST et al. 2020	Population - Not in the specific population	Multiple Sclerosis and Related Disorders 2014 3(6):705 to 11
LOVERA et al. 2015	Intervention not in SR protocol	–
LUBLIN et al. 2014	Population	New England Journal of Medicine 2003 348(1):15 to 23
LUBLIN et al. 2016	Population - progressive MS	Neurology 2007 68(17):1390 to 401
MILLER et al. 2003	Population	Multiple Sclerosis 2011 17(11):1341 to 50
MILLER et al. 2007	Population	–
MONTALBAN et al. 2011	Population	Neurology 2004 62(11):2038 to 43
MONTALBAN et al. 2016	Intervention not in SR protocol	Multiple Sclerosis 2005 11(5):568 to 72
O'CONNOR et al. 2004	Population	Neurodegenerative Disease Management 2022 12(1):1 to 7
O'CONNOR et al. 2005	Population	New England Journal of Medicine 2006 354(9):899 to 910
OH et al. 2022	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2014 Vol.20(1 SUPPL. 1):112 to 113p
POLMAN et al. 2006	Population	Multiple Sclerosis and Related Disorders 2012 1(1):49 to 54
RADUE et al. 2014	Population	Proceedings of the Association of American Physicians 1999 111(1):35 to 44
RAMMOHAN et al. 2012	Population	Annals of Neurology 2007 62(4):335 to 46
ROMINE et al. 1999	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2014 Vol.20(1 SUPPL. 1):100p
RUDICK et al. 2007	Population	Multiple sclerosis (Houndmills, Basingstoke, England) 2011 Vol.17(10 SUPPL. 1):S418-S419p
RUDICK et al. 2014	Population	Multiple Sclerosis 2012 18(9):1269 to 77
SAIDA et al. 2011	Unavailable	Multiple Sclerosis and Related Disorders 2017 11(25 to 31
SAIDA et al. 2012	Population	–
SAIDA et al. 2017 (MS Rel Dis)	Population	Multiple Sclerosis and Related Disorders 2018 26(262):
SAIDA et al. 2017 (Neurol Ther)	Outcome	Multiple Sclerosis Journal 2019 Vol.25(3):466 to 467p
SCHIPPLING et al. 2018	Population	–
SCHIPPLING et al. 2019 (Mul Scle J)	Population	Neurology 1997 Vol.48 Suppl 2(3):A340p
SCHIPPLING et al. 2019 (Eur J Neuro)	Design - extension study	Multiple sclerosis (Houndmills, Basingstoke, England) 2011 Vol.17(10 SUPPL. 1):S411p
SIPE et al. 1997	Population	–
SOELBERG SORENSEN et al. 2011	Outcome	Multiple Sclerosis 1997 3(348):

Author (year)	Reason for exclusion	References
STEINER et al. 2016	Population - progressive MS	Multiple Sclerosis and Related Disorders 2018 26(260):
STELMASIAK et al. 1997	Unavailable	Multiple Sclerosis Journal 2018 Vol.24(2):268 to 269p
VERMERSCH et al. 2018 (MS Rel Dis)	Population	Journal of Neurology 2012 259(5):898 to 905
VERMERSCH et al. 2018 (Mul Scle J)	Population	–
WEINSTOCK-GUTTMAN et al. 2012	Population	Multiple Sclerosis Journal 2017
YAMOUT et al. 2020	Population - Not in the specific population	Multiple Sclerosis 2018 24(11):1461 to 1468
Observational studies		
ADAMEC et al. 2023	Ineligible design - Retrospective	Journal of Neuroimmunology 2023 382 (no pagination)
ALROUGHANI et al. 2023	Ineligible design - Retrospective	Multiple Sclerosis and Related Disorders 2023 74 (no pagination)
ALROUGHANI et al. 2013	Ineligible design - Single arm study	Medical Principles and Practice. 2013 19
ARENA et al. 2023	Ineligible design - Single arm study	Current neuropharmacology. 2023 22
BOSE et al. 2021	Ineligible design - Retrospective	Multiple Sclerosis and Related Disorders 2021 52 (no pagination)
BROWNLEE et al. 2023	Ineligible design - Retrospective	Multiple Sclerosis and Related Disorders 2023 76 (no pagination)
COBO-CALVO et al. 2015	Ineligible design - Single arm study	European Neurology 2015 73(3 to 4):220 to 229
COHEN et al. 2021	Ineligible population – Not highly active disease	Multiple Sclerosis Journal 2021 27(10):1556 to 1563
DEMORTIERE et al. 2023	Ineligible population - Research question	Neurology 2023 10(5)
HAUSSLER et al. 2021	Ineligible intervention	Annals of Clinical and Translational Neurology 2021 8(6):1269 to 1278
KALINCIK et al. 2023	Ineligible intervention	JAMA Neurology 2023 80(7):702 to 713
MAGALASHVILI et al. 2022	Ineligible design - Single arm study	Journal of Neuroimmunology 2022 372 (no pagination)
MAZIBRADA et al. 2018	Ineligible design - Single arm study	Multiple Sclerosis Journal Experimental, Translational and Clinical 2018 4(4)
PANTAZOU et al. 2021 (Rev Neuro)	Ineligible design - Retrospective	Revue Neurologique 2021 177(8):935 to 940
PANTAZOU et al. 2021 (MS Rel Dis)	Ineligible intervention - Discontinuation	Multiple Sclerosis and Related Disorders 2021 51:102918
RASENACK et al. 2016	Ineligible design - Retrospective	PloS One 2016 11(1) (no pagination)

Author (year)	Reason for exclusion	References
RAUMA et al. 2022 (J Neuro)	Ineligible design - Single arm study	Journal of Neurology 2022 269(2):824 to 835
RAUMA et al. 2022 (MS Rel Dis)	Ineligible design - Single arm study	Multiple Sclerosis and Related Disorders 2022 61 (no pagination)
ROLFES et al. 2022	Ineligible design - Single arm study	Multiple Sclerosis and Related Disorders 2022 64 (no pagination)
RUCK et al. 2016	Ineligible design - Single arm study	BMC Neurology 2016 16:34
SMETS et al. 2022	Ineligible population - Not highly active disease	Multiple Sclerosis and Related Disorders 2022 57 (no pagination)
TUOHY et al. 2015	Ineligible design - Single arm study	Journal of Neurology, Neurosurgery and Psychiatry 2015 86(2):208 to 15
ZIEMSSEN et al. 2015	Ineligible design - Single arm study	BMC Neurology 2015 15(1) (no pagination)
BOURDETTE et al. 2009	Ineligible population - Not highly active disease	Current Neurology and Neuroscience Reports 2009 9(5):341 to 342
KAUNZNER et al. 2016	Ineligible design - Retrospective	Neuropsychiatric Disease and Treatment 2016 12:1907 to 1912
SPELMAN et al. 2016	Ineligible design - Retrospective	Neurology: Clinical Practice 2016 6(2):102 to 115
COLES et al. 2011	Ineligible population - Not highly active disease	The Lancet Neurology 2011 10(4):338 to 348
LANZILLO et al. 2016	Ineligible design - Correspondence	Neurology 2016 87(10):1066
MANN et al. 2010	Ineligible design - Correspondence	New England Journal of Medicine 2010 362(18):1738 to 1740

Appendix 4: Summary of Study Characteristics

Table 8: Details of Included RCTs

Study characteristics	CARE-MS I[46,61]	TRANSFORMS[47,62]	CLARITY[49,63]	FREEDOMS[50]	AFFIRM[51,65]
Designs and populations					
Study design	Rater-blinded phase III RCT (post hoc subgroup analysis)	DB phase III RCT (post hoc subgroup analysis)	DB phase III RCT vs PL (post hoc subgroup analysis)	DB phase III RCT vs PL (post hoc subgroup analysis)	DB phase III RCT vs PL (post hoc subgroup analysis)
Enrolment dates	September 7, 2007 to April 17, 2009	May 2006 to September 2007	April 20, 2005 to January 18, 2007	January 2006 to August 2007	November 6, 2001 to NR
Locations	Multicenter: 101 centres in 16 countries	Multicenter: 172 centres in 18 countries	Multicenter: 155 centres in 32 countries	Multicenter: 138 centres in 22 countries	Multicenter: 99 centres in Europe, North America, Australia and New Zealand
Randomized	Subgroup: N = 166 Study: N = 581 Randomized in a 2:1 ratio.	Subgroup: N = 57 Study: N = 1,292 Randomized in a 1:1:1 ratio.	Subgroup: N = 187 Study: N = 1,326 Randomized in a 1:1:1 ratio.	Subgroup: N = 85 Study: N = 1,272 Randomized in a 1:1:1 ratio.	Subgroup: N = 209 Study: N = 942 Randomized in a 2:1 ratio.
Subgroup definition	Patients with highly active relapsing MS: • ≥ 2 relapses within prior year; AND • ≥ 1 Gd-enhancing lesion at baseline.	Treatment-naive patients with highly active disease: • ≥ 2 relapses within prior year; AND • ≥ 1 Gd-enhancing T1 lesion at baseline.	Patients with highly active disease with no prior DMT: • ≥ 2 relapses within prior year; AND • ≥ 1 Gd-enhancing T1 lesion or ≥ 9 T2 lesions.	Treatment-naive severe rapidly evolving relapsing MS: • ≥ 2 relapses within year before baseline; AND • ≥ 1 Gd-enhancing lesion at baseline.	Patients with highly active relapsing MS: • ≥ 2 relapses within prior year; AND • ≥ 1 Gd-enhancing lesion on T1-weighted MRI.
Inclusion criteria (in the study)	• Patients 18 to 50 years. • Relapsing MS according to 2005 McDonald criteria. • Disease duration ≤ 5 years. • ≥ 2 relapses within 2	• Patients 18 to 55 years. • Relapsing MS according to 2005 McDonald criteria. • ≥ 1 documented relapse within prior year, or ≥ 2 documented relapses	• Patients 18 to 65 years. • Relapsing MS according to 2005 McDonald criteria. • ≥ 1 relapse within prior year. • EDSS scores of ≤ 5.5.	• Patients 18 to 55 years. • Relapsing MS according to 2005 McDonald criteria. • ≥ 1 documented relapse within prior year, or ≥ 2 documented relapses	• Patients 18 to 50 years. • Relapsing MS according to 2005 McDonald criteria. • EDSS scores of ≤ 5.5. • Cranial MRI demonstrating lesions

Study characteristics	CARE-MS I[46,61]	TRANSFORMS[47,62]	CLARITY[49,63]	FREEDOMS[50]	AFFIRM[51,65]
	years and ≥ 1 within 1 year. • EDSS scores of ≤ 3.0. • Cranial abnormalities on MRI attributable to MS.	within prior 2 years. • EDSS scores of ≤ 5.5.		within prior 2 years. • EDSS scores of ≤ 5.5.	consistent with MS. • ≥ 1 documented relapse within prior year.
Exclusion criteria (in the study)	• Previous MS therapy (except for corticosteroids). • Prior immunosuppressive, investigational therapy, or monoclonal antibody. • Progressive disease course. • Other clinically significant autoimmune disease.	• Relapse or corticosteroid treatment within 30 days. • Active infection, macular edema, immunosuppression, or concomitant clinically significant systemic disease.	• Failure with ≥ 2 prior DMTs. • Prior immunosuppressive treatment. • Abnormal hematological function. • Concomitant disorder compromising immunity. • Relapse within 28 days.	• Relapse or corticosteroid treatment within 30 days. • Active infection, immunosuppression, or concomitant clinically significant systemic disease.	• Relapse within 50 days. • Cyclophosphamide or mitoxantrone within 1 year. • Interferon beta, glatiramer acetate, cyclosporine, azathioprine, methotrexate, IVIG within 6 months. • Interferon beta or glatiramer acetate for > 6 months.
Drugs					
Intervention	Alemtuzumab 12 mg IV once daily for 5 days at baseline, then for 3 days at 12 months	Fingolimod 0.5 mg orally once daily for 12 months (1.25 mg not in the review)	Cladribine 3.5 mg/kg orally over 2 years (5.25 mg/kg not in the review)	Fingolimod 0.5 mg orally once daily for 24 months (1.25 mg not in the review)	Natalizumab 300 mg IV infusion every 4 weeks
Comparator(s)	Interferon beta-1a 44 mcg SC 3 times/week (once titrated)	Interferon beta-1a 30 mcg IM once weekly for 12 months	Matching placebo	Matching placebo	Matching placebo
Duration					
Length of follow-up	2 years	12 months (1 year)	96 weeks (2 years)	24 months (2 years)	116 weeks (2.5 years)
Outcomes					
Primary outcome	Relapse rate *Defined as:*	Relapse rate *Defined as:*	Relapse rate *Defined as:*	Relapse rate *Defined as:*	Relapse rate *Defined as:*

Study characteristics	CARE-MS I[46,61]	TRANSFORMS[47,62]	CLARITY[49,63]	FREEDOMS[50]	AFFIRM[51,65]
	• New or worsening neurologic symptoms attributable to MS; • Lasting ≥ 48 hours; • With no pyrexia; • Occurring after ≥ 30 days of clinical stability; • With predefined objective change in EDSS.	• New, worsening or recurrent neurologic symptoms; • Occurring after ≥ 30 days of onset of prior relapse; • Lasting ≥ 24 hours; • With no fever or infection; • And predefined increase in EDSS.	• Predefined increase in EDSS; • With no fever; • Lasting ≥ 24 hours; • Preceded by ≥ 30 days of clinical stability.	• Presence of symptoms assessed by neurologist and meeting predefined change in EDSS.	• New or recurrent neurologic symptoms; • No fever or infection; • Lasting ≥ 24 hours; • With neurologic signs identified by neurologist.
Secondary or exploratory outcomes	• Sustained accumulation of disease activity (EDSS) • Radiological activity • Harms	• Radiological activity • Harms	• Sustained accumulation of disease activity (EDSS) • MRI outcomes • Harms	• Disability progression (EDSS) • Harms	• Sustained progression of disability (EDSS) • MRI outcomes • Harms
Notes					
Funding source	Genzyme (Sanofi) and Bayer Schering Pharma	Novartis Pharma	Merck Serono	Novartis	Biogen Idec and Elan Pharmaceuticals
Publications	Subgroup publication: Krieger et al. 2014[46] Related publication: Cohen et al. 2012[61]	Subgroup publication: Cohen et al. 2013[47] Related publications: Cohen et al. 2010[62] Radue et al. 2012[48]	Subgroup publication: Vermersch et al. 2021[49] Related publication: Giovannoni et al. 2010[63]	Subgroup publication: Devonshire et al. 2012[50] Related publications: Kappos et al. 2010[64] Radue et al. 2012[48]	Subgroup publication: Hutchinson et al. 2009[51] Related publication: Polman et al. 2006[65]

DB = double-blind; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; Gd = gadolinium; IVIG = IV immunoglobulin; MS = multiple sclerosis; NR = not reported; PL = placebo; RCT = randomized controlled trial.

Note that this table has not been copy-edited.

Table 9: Details of Included Observational Study

Study characteristics	Prosperini et al. 2017[52]
Designs and populations	
Study design	Prospective comparative cohort study
Enrolment dates	NR
Locations	Multicenter: 8 tertiary MS centres in Italy
N	N = 120 patients (after propensity score matching of the 216 patients enrolled, in a 1:1:1 ratio, based on the nearest neighbour matching procedure)
Selection criteria	Highly active treatment-naive patients: • No prior disease-modifying treatment • ≥ 2 relapses within the prior year • ≥ 1 Gd-enhancing lesion
Drugs	
Interventions	Natalizumab; or Fingolimod; or Interferon beta-1b or beta-1a, high-dose / high-frequency (only if patient's preference or other alternatives unavailable).
Concomitant medications	NR
Duration	
Length of follow-up	24 months (with clinical visits ≥ every 6 months)
Outcomes	
Primary outcome	Proportions of patients who have no evidence of disease activity *Defined as:* Absence of clinical relapses (new neurologic symptom with no fever or infection, lasting for ≥ 24 hours, accompanied by new neurologic signs), disability worsening (prespecified increase in EDSS), and radiological activity (≥ 1 Gd-enhancing lesion or ≥ 1 new T2-hyperintense lesion).

Study characteristics	Prosperini et al. 2017[52]
Secondary or exploratory outcomes	• Time to relapse • Disability worsening • Radiological activity • Occurrence of disability reduction
Notes	
Funding source	Reported as: Independent
Publications	Prosperini et al. 2017[52]

EDSS = Expanded Disability Status Scale; Gd = gadolinium; NR = not reported; MS = multiple sclerosis.

Note that this table has not been copy-edited.

Appendix 5: Risk of Bias Assessment

Table 10: Risk of Bias Assessment Per Outcome Within Each RCT Using RoB2[44]

Study	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
CARE-MS I[46,61]						
Relapse	**Some concern** The subgroup appeared to be defined post hoc. Randomization was not reported to be stratified for the subgroup, raising concerns about the risk of bias.	**High** Patients and treating clinicians aware of assigned intervention, but clinical and MRI raters blinded to treatment assignment and relapses adjudicated by an independent and masked committee. No information as to how patients with missing outcome data were handled. Discontinuations may amount to a sufficient proportion to introduce bias.	**High** No information reported.	**Low** Outcomes measured appropriately and similarly between groups. Outcome assessors unaware of treatment received.	**Some concern** The subgroup analysis was post hoc and data were not analyzed according to a prespecified plan. There was no indication that the results were selected from multiple outcome measurements or data analyses.	**High risk of bias**
Harms			**Low** Data available for all patients (assessed for the overall study population).	**Some concern** Assessors may have guessed treatment assignment based on the specific harms profiles of the interventions. This may introduce bias in subjectively measured AEs.		
TRANSFORMS[47,62]						
Relapse	**Some concern** The subgroup was defined post hoc. Randomization	**High** Patients, study personnel and MRI evaluators blinded to assigned intervention (matching placebo / clinical	**High** No information reported.	**Low** Outcomes measured appropriately and similarly between groups. Outcome assessors unaware of treatment received.	**Some concern** The subgroup analysis was post hoc, data were not analyzed according	**High risk of bias**

Study	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
	was not stratified for the subgroup, raising concerns about the risk of bias.	evaluators blinded to AEs). However: No information as to how patients with missing outcome data were handled. Discontinuations may amount to a sufficient proportion to introduce bias.			to a prespecified plan. There was no indication that the results were selected from multiple outcome measurements or data analyses.	
Imaging outcomes						
Harms			**Low** Data available for all patients (assessed for the overall study population).	**Some concern** Assessors may have guessed treatment assignment based on the specific harms profiles of the interventions. This may introduce bias in subjectively measured AEs.		
CLARITY[49,63]						
Relapse	**Some concern** The subgroup was defined post hoc. Randomization was not stratified for the subgroup, raising concerns about the risk of bias.	**High** Patients, evaluating physicians and central MRI evaluators blinded to assigned intervention (matching placebo / clinical evaluators blinded to laboratory and safety results). However: No information as to how patients with missing outcome data were handled, and on discontinuations or amount of missing data.	**High** No information reported.	**Low** Outcomes measured appropriately and similarly between groups. Outcome assessors unaware of treatment received.	**Some concern** The subgroup analysis was post hoc and data were not analyzed according to a prespecified plan. There was no indication that the results were selected from multiple outcome measurements or data analyses.	**High risk of bias**

Study	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Disability progression						
Imaging outcomes						
Harms			**Low** Data available for all patients (assessed for the overall study population).	**Some concern** Assessors may have guessed treatment assignment based on the specific harms profiles of the interventions. This may introduce bias in subjectively measured AEs.		
Relapse	**Some concern** The subgroup was defined post hoc. Randomization was not stratified for the subgroup, raising concerns about the risk of bias.	**High** Patients and evaluators blinded to assigned intervention (matching placebo / clinical evaluators blinded to assessments with potential for unmasking). However: • No information as to how patients with missing outcome data were handled, and on discontinuations or amount of missing data.	**High** No information reported.	**Low** Outcomes measured appropriately and similarly between groups. Outcome assessors unaware of treatment received.	**Some concern** The subgroup analysis was post hoc, data were not analyzed according to a prespecified plan. There was no indication that the results were selected from multiple outcome measurements or data analyses.	**High risk of bias**
Disability progression						
Harms			**Low** Data available for all patients (assessed for the overall study population).	**Some concern** Assessors may have guessed treatment assignment based on the specific harms profiles of the interventions. This may introduce bias in subjectively measured AEs.		

Study	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
AFFIRM[51,65]						
Relapse	**Some concern** The subgroup was defined post hoc. Randomization was not stratified for the subgroup, raising concerns about the risk of bias.	**High** Patients, study personnel and clinicians blinded to assigned intervention (matching placebo / separate treating and examining neurologists). However: • No information as to how patients with missing outcome data were handled, and on discontinuations or amount of missing data.	**High** No information reported.	**Low** Outcomes measured appropriately and similarly between groups. Outcome assessors unaware of treatment received.	**Some concern** The subgroup analysis was post hoc, data were not analyzed according to a prespecified plan. There was no indication that the results were selected from multiple outcome measurements or data analyses.	**High risk of bias**
Disability progression						
Imaging outcomes						
Harms			**Low** Data available for all patients (assessed for the overall study population).	**Some concern** Assessors may have guessed treatment assignment based on the specific harms profiles of the interventions. This may introduce bias in subjectively measured AEs.		

AE = adverse event; RoB2 = Cochrane Risk of Bias tool, version 2.

Note that this table has not been copy-edited.

Table 11: Risk of Bias Assessment Per Outcome for the Observational Study Using ROBINS-I[45]

Prosperini et al. 2017[52]	Confounding	Patient selection	Classification of interventions	Deviations from intended interventions	Missing data	Outcome measurement	Selection of reported results	Overall
Relapse	**Serious** Potential for confounding of the effect of interventions. Propensity score matching, but publication does not report which potential confounding factors were identified by the authors. No sensitivity analysis performed to control for uncaptured or unknown potential confounding domains.	**Low** Patient inclusion was appropriate. Follow-up initiated when patients were considered clinically stable.	**Low** Interventions well defined and based solely on information collected at time of intervention.	**Low** Deviations from intended interventions reflected usual practice (no information suggested otherwise).	**Low** There was no indication in the publication suggesting that there was any patient with missing data in the study.	**Moderate** Comparable methods of assessment. No evidence of systematic error relative to intervention status. Somewhat subjective outcome measure, assessors aware of treatment received.	**Moderate** Outcome measures and analysis prespecified and clearly defined. No indication of selection of reported analysis or patient cohort.	**Serious** Uncontrolled for confounding. Somewhat subjective outcome assessed while aware of intervention received.
Disability								
Imaging outcomes						**Low** Comparable methods of assessment. No evidence of systematic error relative to intervention status. Objective outcome.		

ROBINS-I = Risk Of Bias In Nonrandomized Studies – Interventions.

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