Common Drug Review
Clinical Review Report

July 2017

Drug	Daclizumab (Zinbryta)
Indication	For the treatment of adult patients with active relapsing-remitting multiple sclerosis who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of multiple sclerosis.
Reimbursement request	As per indication
Dosage form(s)	1.0 mL pre-filled pen or syringe, 150 mg/mL
NOC Date	December 8, 2016
Manufacturer	Biogen Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in neurology with sub-specialization in multiple sclerosis who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

9HPT	9-Hole Peg Test
AE	adverse event
ALT	alanine transaminase
ARR	annualized relapse rate
AST	aspartate transaminase
CDR	CADTH Common Drug Review
CNS	central nervous system
DAC	daclizumab
DB	double-blind
DIC	deviance information criterion
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol 5-Dimensions questionnaire
FE	fixed effect
FS	functional system
Gd	gadolinium
GHQ-12	12-item General Health Questionnaire
HRQoL	health-related quality of life
ITC	indirect treatment comparison
IFN	interferon
IL	interleukin
IM	intramuscularly
INEC	Independent Neurology Evaluation Committee
ITT	Intention to treat
IVMP	intravenous methylprednisolone
MCID	minimal clinically important difference
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
NMA	network meta-analysis
PASAT	Paced Auditory Serial Addition Test
PFP	pre-filled pen
PML	progressive multifocal leukoencephalopathy
PP	per-protocol
QoL	quality of life
RCT	randomized controlled trial
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SC	subcutaneously

SD	standard deviation
SF-12	Short Form (12) Health Survey
SF-36	Short Form (36) Health Survey
T25-FW	Timed 25-Foot Walk
ULN	upper limit of normal
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory disease of the central nervous system (CNS).[1,2] MS causes bothersome or disabling physical symptoms involving mobility problems, vision problems, problems with coordination, cognitive dysfunction, fatigue, and pain. Patient quality of life is significantly impaired by mood disorders and limitations in employment and social functioning. MS is one of the major causes of disability in young adults, affects up to three times as many women as men, and typically has an age of onset between 20 years and 50 years.[56] MS is classified into four clinical subtypes: relapsing-remitting MS (RRMS); primary-progressive MS, secondary-progressive MS, and progressive-relapsing MS. The RRMS subtype comprises 85% to 90% of MS patients at first presentation and is characterized by clearly defined relapses with full recovery or with sequelae and residual deficit upon recovery, with lack of progression of disability during the periods between relapses.[6] MS is associated with major financial burden on patients, families, and the health care system.[6] The Multiple Sclerosis Society of Canada estimates that there are currently 100,000 patients with MS in Canada.[8]

The currently recommended first-line drugs for RRMS are interferon (IFN) beta, glatiramer acetate, teriflunomide, or dimethyl fumarate. Second-line therapies, including alemtuzumab, fingolimod, and natalizumab, may be indicated for patients with a suboptimal response to a first-line drug.[9]

Daclizumab (DAC; Zinbryta) is a monoclonal antibody that binds the α-subunit of the interleukin (IL)-2 receptor, CD25, and modulates IL-2 signalling. DAC is available as a solution for injection as 150 mg per mL in a pre-filled pen or pre-filled syringe. The recommended dose of DAC is 150 mg injected subcutaneously (SC) once a month.[18]

Indication under review
For the treatment of adult patients with active relapsing-remitting multiple sclerosis who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of multiple sclerosis

The objective of this systematic review is to examine the beneficial and harmful effects of DAC SC in the treatment of active RRMS in adult patients.

Results and Interpretation

Included Studies

Two multi-centre, double-blind (DB) RCTs, DECIDE (Study 205MS301, N = 1,841) and SELECT (Study 205MS201, N = 621), met the inclusion criteria for this systematic review.[38,39] DECIDE, a phase III superiority trial, evaluated the efficacy and safety of DAC 150 mg SC once every four weeks compared with IFN beta-1a 30 µg intramuscularly (IM) once weekly. DECIDE enrolled patients from North America, including Canada (1%). SELECT, a dose-finding phase II trial, evaluated the efficacy and safety of DAC 150 mg and 300 mg SC once every four weeks compared with placebo. The primary objective of the two studies was to determine whether DAC, when compared with IFN beta-1a or placebo, was effective in reducing the annualized relapse rate (ARR) between baseline and study end (weeks 96 to 144 in DECIDE, week 52 in SELECT). Patients aged 18 to 55 years meeting the 2005 McDonald criteria for active RRMS were eligible for the studies.

In general, the baseline demographic and disease characteristics in the two studies were well balanced across treatment groups. The majority of patients were female (63% to 68%) and the mean age was approximately 35 to 37 years. The mean number of relapses was two to three in the past three years, and one to two in the past one year, as per the inclusion criteria. In DECIDE, a higher percentage (47.1%) of previous disease-modifying therapies (DMTs) use was noted, while in SELECT, 18.7% of the participants had received prior medications for MS. The majority of patients had received IFN beta therapy in both studies.

Efficacy

Key outcomes identified in this CADTH Common Drug Review (CDR) were: relapse rate, disability, and health-related quality of life (HRQoL). Fatigue and productivity were identified as an important outcome, but they were not specifically assessed in the included studies.

In DECIDE, ARR was statistically significantly lower for patients on DAC (0.22 [95% confidence interval, 0.19 to 0.24]) compared with those on IFN beta-1a (0.39 [95% confidence interval, 0.35 to 0.44]) with a reduction of 45% over 96 to 144 weeks. The proportion of patients who were relapse-free was 72% in the DAC group compared with 57% in the IFN beta-1a group, probability (*P*) < 0.0001. In SELECT, ARR was statistically significantly lower for patients on DAC (0.21 [95% confidence interval, 0.16 to 0.29]) compared with those on placebo (0.46 [95% confidence interval, 0.37 to 0.57]) with a reduction of 54% over 52 weeks. The proportion of patients who were relapse-free was 81% in the DAC group compared with 65% in the placebo group, *P* < 0.0001.

In DECIDE, treatment with DAC 150 mg was associated with a 16% reduction in three-month confirmed disability progression over 96 to 144 weeks; however, the between-group difference did not reach statistical significance. The six-month confirmed disability progression was also measured in both studies, and the differences between DAC and placebo, or between DAC and IFN beta-1a, were statistically significant. In SELECT, over 52 weeks, treatment with DAC 150 mg was associated with a 57% reduction in the risk of three-month confirmed disability progression compared with placebo, and the difference was statistically significant. The three and six-month confirmed disability progressions in SELECT and the six-month disability progression in DECIDE were tertiary and/or supportive end points; therefore, these were not included in a sequential closed testing procedure to control for potentially inflated type I error rate. The results need to be interpreted with caution. A number of scales or questionnaires were measured in DECIDE and SELECT to explore the clinical benefits of the study drug on patient-reported outcomes, such as generic HRQoL assessment tools (i.e., EuroQol 5-Dimensions questionnaire [EQ-5D], Short Form [12] Health Survey [SF-12]) or disease-specific questionnaires (i.e., Expanded Disability Status Scale [EDSS], Multiple Sclerosis Impact Scale-29 [MSIS-29] and Multiple Sclerosis Functional Composite [MSFC]). For many of these outcomes, even though statistical significance has been achieved for between-group differences, the clinical relevance may still remain uncertain due to the lack of minimal clinically important difference (MCID), or the scale has not been well validated in the study population.

Compared with IFN beta-1a or placebo, patients treated with DAC had fewer numbers of new or newly enlarging T2 hyperintense lesions and fewer numbers of new gadolinium (Gd)-enhancing lesions on MRI scans.

Harms

The overall adverse event (AE) rates were similar between DAC (91%) and IFN beta-1a (91%) in DECIDE, and between DAC (73%) and placebo (79%) in SELECT. After excluding MS relapse, the most common AEs among patients treated with DAC included nasopharyngitis, headache, and upper respiratory tract infection, while influenza-like illness was more frequently reported in the IFN beta-1a group in DECIDE.

The frequency of serious adverse events (SAEs) was higher in the DAC group than in the IFN beta-1a group or placebo group at study end (DECIDE: 15% DAC versus 10% IFN beta-1a; SELECT: 7% DAC versus 6% placebo) after MS relapses were removed from the counts. More patients in the DAC group withdrew the treatment due to an AE compared with IFN beta-1a or placebo (DECIDE: 15% DAC versus 12% IFN beta-1a; SELECT: 3% DAC versus < 1% placebo).

In both studies, treatment with DAC 150 mg was associated with higher frequency of elevated liver enzymes, depression, serious infection, and lymphadenopathy, compared with IFN beta-1a or placebo.

In DECIDE, one death in the DAC group and four deaths in the IFN beta-1a group were reported, and none of them was considered to be treatment-related, while in SELECT, one death was reported in the DAC treatment group, and it was considered to be treatment-related.

Patients who had completed DECIDE or SELECT were eligible to enter the extension phase of the two studies, EXTEND (up to five years) and Study 202 (SELECTION, 52 weeks). The findings of Study 202 suggested that measures of MS disease activity, such as ARR, were similar in the extension phase and SELECT. In patients who began to receive DAC 150 mg in Study 202 after being on placebo in SELECT, reduction in MS disease activity measures (i.e., ARR) were apparent in the second year. EXTEND is ongoing. The major limitation of the extension studies was a lack of control group.

The manufacturer provided an indirect treatment comparison (ITC) analysis to evaluate the comparative efficacy and safety of DAC versus currently available DMTs for RRMS.[50] A second ITC (by Tramacere et al.[16]) was identified in a supplemental literature search for this review. The manufacturer–provided ITC indicated that DAC statistically significantly reduced the ARR compared with IFN beta-1a 30 µg once weekly, IFN beta-1a 44 µg three times a week, IFN beta-1b 250 µg every other day, glatiramer acetate 20 mg once daily, glatiramer acetate 40 mg three times a week, and teriflunomide 14 mg once daily. Conversely, Tramacere et al. reported no statistically significant differences between DAC and these drugs for reducing ARR. The Tramacere et al. ITC only included the SELECT study; DECIDE was ongoing at the time of the analysis. Significant clinical heterogeneity among the included clinical trials and uncertainty as to whether or not transitivity was satisfied were key limitations of both ITCs. Therefore, given the degree of uncertainty in the relative treatment effect estimates, there is insufficient evidence to determine if there is a meaningful clinical difference between DAC and other DMTs for the treatment of RRMS, particularly in the population specified in the Health Canada–approved indication for DAC.

Conclusions

In two DB RCTs in patients with RRMS, DAC was associated with a lower rate of relapse and delayed disability progression (sustained for three months and six months), versus placebo and IM IFN beta-1a. The effects of DAC on patient-reported outcomes, such as HRQoL and function, are uncertain. After treatment, the numbers of Gd-enhancing lesions and new/enlarging T2-weighted lesions observed on MRI scans were statistically significantly reduced in the DAC group compared with placebo or IFN beta-1a.

With respect to safety, the overall incidence of AEs was similar between DAC and IFN beta-1a or placebo; however, there were more SAEs reported in the DAC group, primarily due to infections. The use of DAC was also associated with higher frequency of serious hepatic AEs and skin disorders. The comparative safety of DAC and other medications for RRMS is uncertain due to the lack of long-term head-to-head trials.

There was insufficient evidence, associated with a high degree of uncertainty, from ITCs regarding the comparative efficacy and safety of DAC and other DMTs for RRMS.

TABLE 1: SUMMARY OF RESULTS

	DECIDE		SELECT	
Efficacy				
	DAC 150 mg (N = 919)	**IFN beta-1a 30 µg (N = 922)**	**DAC 150 mg (N = 201)**	**PL (N = 196)**
Adjusted ARR[a]				
ARR (95% CI)	0.216 (0.191 to 0.244)	0.393 (0.353 to 0.438)	0.211 (0.155 to 0.287)	0.458 (0.370 to 0.566)
Rate ratio (95% CI)	0.550 (0.469 to 0.645)		0.461 (0.318 to 0.668)	
P value	< 0.0001		< 0.0001	
Proportion of patients experiencing relapses, n (%)				
0 ≥ 1	659 (72) 260 (28)	530 (57) 392 (43)	163 (81) 38 (19)	127 (65) 69 (35)
HR for risk of relapse (95% CI)	0.59 (0.50 to 0.69)		0.45 (0.30 to 0.67)	
P value	< 0.0001		< 0.0001	
3-month confirmed disability progression (measured by increase in EDSS)				
Number of patients progressed at week 12, n (%)	121 (13)	140 (15)	11 (5)	25 (13)
Estimated % of patients with progression	12.0 at week 96 16.2 at week 144	14.3 at week 96 20.3 at week 144	5.9 (at week 52)	13.3 (at week 52)
HR (95% CI)	0.84 (0.66 to 1.07)		0.43 (0.21 to 0.88)	
P value	0.1575		0.0211	
6-month confirmed disability progression (measured by increase in EDSS)				
Number of patients progressed at week 24, n (%)	80 (9)	99 (11)	5 (2)	21 (11)
Estimated % of patients with progression	9.2 at week 96 12.7 at week 144	12.1 at week 96 18.3 at week 144	2.6 at week 52	11.1 at week 52
HR (95% CI)	0.73 (0.55 to 0.98)		0.24 (0.09 to 0.63)	
P value	0.0332		0.0037	
EDSS scores				
Change from baseline, mean (SD)	–0.02 (0.698) at week 96; –0.03 (0.855) at week 144	–0.01 (0.783) at week 96; –0.03 (0.922) at week 144	–0.08 (0.518)	0.09 (0.710)
Between-group difference (95% CI)	NR		NR	
P value	0.3742 at week 96; *P* value after week 96 not reported		0.0102	

	DECIDE		SELECT	
MSIS-29 physical impact score				
Change from baseline, mean (SD)	–0.84 (14.16)	1.15 (14.06)	–1.0 (11.80)	3.0 (13.52)
Between-group difference, mean (95% CI)	–2.09 (–3.32 to –0.86)		–4.27 (–6.76 to –1.78)	
P value	0.0008		0.0008	
MSFC z score				
Change from baseline, median (25th, 75th percentile)	0.091 (–0.096 to 0.287)	0.055 (–0.136 to 0.240)	NR	
Between-group difference, mean (95% CI)	NR			
P value	0.0007			
Harms				
N (safety set)	919	922	208	204
Death	1	4	1	0
AEs, n (%)	838 (91)	842 (91)	151 (73)	161 (79)
SAEs, n (%)	142 (15)	88 (10)	15 (7)	12 (6)
WDAEs, n (%)	64 (7)	66 (7)	6 (3)	2 (< 1)
Notable harm, n (%)				
Depression	75 (8)	57 (6)	10 (5)	3 (1)
ALT increased	≥ 3 ULN: 87 (9)	≥ 3 ULN: 76 (8)	> 3-5 ULN: 7 (3)	> 3-5 ULN: 6 (3)
ALT increased	> 5 ULN: 53 (6)	> 5 ULN: 30 (3)	> 5-20 ULN: 6 (3)	> 5-20 ULN: 1 (< 1)
AST increased	≥ 3 ULN: 63 (7)	≥ 3 ULN: 34 (4)	> 3-5 ULN: 1 (<1)	> 3-5 ULN: 0
AST increased	> 5 ULN: 37 (4)	> 5 ULN: 14 (2)	> 5-20 ULN: 5 (2)	> 5-20 ULN: 1 (< 1)
Serious infections	40 (4)	15 (2)	6 (3)	0
Lymphadenopathy	47 (5)	7 (< 1)	0	0

AE = adverse event; ALT = alanine transaminase; ARR = annualized relapse rate; AST = aspartate transaminase; CI = confidence interval; DAC = daclizumab; EDSS = Expanded Disability Status Scale; HR = hazard ratio; IFN = interferon; MSFC = Multiple Sclerosis Functional Composite; MSIS-29 = Multiple Sclerosis Impact Scale-29; n = number of patients with event; N = number of patients; NR = not reported; *P* = probability; PL = placebo; SAE = serious adverse event; SD = standard deviation; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.

[a] In both DECIDE and SELECT, treatment-group differences were compared using a negative binomial regression model adjusted for the number of relapses in the three years (DECIDE) or one year (SELECT) before study entry, baseline EDSS, and age. History of prior IFN beta-1a use was also adjusted in DECIDE.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory disease of the central nervous system (CNS).[1,2] While the etiology of MS is unknown, it is believed that an abnormal immune response to environmental triggers in people who are genetically predisposed results in immune-mediated acute, and then chronic, inflammation.[1] Previous research suggested that auto-reactive T-cells cross the blood-brain barrier, attack the myelin sheath and axons leading to a cascade of inflammation, and subsequently affect the brain or spinal cord through a process called demyelination.[1,3] In the majority of patients (85%), the first presentation of MS is often a clinically isolated syndrome, which is the first attack of a disease compatible with MS (i.e., various motor or sensory deficits).[2,4] After the initial disease phase, a patient may experience a series of relapses and remissions. MS causes bothersome or disabling physical symptoms involving mobility problems, vision problems, problems with coordination, cognitive dysfunction, fatigue, and pain. Patient quality of life (QoL) is significantly impaired by mood disorders and limitations in employment and social functioning. MS is one of the major cause of disability in young adults.[5] MS affects up to three times as many women as men and typically has an age of onset between 20 years to 50 years.[6]

According to the McDonald criteria (2010), MS can be diagnosed on the basis of evidence of at least two relapses (clinical and/or MRI) achieved through a detailed medical history and neurological examination. Diagnosis is confirmed by objective clinical evidence of at least two lesions that are disseminated in space and time as demonstrated clinically or by MRI.[2,7] MS is classified into four clinical subtypes: relapsing-remitting MS (RRMS); primary-progressive MS, secondary-progressive MS, and progressive-relapsing MS. The RRMS subtype comprises 85% to 90% of MS patients at first presentation and is characterized by clearly defined relapses with full recovery or with sequelae and residual deficit upon recovery, with lack of progression of disability during the periods between relapses.[6] The relapsing forms of MS are associated with better prognosis than progressive forms of the disease.

MS is associated with major financial burden on patients, families, and the health care system.[6] The Multiple Sclerosis Society of Canada estimates that there are currently 100,000 patients with MS in Canada, which is one of the highest prevalence rates in the world.[8]

1.2 Standards of Therapy

As there is currently no cure for MS, the goal of therapy is to decrease the number and severity of relapses, reduce MRI burden of disease, limit disability progression, and maintain patient QoL through the use of disease-modifying therapies (DMTs; Table 2). [9] According to the Canadian Multiple Sclerosis Working Group (2013), the currently recommended first-line drugs for RRMS are interferon (IFN) beta, glatiramer acetate, teriflunomide, and dimethyl fumarate, with the choice of drug being guided by the adverse event (AE) profile, dosage schedule, reimbursement, and patient preference.[9-12] In 2013, CADTH published a therapeutic review of RRMS.[13] The report concluded that all active treatments with DMTs produce statistically significant reductions in the annualized relapse rate (ARR) compared with no treatment, and there are differences in ARR between various DMTs. AEs of note were treatment-specific and included influenza-like symptoms for IFNs, injection-site reactions and hypersensitivity for glatiramer acetate, cardiovascular disorders for fingolimod, infusion reactions and progressive multifocal leukoencephalopathy (PML) for natalizumab, flushing for dimethyl fumarate, thyroid disorders for alemtuzumab, and alopecia for teriflunomide. Based on this review and accompanying pharmacoeconomic analysis, the CADTH Canadian Drug Expert Committee (CDEC) recommended

glatiramer and IFN beta-1b as the initial therapies of choice for RRMS.[13] Pegylated (peg)-IFN beta-1a (Plegridy) was not included in the therapeutic review. Previous studies suggested that it was superior to placebo in lowering ARR and delaying disability progression, but had comparable treatment effect to other DMTs for MS. Its safety profile was similar to the other IFN products for MS (i.e., injection-site reactions and influenza-like symptoms are common).[14-16]

Treatment selection or a change in therapy should be guided by the level of disease activity, disability progression, and MRI findings, and is highly individualized.[9] A lateral switch between first-line drugs may be indicated for patients who have had adequate treatment response but poor tolerability to a medication. Second-line therapies, including alemtuzumab, fingolimod, and natalizumab, may be indicated for patients with a suboptimal response to a first-line drug.[9] A recently published study also indicated that newer treatments (i.e., fingolimod, natalizumab, and alemtuzumab) may be more effective but have a less favourable safety record compared with the older treatments (i.e., IFNs and glatiramer acetate) that are moderately effective but have rare life-threatening AEs.[17]

Although no clinical criteria have been established to identify patients who should discontinue treatment, the Canadian Multiple Sclerosis Working Group suggests that it may be necessary to consider stopping treatment in patients with significant disease progression (Expanded Disability Status Scale [EDSS] > 6) who have not experienced a relapse in the preceding two years.[9]

1.3 Drug

Daclizumab (DAC; Zinbryta) is a monoclonal antibody that binds the α-subunit of the interleukin (IL)-2 receptor, CD25. It modulates IL-2 signalling by selectively blocking CD25-dependent, high-affinity IL-2 receptor signalling, resulting in higher levels of IL-2 available for signalling through the CD25-independent intermediate-affinity IL-2 receptor.[18] Subsequently DAC is able to inhibit T-cell expansion and reduce brain inflammation in MS patients, and reduce the severity of associated symptoms.[19]

DAC is available as a solution for injection as 150 mg/mL in a pre-filled pen or pre-filled syringe. The recommended dose of DAC is 150 mg injected subcutaneously (SC) once a month. A notice of compliance (NOC) for DAC for the management of RRMS was granted by Health Canada on December 8, 2016.[20]

Indication under review
For the treatment of adult patients with active relapsing-remitting multiple sclerosis who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of multiple sclerosis
Reimbursement criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF DISEASE-MODIFYING TREATMENTS FOR MULTIPLE SCLEROSIS

	Mechanism of Action	Approved Indications [a]	Route of Administration	Recommended Dose	Serious Side Effects or Safety issues
Daclizumab (Zinbryta)[18]	Binds to CD25.	RRMS; patients who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of MS	SC injection	150 mg once a month	Contraindicated in patients with pre-existing hepatic disease or hepatic impairment, a history of autoimmune hepatitis or other autoimmune condition involving the liver, or a history of severe hypersensitivity to daclizumab or any of the components of the product.
Peg-IFN beta-1a (Plegridy)	Its effects in MS are 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 µg every 2 weeks	Patients with a history of hypersensitivity to natural or recombinant IFN beta or peg-IFN, or any other component of the formulation or the container.
Alemtuzumab (Lemtrada)	Binds to CD52.	RRMS; patients who have had an inadequate response to IFN beta or other disease-modifying therapies	IV infusion	Initial treatment cycle: 12 mg/day for 5 consecutive days Second treatment cycle: 12 mg/day for 3 consecutive days administered 12 months after the initial treatment course	Contraindicated in patients 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, and/or have a history of PML.
Dimethyl fumarate (Tecfidera)	Effects are not completely understood; activates the Nrf2 pathway.	RRMS	Oral capsule	240 mg twice daily	Contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.
Fingolimod (Gilenya)	Its effects in MS are not fully known; its	RRMS; generally recommended in MS	Oral capsule	0.5 mg/day	Contraindicated in patients who are hypersensitive to fingolimod, who are

	Mechanism of Action	Approved Indications [a]	Route of Administration	Recommended Dose	Serious Side Effects or Safety issues
	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 the CNS.	patients who have had inadequate response to, or are unable to tolerate, one or more therapies for MS			at risk for an opportunistic infection, are immunocompromized due to treatment or to disease, and/or have hepatic insufficiency, active severe infections, or known active malignancies. Varicella zoster vaccination recommended.
Glatiramer acetate (Copaxone)	Likely modifies the immune processes responsible for pathogenesis of MS.	RRMS; single demyelinating event, accompanied by abnormal MRI scans and considered to be at risk of developing CDMS	SC injection	20 mg/day	Contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.
IFN beta-1a (Avonex; Rebif)	Its effects in MS are 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 with relapses; 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	Contraindicated in patients with known hypersensitivity to natural or recombinant IFN, patients with liver disease, and pregnant women.
IFN beta-1b (Betaseron; Extavia)	Its effects in MS are not completely understood. It exerts its biological effects by binding to specific	RRMS; SPMS; single demyelinating event accompanied by at least two clinically silent lesions typical of	SC injection (Betaseron, Extavia)	0.25 mg every other day	Contraindicated in patients with known hypersensitivity to natural or recombinant IFN, patients with liver disease, pregnant women.

	Mechanism of Action	Approved Indications [a]	Route of Administration	Recommended Dose	Serious Side Effects or Safety issues
	receptors on the surface of human cells and inducing the expression of numerous IFN-induced gene products.	MS			
Natalizumab (Tysabri)	Binds to the α4-subunit of human integrin: blocks interaction of α4β1 integrin with VCAM-1 and blocks the interaction of α4β7 integrin with MadCAM-1.	RRMS; 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	Contraindicated in patients who have had PML, are at risk for PML; are hypersensitive to this drug or to any ingredient in the formulation or any component of the drug; are immunocompromized, including those immunocompromized due to immunosuppressant or antineoplastic therapies, or immunodeficiencies.
Teriflunomide (Aubagio)	Not completely understood; may reduce numbers of activated lymphocytes available for migration into the CNS.	RRMS	Oral tablet	14 mg once daily	Contraindicated in patients who are hypersensitive to this drug or to leflunomide; patients currently treated with leflunomide; patients with severe hepatic impairment; pregnant women or women of child-bearing age who are not using contraception; patients with immunodeficiency states such as AIDS, serious active infection, or impaired bone marrow function; or with significant anemia, leucopenia, neutropenia, or thrombocytopenia.

AIDS = acquired immunodeficiency syndrome; CDMS = clinically definite multiple sclerosis; CNS = central nervous system; HIV = human immunodeficiency virus; IFN = interferon; IL = interleukin; IM = intramuscular; IV = intravenous; MadCAM-1 = mucosal addressin cell adhesion molecule-1; MRI = magnetic resonance imaging; MS = multiple sclerosis; peg = pegylated; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis; TB = tuberculosis; VCAM-1 = vascular cell adhesion molecule-1.

[a] Health Canada indication.

Source: Health Canada product monographs.[11,12,21-29]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of DAC beta for the treatment of active RRMS in adult patients.

2.2 Methods

All manufacturer–provided trials considered pivotal by Health Canada will be included in the systematic review. Phase III studies will be selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient population	Patients with RRMS who have experienced an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of MS.
Intervention	Daclizumab beta, 150 mg SC once a month
Comparators	Disease-modifying therapy: • Dimethyl fumarate p.o. • Teriflunomide p.o. • IFN beta-1a IM, SC • IFN beta-1b SC • Pegylated IFN beta-1a SC • Glatiramer acetate SC • Natalizumab IV • Fingolimod p.o. • Alemtuzumab IV
Outcomes	**Key efficacy outcomes:** • Relapse (e.g., relapse rate and relapse-free rate)* • Disability progression or improvement using a validated scale (e.g., Daclizumab, MSFC)* • HRQoL using a validated scale (e.g., SF-36)* • Fatigue* **Other efficacy outcomes:** • Brain lesions on MRI (e.g., Gd-enhancing lesions, new or enlarging T2 lesions) • Brain atrophy or brain volume on MRI • Productivity (ability to attend work or school)* • Medication acceptance • Relapse requiring corticosteroids **Harms outcomes:** • AEs, SAEs, WDAEs, mortality • Notable harms/harms of special interest: immune-mediated disorders (e.g., autoimmune hepatitis, lymphadenopathy, skin reactions, and autoimmune hemolytic anemia), liver toxicities, depression including suicidal ideation, serious infection, herpetic infection, and PML
Study design	Published and unpublished phase III RCTs

AE = adverse event; Gd = gadolinium; IFN = interferon; IM = intramuscularly; IV = intravenously; HRQoL = health-related quality of life; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; PML = progressive multifocal leukoencephalopathy; p.o. = oral; RCT = randomized controlled trial; RRMS = relapse-remitting multiple sclerosis; SAE = serious adverse event; SC = subcutaneously; SF-36 = Short Form (36) Health Survey; WDAE = withdrawal due to adverse event.

* These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Zinbryta (daclizumab) and relapsing-remitting multiple sclerosis.

Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs). Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on January 25, 2017. Regular alerts were established to update the search until the meeting of CDEC on May 17, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), and Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

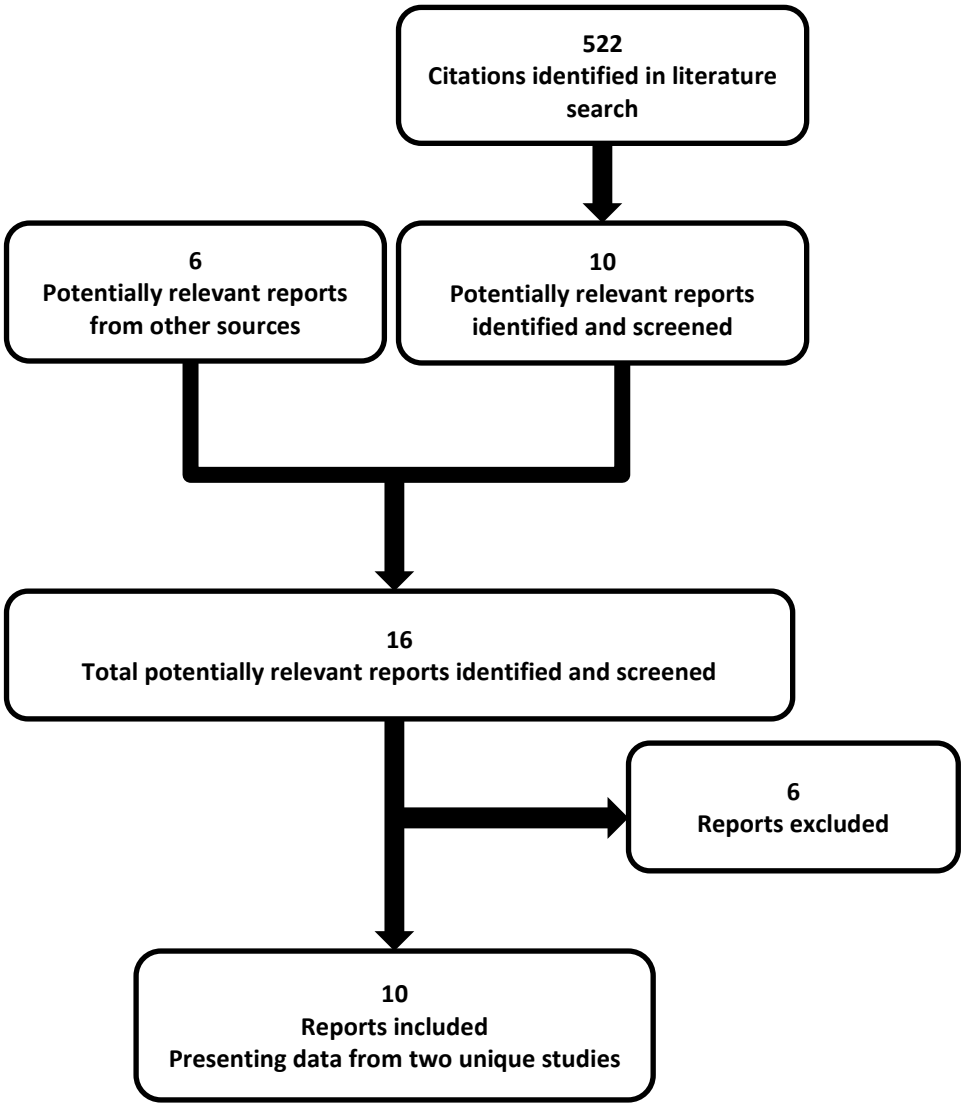


TABLE 4: DETAILS OF INCLUDED STUDIES

		DECIDE (205MS301)	SELECT (205MS201)
DESIGNS & POPULATIONS	**Study design**	Multi-centre DB RCT, phase III, active-controlled, superiority trial	Multi-centre DB RCT, phase II, dose-ranging, 3-group, PL-controlled
	Locations	246 sites in 28 countries including Canada, the US, Western European countries, Eastern European countries, Australia, and Israel	78 sites in 9 European and Asian countries
	Randomized (N)	1,841	621
	Inclusion criteria	Patients 18 to 55 years of age, confirmed diagnosis of RRMS according to McDonald criteria 1 to 4, baseline EDSS score 0 to 5; patients were treatment-naive or treatment experienced	
		≥ 2 clinical relapses within the previous 3 years with ≥ 1 clinical relapse in the 12 months before randomization OR ≥ 1 clinical relapses and ≥ 1 new MRI lesions (Gd-enhancing and/or T2 hyperintense lesion) within the previous 2 years, with ≥ 1 of these events in the 12 months before randomization	≥ 1 relapse within the 12 months before randomization, with a cranial MRI demonstrating lesion(s) consistent with MS OR Evidence of Gd-enhancing lesions of the brain on an MRI performed < 6 weeks before randomization
	Exclusion criteria	Diagnosis of primary-progressive, secondary-progressive or progressive-relapsing MS; MS relapse < 50 days before randomization and/or the patient had not stabilized from a previous relapse before randomization; infection requiring hospitalization or IV antibiotics within 8 weeks before randomization; a history of prior treatment with most other disease-modifying or immunosuppressive therapies for MS if the treatment had occurred within a specified interval varying from 30 days to 1 year. In DECIDE, patients with known intolerance, contraindication to, or a history of non-compliance to IFN beta-1a 30 µg were excluded.	
DRUGS	**Intervention**	150 mg DAC (SC once every 4 weeks for 96 to 144 weeks) + IFN beta-1a matching PL (IM once weekly for 96 to 144 weeks)	DAC 150 mg (SC every 4 weeks for a total of 13 doses) DAC 300 mg (SC every 4 weeks for a total of 13 doses)
	Comparator(s)	IFN beta-1a 30 µg (IM once weekly for 96 to 144 weeks) + DAC matching PL (SC once every 4 weeks for 96 to 144 weeks)	PL (SC every 4 weeks for a total of 13 doses)
DURATION	**Phase**		
	Run-in	4 weeks	3 weeks
	DB	96 to 144 weeks	52 weeks
	Follow-up	24 weeks safety follow-up for patients who did not enter the open-label extension Study 205MS303	• No follow-up period for patients enrolling in the blinded extension Study 205MS202 • 20 weeks safety follow-up for patients who did not enter extension study

		DECIDE (205MS301)	SELECT (205MS201)
OUTCOMES	**Primary end point**	Change in ARR from baseline to study end point	
	Other end points	• MRI: number of new or newly enlarging T2 hyperintense lesions/number of Gd-enhancing lesions/brain atrophy • Disability or disability progression measured by EDSS and MSFC scores • HRQoL measured by MSIS-29, EQ-5D • Health resource utilization • Safety	• MRI: number of new Gd-enhancing lesions/number of new or newly enlarging T2 hyperintense lesions/brain volume • Disability or progression of disability measured by EDSS scores • HRQoL measured by MSIS-29, SF-12, and EQ-5D • Safety
NOTES	**Publications**	Kappos 2015[30] Liu 2017[31] Krueger 2016[32]	Gold 2013[33]

ARR = annualized relapse rate; CSR = Clinical Study Report; DAC = daclizumab; DB = double-blind; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions questionnaire; Gd = gadolinium; HRQoL = health-related quality of life; IFN = interferon; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSIS-29 = Multiple Sclerosis Impact Scale-29; N = number of patients; PL = placebo; RCT = randomized controlled trial; SC = subcutaneous; SF-12 = Short Form (12) Health Survey.
Note: Four additional reports were included (manufacturer's submission,[34] FDA Medical Review,[35] FDA Statistical Review,[36] Health Canada Reviewer's Report[37]).
Source: CSRs for DECIDE[38] and SELECT.[39]

3.2 Included Studies

3.2.1 Description of Studies

Two multi-centre, double-blind (DB) RCTs met the inclusion criteria for this systematic review.[38,39]

DECIDE (Study 205MS301, N = 1,841) was a phase III, DB, double-dummy, active-controlled trial. Its primary objective was to assess the superiority of DAC to IFN beta-1a in preventing MS relapse in patients with RRMS. Eligible participants were randomized in a 1:1 ratio to receive DAC 150 mg SC once every four weeks or IFN beta-1a 30 µg intramuscularly (IM) once weekly for 96 to 144 weeks. Randomization was stratified by site and prior use of IFN beta. Patients were eligible to enrol in the open-label extension study 205MS303 (EXTEND) to continue dosage with DAC if they completed the DECIDE treatment period and met the extension study entry criteria. Patients who did not enrol in EXTEND remained in a 24-week blinded, post-dosage safety follow-up period of DECIDE. All study participants were required to take prophylactic treatment for flu-like symptoms for the first six months of treatment to minimize potential unblinding due to this IFN-related AE. Separate study personnel were assigned to treat patients and to conduct efficacy assessment.

SELECT (Study 205MS201, N = 621) was a phase II study evaluating the efficacy and safety of DAC 150 mg or DAC 300 mg SC once a month compared with placebo SC injection over a duration of 52 weeks.[39] The primary objective of SELECT was to determine whether DAC, when compared with placebo, was effective in reducing the rate of relapses between baseline and week 52. After the screening phase, eligible participants were randomized in a 1:1:1 ratio to one of the DAC doses (150 mg or 300 mg) or placebo. It was unclear whether the randomization was stratified by any factors. The Health Canada–approved dose for DAC is 150 mg, and as such, only data associated with this dose are reported in the present review. Patients who completed the 52-week treatment phase without a major change in their medical status were eligible to enrol in the blinded extension Study 205MS202 (SELECTION) to continue dosage with DAC (APPENDIX 6: SUMMARY OF OTHER STUDIES); therefore, they did not participate in the

follow-up period of the core study. Patients who did not enrol in SELECTION remained in a 20-week blinded, post-dosage safety follow-up period, from week 52 to week 72. All site personnel (treating neurologist, treating nurse or study coordinator, examining neurologist, MRI technician, and pharmacist) were blinded to treatment assignment throughout the entire study, except for the pharmacist who was responsible for preparing and distributing the study treatment. In a medical emergency when knowledge of the patient's treatment assignment could have influenced the patient's clinical care, unblinding was allowed.

In both studies, randomization at baseline was conducted by the Interactive Voice Response System. To further ensure the adequacy of study blinding, an Independent Neurology Evaluation Committee (INEC) including treatment-blinded neurologists was used to determine all relapses in a blinded manner according to the protocol definition. Reading MRI images was centralized and blinded in DECIDE and SELECT.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The eligible study participants were required to have a confirmed diagnosis of RRMS using the 2005 McDonald criteria and recent disease activities.

In DECIDE, participants were required to have had: 1) at least two clinical relapses (defined as neurological signs and/or symptoms documented in the medical record of at least 24 hours duration) within the previous three years with at least one clinical relapse in the 12 months before randomization or; 2) one or more clinical relapses and one or more new MRI lesions within the previous two years with at least one of these events in the 12 months before randomization. Patients in DECIDE who were receiving an approved IFN beta preparation were not required to washout from IFN beta before randomization, but IFN beta treatment must have been discontinued before randomization.

In SELECT, participants had to have experienced: 1) at least one relapse (defined as neurologic signs and/or symptoms documented in the medical record and of at least 24 hours duration) within the 12 months before randomization, with a cranial MRI demonstrating lesion(s) consistent with MS; or 2) showed evidence of gadolinium (Gd)-enhancing lesions of the brain on an MRI performed within six weeks.

In both studies, patients with a history of prior treatment with most other DMTs or immunosuppressive therapies for MS were excluded if the treatment had occurred within a specified interval varying from as long as one year (e.g., natalizumab in DECIDE) to as short as 30 days (e.g., intravenous or oral corticosteroids) before randomization. Treatment-naive patients were also eligible in both studies.

b) Baseline Characteristics

In general, the baseline demographic and disease characteristics in the two studies were well balanced across treatment groups in the intention-to-treat (ITT) population (Table 5). The majority of patients were female (63% to 68%) and the mean age was approximately 35 years to 37 years. The mean number of relapses was one to two in the past one year and two to three in the past three years, per the inclusion criteria.

In DECIDE, 47.1% of the participants had received prior medications for MS, while in SELECT, a lower percentage (18.7%) of previous DMT use was noted. The majority of patients had received IFN beta therapy.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS (INTENTION-TO-TREAT POPULATION)

	SELECT		DECIDE	
	DAC 150 mg (N = 208)	**PL (N = 204)**	**DAC 150 mg (N = 919)**	**IFN beta-1a 30 µg (N = 922)**
Age (years), mean (SD)	35.3 (8.94)	36.6 (9.02)	36.4 (9.36)	36.2 (9.32)
Female, n (%)	140 (67)	128 (63)	625 (68)	627 (68)
Race, n (%)				
White	202 (97)	197 (97)	823 (90)	828 (90)
Asian	6 (3)	7 (3)	27 (3)	28 (3)
Other	0	0	40 (4)	41 (4)
Not reported	–	–	29 (3)	25 (3)
Weight (kg), mean (SD)	68.31 (15.88)	69.99 (14.44)	72.16 (16.61)	70.92 (16.16)
McDonald Criteria, n (%)				
1	165 (79)	156 (76)	784 (85)	776 (84)
2	27 (13)	32 (16)	83 (9)	87 (9)
3	12 (6)	14 (7)	31 (3)	31 (3)
4	4 (2)	2 (< 1)	21 (2)	28 (3)
Baseline EDSS score				
Mean (SD)	2.8 (1.15)	2.7 (1.17)	2.48 (1.21)	2.54 (1.26)
Median (range)	3.0 (0 – 5)	2.5 (0 – 5)	2.00 (0 – 5.5)	2.25 (0 – 6)
Time since onset of symptoms (years), mean (SD)	7.3 (6.3)	7.4 (6.9)	7.0 (6.3)	6.9 (6.3)
Time since diagnosis (years), mean (SD)	4.5 (5.0)	4.1 (5.3)	4.2 (4.97)	4.1 (4.70)
Number of relapses during the previous 3 years, mean (SD)	2.5 (1.3)	2.3 (1.1)	2.7 (1.2)	2.7 (1.3)
Number of relapses during the past 12 months, mean (SD)	1.4 (0.73)	1.3 (0.60)	1.5 (0.7)	1.6 (0.8)
MRI evaluation				
Number of T2 hyperintense lesions, mean (SD)	44.6 (34.71)	39.5 (32.17)	49.2 (35.5)	51.8 (37.4)
Number of Gd-enhancing lesions, mean (SD)	2.1 (3.47)	2.0 (4.48)	2.0 (5.86)	2.3 (5.85)
Normalized brain volume (mL), mean (SD)	1,501.3 (88.24)	1,512.9 (87.62)	1,500.3 (91.10)	1,495.8 (90.70)
Number of patients with prior use of approved RRMS therapy, n (%)	41 (20)	26 (13)	439 (48)	428 (46)
IFN beta-1b	20 (10)	8 (4)	132 (14)	136 (15)
IFN beta-1a	15 (7)	10 (5)	207 (23)	201 (22)
Glatiramer	9 (4)	8 (4)	110 (12)	111 (12)
Natalizumab	2 (< 1)	0	17 (2)	12 (1)
Mitoxantrone	0	1 (< 1)	15 (2)	17 (2)

CSR = Clinical Study Report; DAC = daclizumab; EDSS = Expanded Disability Status Scale; Gd = gadolinium; IFN = interferon; MRI = magnetic resonance imaging; n = number of patients with event; N = number of patients; PL = placebo; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation.
Source: CSRs for DECIDE[38] and SELECT.[39]

3.2.3 Interventions

In DECIDE, patients were equally randomized (1:1) to receive DAC 150 mg plus IFN placebo or IFN beta-1a (Avonex) 30 µg plus DAC placebo. DAC and matching placebo were administered in the clinic, and IFN beta-1a and matching placebo were self-administered at home after the initial dose taken in the clinic. The treatments started at week 0 and ended at week 144 or when the last patient enrolled had completed the week 96 visit, whichever was sooner. All study participants were required to take prophylactic treatment for flu-like symptoms during the first six months of treatment to minimize potential unblinding due to this IFN-related AE. The prophylactic treatment could be acetaminophen or ibuprofen, or other nonsteroidal anti-inflammatory drugs before or 24 hours after each IFN beta-1a (or matching placebo) injection at the recommended dose and frequency per the local labels. Concomitant therapies with medications that had established risks of hepatotoxicity or serious rash were discouraged although they were not prohibited.

In SELECT, patients were equally randomized (1:1:1) to receive DAC at doses of 150 mg or 300 mg every four weeks or placebo. DAC was administered by either the treating neurologist or the treating nurse for 48 weeks. The placebo for this study was supplied as a liquid in matching vials containing excipient materials only. In this study, as long as the patient experienced an INEC-confirmed relapse, concomitant use of IFN beta was allowed starting at month 6 in order to minimize the risks of further MS relapses during the treatment with placebo. Methylprednisolone, given once a day or in divided doses, was also allowed in SELECT.

During treatment in both studies, patients who experienced an acute MS relapse could be managed with intravenous methylprednisone (IVMP) 1,000 mg per day for three to five days, at the discretion of the treating neurologist. IVMP was the only protocol-approved treatment for MS relapse. Symptomatic therapy — such as treatment for spasticity, depression, or fatigue — were not restricted, but were optimized as early as possible during screening.

In both DECIDE and SELECT, concomitant treatment with any of the following was not allowed during the study, unless approved by the Biogen Idec Medical Director or the Advisory Committee, or as otherwise described in the protocol:

- any alternative disease-modifying MS drug treatments, such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to IFN beta or IFN-alpha), with the exception of acute management of a protocol-defined relapse in SELECT
- any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications
- systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IVMP, except for protocol-defined treatment of relapses as described in the preceding; steroids that were administered by non-systemic routes (e.g., topical, inhaled) were allowed.

3.2.4 Outcomes

The outcomes of interest identified in the protocol are described in the following. For a more detailed description of study outcomes, see APPENDIX 5: VALIDITY OF OUTCOME MEASURES.

a) Relapse

For both trials, protocol-defined relapses were defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. The records of all patients who

developed a suspected relapse as determined by the treating neurologist and the examining neurologist were reviewed by INEC. INEC-confirmed relapses (without knowledge of the patient's treatment assignment and without MRI data) were the primary way to define relapse in efficacy analyses.

The change in ARR between baseline and study end point was the primary outcome in both SELECT and DECIDE.

b) Disability Progression or Improvement

EDSS

In both studies, confirmed disability progression was defined as at least a 1.0-point increase on the EDSS from a baseline EDSS greater than or equal to 1.0 sustained for 12 weeks to 24 weeks, or a greater than or equal to 1.5-point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks to 24 weeks.

In DECIDE, the efficacy of DAC in slowing disability progression with 12-week confirmation and disability progression with 24-week confirmation, which were measured with a proportion of patients with confirmed disability progression and change in EDSS score, were exploratory end points.

In SELECT, change in EDSS score from baseline was a tertiary end point and supportive end point, respectively.

c) Health-Related Quality of Life

Multiple Sclerosis Impact Scale-29 (MSIS-29)

The MSIS-29 is a disease-specific self-reported measure that has been developed to examine the physical and psychological impact of MS from the patient's perspective. The MSIS-29 consists of 20 physical items (associated with a physical scale and related physical impact score) and nine psychological items (associated with a psychological scale and related psychological impact score). Each item of the MSIS-29 includes five response options from 1 (not at all) to 5 (extremely). The physical impact score and psychological impact score are generated according to the responses and are converted to a 0 to 100 scale. Higher scores indicate greater impact of the disease on daily function and negative change indicates improvement.[40] Previous study suggests that a change of 7.5 points in MSIS-29 is the minimal clinically important difference (MCID).[41]

Proportion of patients with a greater than or equal to 7.5-point worsening from baseline in the MSIS-29 physical impact score at week 96 was a secondary end point in DECIDE. Change in MSIS-29 physical impact score was a tertiary end point in DECIDE.

Improving QoL as measured by MSIS-29 physical impact score at week 52 was the secondary end point for SELECT.

Multiple Sclerosis Functional Composite (MSFC)

The MSFC includes three objective and quantitative continuous scales that assess leg function/ambulation (with Timed 25-Foot Walk [T25-FW]), arm/hand function (with the 9-Hole Peg Test [9-HPT]) and cognitive function (with the Paced Auditory Serial Addition Test [PASAT] 3 test). Scores on component measures are converted to standard scores (z scores), which are averaged to form a single MSFC score. A positive change in the composite z score indicates improvement, and a negative change indicates worsening. A 20% change in scores on T25-FW trials and 9HPT, and a 0.5 standard deviation

change on PASAT 3 are considered clinically meaningful.[42,43] An MCID for overall MSFC score has not been reported. Change in MSFC score at study end point was an exploratory variable in DECIDE.

EuroQol 5-Dimensions Questionnaire (EQ-5D)
The EQ-5D is a standardized generic health-related quality of life (HRQoL) measure for a wide range of health conditions and treatments developed by the European Quality of Life Group. It consists of two sections. The first of two sections of the EQ-5D consist of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[44,45] The second section is a 20 cm visual analogue scale (EQ VAS) that records the respondent's self-rated health state ranging from 0 to 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Scores fewer than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 100 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for this scale, although not specific for MS patients, have ranged from 0.033 to 0.074.[46] No studies specifically validating EQ-5D in patients with MS were identified.

Change in QoL on EQ-5D was an exploratory end point in DECIDE.

Short Form (12) Health Survey (SF-12)
An SF-12 scale is a self-reported generic HRQoL instrument consisting of 12 items (in eight domains commonly represented in health surveys: physical functioning, role functioning [physical], bodily pain, general health, vitality, social functioning, role functioning [emotional], and mental health) to measure functional health and well-being. The 12 items create two summary scores: the physical component summary and mental component summary (MCS). Higher scores indicate better physical and mental function. No MCID was available for the SF-12 with regard to patients with MS.

Measurement of SF-12 scores was a tertiary end point in SELECT.

d) Fatigue
This outcome was not specifically assessed in either study.

e) MRI Outcomes
Brain Lesions on MRI
In DECIDE, the number of new or newly enlarging T2 hyperintense lesions on brain MRI more than 96 weeks was a secondary end point.

In SELECT, the MRI assessments were conducted at baseline and at weeks 24, 36, and 52. In an MRI-intensive cohort (the first 307 participants in the study), MRI scans were also performed every four weeks between baseline and week 24. The reduction in number of new or newly enlarging T2 hyperintense lesions at week 52 was a secondary end point in this study. The efficacy of DAC in reducing the number of Gd-enhancing lesions at week 52 compared with baseline was an exploratory end point.

In both studies, the MRI results were sent to the MRI central reader centre for review.

Brain Atrophy or Brain Volume on MRI
Brain atrophy was an exploratory end point in both studies.

f) Productivity
This outcome (e.g., ability to attend work or school) was not assessed in either study.

g) Medication Acceptance
This outcome was not assessed in either study.

h) Relapse Requiring Corticosteroids
This outcome was not assessed in either study.

i) Harms
AEs, serious adverse events (SAEs), and withdrawals due to adverse events (WDAEs) data were collected and reported based on accepted or standard definitions for measuring harms in RCTs.

3.2.5 Statistical Analysis

a) Sample Size Calculation
In DECIDE, a sample size of 900 participants per treatment group, or 1,800 participants in total, was estimated for 90% power to detect a 24% reduction in ARR between the IFN beta-1a group and the DAC group based on a negative binomial regression model with a 5% type I error rate, a 21% dropout rate, an average of 2.4 years of follow-up, and an ARR of 0.27 in the IFN beta-1a group.

In SELECT, a sample size of 198 participants per treatment group, or 594 participants in total, was estimated to achieve approximately 90% power to detect a 50% reduction in ARR between a DAC treatment group and placebo, based on a negative binomial distribution, a 10% dropout rate, and a 5% type I error rate.

A rationale for these assumptions was not provided in either study.

b) Statistical Testing
DECIDE
The primary analysis of the ARR was conducted using a negative binomial regression model, adjusted for the baseline relapses rate, baseline EDSS (EDSS ≤ 2.5 versus EDSS > 2.5), baseline age (age ≤ 35 versus age > 35 years), and history of IFN beta-1a use. A Cox proportional hazards model was used for the proportion of relapsing patients, disability progression, and proportion of patients with a greater than or equal to 7.5-point worsening from baseline in the MSIS-29 physical impact score at week 96. A negative binomial regression model was used for the number of new or newly enlarging T2 hyperintense lesions on brain MRI.

In order to control for inflation of type I error due to multiple treatment comparisons for the secondary end points, a sequential closed testing procedure was employed. If the first comparison (number of new or newly enlarging T2 hyperintense lesions more than 96 weeks) was statistically significant (probability [*P*] < 0.05), the second comparison (disability progression) was then tested at the alpha (α) = 0.05 significance level. However, if the first (or any subsequent) comparison was not statistically significant, then all end point(s) of a lower rank were not considered statistically significant. The ranked secondary end points for DECIDE were:

1. number of new or newly enlarging T2 hyperintense lesions on brain MRI more than 96 weeks
2. proportion of patients with three-month confirmed disability progression
3. proportion of patients who were relapse-free at week 144
4. proportion of patients with a greater than or equal to 7.5-point worsening from baseline in the MSIS-29 physical impact score at 96 weeks.

Subgroup analyses were performed for the primary and secondary efficacy outcomes based on patients' demographic and baseline MS characteristics, such as EDSS scores, age, number of relapses in the past 12 months, number of relapses in the past three years, prior IFN beta use, prior immunomodulatory MS treatment excluding steroids, disease activity, or geographic region.

Sensitivity analyses were performed using a different population (i.e., per-protocol [PP] set, all protocol-defined relapses no matter if they were INEC-approved or not, etc.), different modelling assumptions, selection of cut-off date for relapse inclusion, relapses confirmed or not confirmed by the INEC, alternative MS therapies, and protocol violation. Various approaches were employed to handle the missing post-baseline data, such as the last observation carried forward method, imputing missing values using the mean from patients from the same treatment group in the same visit, or using the mean of the non-missing items or estimation with a random-effects model (i.e., missing MSIS-29 item data).

SELECT

The primary analysis of the ARR was conducted using a negative binomial regression model, adjusted for the number of relapses in the one-year interval before study entry, baseline EDSS (EDSS ≤ 2.5 versus EDSS > 2.5), and baseline age (age ≤ 35 versus age > 35 years). These covariates were selected to be consistent with factors found to be important in other controlled MS trials, and they were all pre-specified. For the disability progression end point, the model included a term for baseline EDSS (EDSS ≤ 2.5 versus EDSS > 2.5) and baseline age (age ≤ 35 versus age > 35 years). Other secondary and tertiary analyses included a term for treatment group and the baseline factor (EDSS and age) only. A Cox proportional hazards model was used for the proportion of patients relapsed. A negative binomial regression model and ordinal logistic regression model were used for the number of new or newly enlarging T2 hyperintense lesions and Gd-enhancing lesions on brain MRI. An analysis of covariance (ANCOVA) model was used to evaluate the change in the mean MSIS-29 physical score. Similar to DECIDE, in order to control for type I error rate that might result from multiple comparisons when analyzing the secondary end points, a sequential, closed testing procedure was used. If the first comparison (DAC 300 mg versus placebo) was statistically significant ($P \leq 0.05$), then the second comparison (DAC 150 mg versus placebo) was tested at the $\alpha = 0.05$ significance level. However, if the first comparison was not statistically significant, then the second comparison was not considered statistically significant. Secondary end points were rank prioritized in the following order:

1. the number of new Gd-enhancing lesions on more than five brain MRI scans at weeks 8, 12, 16, 20, and 24 (calculated as the sum of these five MRIs) in a subset of patients (the first 307 patients enrolled in the study)
2. the number of new or newly enlarging T2 hyperintense lesions at week 52
3. the proportion of relapsing patients between baseline and week 52
4. the change in MSIS-29 physical score at week 52 compared with baseline.

If statistical significance was not achieved for an end point, all end points of a lower rank were not considered statistically significant. Tertiary supportive analyses did not include adjustments made for multiple comparisons and end points.

Subgroup analyses were performed for the primary and secondary efficacy outcomes based on patients' demographic and baseline MS characteristics, such as EDSS scores, age, number of relapses in the past 12 months, prior immunomodulatory MS treatment excluding steroids, disease activity, or geographic region. Multiple sensitivity analyses were performed to assess the robustness of the primary analysis, using various models or altering regression model parameters. Various approaches were employed to handle missing data, such as the last observation carried forward method, imputing value using the mean from patients from the same treatment group in the same visit, or using the mean of the non-missing items or estimation with a random-effects model (i.e., missing MSIS-29 item data).

In both studies, the primary analysis of ARR was based on INEC-confirmed relapses, and it included data from all study participants in the study-defined ITT population until either the end of the treatment period, a switch to alternative MS medication, or withdrawal from the study. The unadjusted ARR for each treatment group was calculated as the total number of relapses experienced in the group divided by the total number of days in the study at the end of treatment period visit or at the time of censoring for the group, and the ratio then multiplied by 365.25.

c) Analysis Populations

In DECIDE, the following data sets were defined:
ITT population: included all randomized patients who received at least one dose of any study treatment. Patients were analyzed in the group to which they were randomized.

PP population: Included patients from the ITT population who were adherent with study treatments and who did not permanently discontinue study treatment before week 96.

Safety population: Included all patients who received at least one dose of any study treatment.

In SELECT, the following data sets were defined:
ITT population: Consisted of all randomized patients who received at least one dose of any study medication, excluding 21 patients from Site 903 due to systematic misdosing by the unblinded pharmacist at the site. Patients were analyzed according to the treatment group to which they were randomized.

Efficacy-evaluable population: Included patients in the ITT population with non-missing MRI data from weeks 8, 12, 16, 20, and 24 who did not take prohibited alternative MS medications during the treatment period and who had their baseline MRI scan before their first dose of study treatment. Patients must have had their MRI scans carried out within 14 days of the target study day as indicated on the study activities chart.

Safety population: Included all patients who received at least one dose of study treatment and had at least one post-baseline assessment of the safety parameter being analyzed.

In both studies, all efficacy end points were evaluated in the ITT population. The number of new Gd-enhancing lesions end point was evaluated in both the ITT and efficacy-evaluable populations. The analyses performed on the ITT population are considered the primary analyses, while the analyses in the efficacy-evaluable population are considered supportive. All safety analyses were based on the safety population.

3.3 Patient Disposition

The disposition of patients in SELECT and DECIDE is presented in Table 6.

In DECIDE, approximately 30% of participants did not complete the two- to three-year treatment. In SELECT, approximately 10% of study participants discontinued the treatment before one year. Withdrawal of consent and AEs were the main reasons for treatment discontinuation in the two studies. Patients randomized to DAC 150 mg were more likely to withdraw compared with those in the IFN beta-1a group in DECIDE (14% versus 9%) or placebo group in SELECT (3% versus < 1%).

Major protocol deviations were determined when changes from the protocol had the potential to affect data integrity or patient safety and were categorized into one or more of the following categories: informed consent, eligibility criteria, study treatment administration, prohibited concomitant medication, key study procedures, or other. The incidence and category of major protocol deviations were similar across the treatment groups in DECIDE and SELECT.

TABLE 6: PATIENT DISPOSITION

	DECIDE		SELECT		
	DAC 150 mg	**IFN beta-1a 30 µg**	**DAC 150 mg**	**DAC 300 mg**	**PL**
Screened, N	**1,841**		**739**		
Randomized, N (%)	919 (100)	922 (100)	208 (100)	Not a Health Canada–approved dosage. Data not presented.	204 (100)
Completed treatment, N (%)	653 (71)	644 (70)	189 (91)		186 (91)
Discontinued, N (%)	266 (29)	278 (30)	19 (9)		18 (9)
Withdrawal of consent	68 (7)	91 (10)	9 (4)		11 (5)
Lack of efficacy	31 (3)	68 (7)	–		–
AEs	130 (14)	83 (9)	6 (3)		2 (< 1)
Lost to follow-up	5 (< 1)	10 (1)	1 (< 1)		0
Investigator decision	5 (< 1)	5 (< 1)	0		1 (< 1)
Patient non-compliance	10 (1)	8 (< 1)	0		2 (< 1)
Death	0	3 (< 1)	0		0
Became pregnant	12 (1)	7 (< 1)	–		–
Site closure	5 (< 1)	3 (< 1)	–		–
Other	–	–	3 (1)		2 (< 1)
ITT, N (%)	919 (100)	922 (100)	201 (97)		196 (96)
PP, N (%)	717 (78)	676 (73)	NR		
Efficacy evaluable, N (%)	NR		78 (38)		82 (40)
Safety, N (%)	919 (100)	922 (100)	208 (100)		204 (100)

AE = adverse event; CSR = Clinical Study Report; DAC = daclizumab; IFN = interferon; ITT = intention-to-treat; N = number of patients; PL = placebo; PP = per-protocol.
Source: CSRs for DECIDE[38] and SELECT.[39]

3.4 Exposure to Study Treatments

In DECIDE, the mean time on treatment was 102.04 weeks (standard deviation 108.71) for the DAC group and 100.54 weeks (standard deviation 111.43) for the IFN beta-1a group. Over the course of the study, more than 90% of patients in both treatment groups (98% in the DAC group and 94% in the IFN beta-1a group) received at least 90% of the planned study treatment. Overall compliance was approximately 98% in both treatment groups.

The majority of patients (99% in the DAC group and 98% in the IFN beta-1a group) used at least one concomitant medication. Methylprednisolone was the only medication permitted for the treatment of an MS relapse while on blinded treatment, and was used by fewer patients in the DAC group (32%) than the IFN beta-1a group (43%). The most frequently used protocol-specified medications for the patients to reduce flu-like symptoms in the first 24 weeks of the study (≥ 10% of patients) were primarily paracetamol (76% in both groups), ibuprofen (33% in the DAC group versus 41% in the IFN beta-1a group), and methylprednisolone (32% versus 43%). The most commonly used alternative MS medications were IFN beta-1a (15 patients [2%] in the DAC group versus 14 patients [2%] in the IFN beta-1a group), natalizumab (five patients [< 1%] versus 20 patients [2%]), and glatiramer acetate (eight patients [< 1%] versus seven patients [< 1%]).

The average time on study was 320.5 days (standard deviation 59.35) for DAC 150 mg and 323.0 days (standard deviation 49.02) for placebo in SELECT. The number of patients who received all planned doses (13 doses) was high and similar across treatment groups (84% in the DAC group and 87% in the placebo group).

With respect to the concomitant medications during SELECT, methylprednisolone was the most common medication taken across all treatment groups (DAC 150 mg, 18%; placebo, 35%), as it was the protocol-defined treatment for relapse. Other concomitant corticosteroids used by small numbers of patients included dexamethasone (1%), prednisolone (< 1%), hydrocortisone (< 1%), and prednisone (< 1%). The alternative MS medication used during the study was glatiramer (one patient in the placebo group). IFN beta was taken as a protocol-allowed concomitant medication after month 6 in patients experiencing a relapse, by seven patients in the study (one each in the DAC 150 mg and DAC 300 mg groups and five in the placebo group). Other commonly used concomitant medications included paracetamol (17% overall), omeprazole (11% overall), ibuprofen (10% overall), and potassium (7% overall).

3.5 Critical Appraisal

3.5.1 Internal Validity

DECIDE and SELECT were DB RCTs evaluating the superiority of DAC to an active control (IFN beta-1a) or placebo in patients with RRMS. DECIDE was a phase III trial. IFN beta-1a is an appropriate comparator in the study population. SELECT is a dose-finding, phase II trial evaluating the efficacy and safety of DAC 150 mg and 300 mg SC once every four weeks compared with placebo, which is a limitation of the trial. Treatment allocation was carried out using a computer-generated central randomization schedule. The method of blinding was acceptable where the patients and treating physicians were blinded. The frequency and category of major protocol deviations were similar across the treatment groups in DECIDE and SELECT. The occurrence of MS relapse in both studies was reviewed by blinded examining neurologists in an attempt to minimize bias and ensure consistency in the assessment of EDSS for disability and relapse end points. In addition, relapses determined by a treating neurologist and examining neurologist would be further reviewed by INEC, without knowledge of the patient's treatment allocation and the MRI results. The primary analysis on ARR was based on the INEC-confirmed relapses to ensure the accuracy of the data. On the other hand, MRI results were sent to the MRI central reader centre for review to minimize bias.

Fatigue was identified as an important patient outcome by the patient group; however, it was not assessed using a specific questionnaire in the included studies, although the MSIS-29 does include questions with a physical/mental fatigue component, as well as questions related to life with limitations in social and leisure activities or cutting down the amount of time spent on work or other daily activities.

HRQoL (SF-12, EQ-5D, etc.) and MSIS-29 assessed patient-reported outcomes. HRQoL and MSIS-29 physical impact score were tertiary end points in DECIDE, and MSIS-29 physical impact score was a secondary end point in SELECT. In DECIDE, the validity of the results for patient-reported outcomes may be limited by the approximately 30% of patients discontinuing treatment in each treatment group. A large proportion of data would have been imputed in order to conduct the analyses. While methods for handling missing data were consistent with the recommendations from the instrument developers, there remains a degree of uncertainty as to what conclusions can be drawn from the patient-reported outcomes, such as HRQoL. The rate of missingness was not differential between the treatment groups in DECIDE; therefore, the risk to internal validity due to missing data was considered low to moderate.

In DECIDE, participants who were receiving an approved IFN beta preparation before study entry were not required to washout from IFN beta before randomization. Even though IFN beta treatment was required to be discontinued before randomization, the potential carry-over effect from the previous IFN use may complicate the interpretation of the study findings, such as the comparison of patient-reported outcomes and drug-related AEs between treatment groups. However, any early impact of carry-over effects would likely be mitigated by the relatively longer duration of DECIDE.

The discontinuation rates between treatment groups were similar in DECIDE and SELECT; however, patients randomized to DAC 150 mg were more likely to withdraw because of AEs due to the treatment, compared with those in the IFN beta-1a group in DECIDE (14% versus 9%) or placebo group in SELECT (3% versus < 1%). The uneven discontinuation of treatment due to lack of efficacy (3% versus 7%) and AEs (14% versus 9%) between DAC and IFN beta-1a would have made the final assessment of benefit-risk be more favourable to DAC. The dropout rates were higher in DECIDE, which had a two– to three-year treatment duration. The clinical expert consulted for this review considered a 30% discontinuation rate consistent with other MS trials.

A modified ITT population used in DECIDE and SELECT, in which patients received at least one dose of any study medication, formed the ITT population. Although this was not a true ITT population, since the number of patients in the modified ITT population was the same (in DECIDE) or similar (in SELECT) to the number of randomized patients, it is unlikely that it would significantly affect the study results. Sensitivity analyses were performed to explore the impact of various covariates and assess the robustness of the primary analysis. The results of sensitivity analyses were consistent with those from the primary analyses. Subgroup analyses based on patients' baseline demographic and disease characteristics were also performed.

A closed testing procedure was used for the secondary outcomes to control for multiple comparisons, but no control for multiple comparisons was employed in statistical testing of tertiary outcomes. Some of the tertiary outcomes in the two studies, such as three-month or six-month confirmed disability progression, were deemed important for patients with MS by the clinical expert involved in the review and the patient group who provided input to this review. In addition, patient-reported outcomes such as HRQoL were tertiary end points in the two studies, and were thus not considered in the list. Thus, all statistically significant findings for tertiary outcomes are subject to multiplicity and should be interpreted with caution. Moreover, it is unclear how the secondary end points were ranked; a clear rationale for the decision was not provided.

The incomplete reporting of results in the two studies (e.g., between-group differences in change in EDSS scores from baseline or change in MSIS-29 physical impact score from baseline) also limits the ability to interpret the clinical significance of the efficacy results.

3.5.2 External Validity

The included studies were multi-centre trials enrolling patients from different countries; however, only a small percentage of patients (approximately 13%: 20 patients [1%] from Canada, 216 patients [12%] from the US in DECIDE; none in SELECT) were recruited from North America. Also, certain inclusion and exclusion criteria were restrictive: for example, patients in the included studies were required to have a baseline EDSS score no greater than five. Nonetheless, following discussion with the clinical expert involved in the review based on patients' baseline demographic characteristics and disease characteristics, the study population is considered to likely reflect a typical Canadian RRMS population that would usually be seen in clinical setting. The choice of IFN beta and the dosage studied in DECIDE was considered to be appropriate and applicable to clinical practice. In DECIDE, only 46% to 48% were treatment-experienced with majority on IFN beta-1a or 1b. This largely restricted the applicability of these two trials' findings to the indicated population, adult patients with active RRMS who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of MS.

The active-controlled study DECIDE assessed the effects of DAC relative to IFN beta-1a during a two– to three-year period; therefore, it is possible to explore the comparative longer-term efficacy and safety of the study drug in the patient population. The duration of DECIDE was similar to trials of other biologics for the treatment of RRMS.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in the following (Section 2.2, Table 3). See Table 7 for detailed efficacy data.

3.6.1 Relapse

a) Relapse Rate

In DECIDE, a negative binomial regression model was used and baseline relapse rate, history of prior IFN beta-1a use, baseline EDSS score, and age were adjusted for. A total of 260 patients (28%) in the DAC group had INEC-confirmed relapses, compared with 392 patients (43%) in the IFN beta-1a group at the end of the study at weeks 96 to 144. The adjusted ARRs were 0.216 (95% confidence interval, 0.191 to 0.244) in the DAC 150 mg group compared with 0.393 (95% confidence interval, 0.353 to 0.438) in the IFN beta-1a group. The adjusted ARR ratio (DAC/IFN beta-1a) was 0.550 (95% confidence interval, 0.469 to 0.645), indicating that DAC reduced the ARR by 45% (95% confidence interval, 35% to 53%) compared with IFN beta-1a, $P < 0.0001$. This difference is likely to be clinically significant. The results of sensitivity analyses (based on modelling assumptions, selection of cut-off date for relapse inclusion, INEC confirmation, alternative MS therapies, and protocol violations) were consistent with the primary analysis.

In SELECT, a total of 38 patients (19%) in the DAC group had INEC-confirmed relapses, compared with 69 patients (35%) in the placebo group at the end of the study at week 52. The adjusted ARR in the DAC 150 mg group was 0.211 (95% confidence interval. 0.155 to 0.287) compared with 0.458 (95% confidence interval, 0.370 to 0.566) in the placebo group. The adjusted ARR ratio (DAC/IFN beta-1a) was 0.461 (95% confidence interval, 0.318 to 0.668), indicating that DAC statistically significantly reduced the ARR by 54% (95% confidence interval, 33% to 68%; $P < 0.0001$) compared with placebo. This difference is likely to be clinically significant. The results of sensitivity analyses (a range of factors were considered including modelling assumptions, use of concomitant therapies that can affect ARR, and the exclusion of patients from one site from the ITT population) were similar to that from the primary analysis.

b) Relapse-Free Rate

In DECIDE, 72% of the study participants in the DAC group were relapse-free at weeks 96 144, compared with 57% in the IFN beta-1a group. The hazard ratio (derived from a Cox proportional hazards model; baseline relapse rate, history of prior IFN beta use, baseline EDSS, and baseline age were adjusted for) for DAC/IFN beta-1a was 0.59 (95% confidence interval, 0.50 to 0.69), indicating that the risk of relapse was reduced by 41% in the DAC 150 mg group ($P < 0.0001$) compared with IFN beta-1a.

In SELECT, a Cox proportional hazards model adjusting for the number of relapses in the one-year interval before study entry, baseline EDSS, and baseline age was used to analyze the relapse rates. At week 52, 81% of the study participants in the DAC group remained relapse-free, compared with 65% in the placebo group. The hazard ratio for DAC/placebo for the risk of relapse was 0.45 (95% confidence interval, 0.30 to 0.67), indicating that the risk of relapse was reduced by 55% in the DAC 150 mg group ($P < 0.0001$) compared with placebo.

3.6.2 Disability Progression or Improvement

a) Three-Month Confirmed Disability Progression

In DECIDE at week 96, the proportion of patients with three-month confirmed disability progression was 12.0% in the DAC 150 mg group and 14.3% in the IFN beta-1a group. At week 144, it was 16.2% in the DAC 150 mg group and 20.3% in the IFN beta-1a group. The hazard ratio for DAC/IFN beta-1a was 0.84 (95% confidence interval, 0.66 to 1.07; $P = 0.1575$) at week 144.

In SELECT, the proportion of patients with three-month confirmed disability progression was 5.9% in the DAC 150 mg group and 13.3% in the placebo group, and the hazard ratio for DAC/placebo for disability progression was 0.43 (95% confidence interval, 0.21 to 0.88; $P = 0.0211$). This result indicated that the risk of disability progression was reduced by 57% in the DAC 150 mg group compared with placebo.

Six-Month Confirmed Disability Progression

In DECIDE at week 96, the proportion of patients with six-month confirmed disability progression was 9.2% in the DAC 150 mg group and 12.1% in the IFN beta-1a group; at week 144, it was 12.7% in the DAC 150 mg group and 18.3% in the IFN beta-1a group. The hazard ratio for DAC/IFN beta-1a was 0.73 (95% confidence interval, 0.55 to 0.98; $P = 0.0332$) at week 144, indicating that the risk of six-month disability progression was reduced by 27% in the DAC 150 mg group compared with IFN beta-1a.

In SELECT, the proportion of patients with six-month confirmed disability progression was 2.6% in the DAC 150 mg group and 11.1% in the placebo group, and the hazard ratio for DAC/placebo was 0.24 (95% confidence interval, 0.09 to 0.63; $P = 0.0037$). This result indicated that the risk of disability progression was reduced by 76% in the DAC 150 mg group compared with placebo.

Change in EDSS Scores

In DECIDE, the mean (SD [standard deviation]) change in EDSS score from baseline to week 96 was –0.02 (0.698) in the DAC 150 mg group and –0.01 (0.783) in the placebo group; $P = 0.3742$. The mean (SD) change in EDSS score from baseline to week 144 was –0.03 (0.855) in the DAC 150 mg group and –0.03 (0.922) in the placebo group. *P* value was not reported for between-group comparison at week 144.

In SELECT, the mean (SD) change in EDSS score from baseline to week 52 was –0.08 (0.518) in the DAC 150 mg group and 0.09 (0.710) in the placebo group; $P = 0.0102$.

3.6.3 Health-Related Quality of Life

a) MSIS-29 Physical Impact Score

In DECIDE at weeks 96 to 144, statistically significant difference in MSIS-29 physical impact score was observed between DAC and IFN beta-1a, –2.09 (95% confidence interval, –3.32 to –0.86), *P* = 0.0008. At 96 weeks, 171 patients (19%) in the DAC group had a greater than or equal to 7.5-point worsening from baseline compared with 213 patients (23%) in the IFN beta-1a group. The odds ratio (DAC/IFN beta-1a) was 0.76 (95% confidence interval, 0.60 to 0.95; *P* =0.0176), indicating that the risk of a clinically meaningful worsening on the patient-reported physical impact of MS was reduced by 24% in the DAC group compared with the IFN beta-1a group.

In SELECT, the difference in MSIS-29 physical impact score between DAC 150 mg and placebo at week 52 was –4.27 (95% confidence interval, –6.76 to –1.78), *P* = 0.0008. However, the difference for DAC 150 mg versus placebo was not considered statistically significant in accordance with the sequential closed testing procedure because a higher order comparison did not achieve statistical significance.

b) MSFC z Score

In DECIDE, the mean (25^{th}, 75^{th} percentile) change from baseline to week 96 in the MSFC z score was 0.091 (–0.096, 0.287) in the DAC 150 mg group and 0.055 (–0.136, 0.240) in the IFN beta-1a group (*P* = 0.0007). The between-group difference for the MSFC z score was not reported. MSFC was not assessed in Study SELECT.

c) SF-12

SF-12 was not assessed in DECIDE.

In SELECT, the mean (SD) change from baseline to week 52 in the SF-12 physical component summary score was 1.2 (7.32) in the DAC 150 mg group and –0.4 (7.03) in the placebo group (*P* = 0.0116). The mean (SD) change in the SF-12 MCS score from baseline to week 52 was 0.7 (9.58) in the DAC 150 mg group and –1.4 (9.24) in the placebo group (*P* = 0.0118). The between-group mean differences for the physical component summary score or mental component summary score were not reported.

d) EQ-5D

In DECIDE, the mean (SD) change in the patient's EQ-5D summary health index from baseline to week 96 was 0.028 (0.176) in the DAC 150 mg group and 0.004 (0.194) in the IFN beta-1a group (*P* = 0.0048). The mean (SD) change in the patient's EQ-5D global impression of well-being on the VAS from baseline to week 96 was 2.69 (18.12) in the DAC 150 mg group and 0.33 (18.00) in the IFN beta-1a group (*P* = 0.0006). The between-group mean differences for the summary health index or VAS scores were not reported.

In SELECT, the mean (SD) change in the patient's EQ-5D summary health index from baseline to week 52 was 0.01 (0.178) in the DAC 150 mg group and –0.04 (0.195) in the placebo group (*P* = 0.0091). The mean (SD) change in the patient's EQ-5D global impression of well-being on VAS from baseline to week 52 was 2.9 (13.26) in the DAC 150 mg group and –1.8 (13.22) in the placebo group (*P* < 0.0001). The between-group mean differences for the summary health index or VAS score were not reported.

3.6.4 Fatigue

Not reported in SELECT or DECIDE.

3.6.5 Brain Lesions on MRI

In DECIDE, the adjusted mean (95% confidence interval) number of new or newly enlarging T2 lesions at week 96 was 4.31 (95% confidence interval, 3.85 to 4.81) in the DAC group and 9.44 (95% confidence interval, 8.46 to 10.54) in the IFN beta-1a group. Treatment with DAC 150 mg was associated with a reduction in the number of new or newly enlarging T2 lesions at week 96 by 54%, compared with IFN beta-1a ($P < 0.0001$). At week 96, the mean (SD) number of new Gd-enhancing lesions was 0.4 (1.41) in the DAC 150 mg group and 1.0 (2.82) in the IFN beta-1a group. Treatment with DAC significantly reduced the risk of having greater Gd-enhancing lesion activity by 75% (95% confidence interval, 68% to 80%) in the DAC 150 mg relative to IFN beta-1a ($P < 0.0001$).

In SELECT, the adjusted mean (95% confidence interval) number of new or newly enlarging T2 lesions at week 52 was 2.42 (95% confidence interval, 1.96 to 2.99) in the DAC group and 8.13 (95% confidence interval, 6.65 to 9.94) in the placebo group. Treatment with DAC 150 mg was associated with a reduction in the number of new or newly enlarging T2 lesions at week 52 by 70%, compared with placebo ($P < 0.0001$). At week 52, the mean (SD) number of new Gd-enhancing lesions was 0.3 (0.86) in the DAC 150 mg group and 1.4 (2.29) in the placebo group. Treatment with DAC significantly reduced the risk of having greater Gd-enhancing lesion activity by 85% (95% confidence interval, 75% to 91%) in the DAC 150 mg relative to placebo ($P < 0.0001$).

3.6.6 Brain Atrophy or Brain Volume on MRI

In DECIDE, the mean (SD) values for percentage change in brain volume from week 24 to week 96 were –0.52% (0.40) in the DAC 150 mg group and –0.56% (0.43) in the IFN beta-1a group ($P < 0.0001$).

In SELECT, analysis of this end point did not demonstrate statistically significant differences between the DAC 150 mg group and the placebo group over the 52-week treatment period. The mean (SD) values for percentage change in brain volume from baseline to week 52 were –0.79% (0.832) in the DAC 150 mg group and –0.74% (0.904) in the placebo group ($P = 0.3263$).

3.6.7 Productivity (Ability to Attend Work or School)

Not assessed in either study.

3.6.8 Medication Acceptance

Not assessed in either study.

3.6.9 Relapse Requiring Corticosteroids

Not assessed in either study.

TABLE 7: KEY EFFICACY OUTCOMES AT STUDY END (WEEK 52 FOR SELECT AND WEEKS 96 AND 144 FOR DECIDE) — INTENTION-TO-TREAT POPULATION

	DECIDE		SELECT	
	DAC 150 mg (N = 919)	**IFN beta-1a 30 µg (N = 922)**	**DAC 150 mg (N = 201)**	**PL (N = 196)**
Relapse Assessment				
Adjusted annualized relapse rate[a]				
ARR (95% CI)	0.216 (0.191 to 0.244)	0.393 (0.353 to 0.438)	0.211 (0.155 to 0.287)	0.458 (0.370 to 0.566)
Rate ratio (95% CI)	0.550 (0.469 to 0.645)		0.461 (0.318 to 0.668)	
P value	< 0.0001[b]		< 0.0001[c]	
Number of patients experiencing relapses, n (%)				
0 ≥ 1	659 (72) 260 (28)	530 (57) 392 (43)	163 (81) 38 (19)	127 (65) 69 (35)
HR for risk of relapse (95% CI)	0.59 (0.50 to 0.69)		0.45 (0.30 to 0.67)[d]	
P value	< 0.0001[b]		< 0.0001[c]	
Disability Assessment				
3-month confirmed disability progression[e] (measured by increase in EDSS)				
Number of patients progressed at week 12, n (%)	121 (13)	140 (15)	11 (5)	25 (13)
Estimated % of patients with progression	12.0 at week 96 16.2 at week 144	14.3 at week 96 20.3 at week 144	5.9 (at week 52)	13.3 (at week 52)
HR (95% CI)	0.84 (0.66 to 1.07)		0.43 (0.21 to 0.88)	
P value	0.1575		0.0211[c]	
6-month confirmed disability progression[e] (measured by increase in EDSS)				
Number of patients progressed at week 24, n (%)	80 (9)	99 (11)	5 (2)	21 (11)
Estimated % of patients with progression	9.2 at week 96 12.7 at week 144	12.1 at week 96 18.3 at week 144	2.6 at week 52	11.1 at week 52
HR (95% CI)	0.73 (0.55 to 0.98)		0.24 (0.09 to 0.63)	
P value	0.0332		0.0037	
EDSS scores[f]				
Change from baseline, mean (SD)	–0.02 (0.698) at week 96; –0.03 (0.855) at week 144	–0.01 (0.783) at week 96; –0.03 (0.922) at week 144	–0.08 (0.518)	0.09 (0.710)
Between-group difference (95% CI)	NR		NR	
P value	0.3742[b] at week 96; *P* value after week 96 not reported		0.0102[c]	
HRQoL				
MSIS-29 physical impact score[g]				
Change from baseline, mean (SD)	–0.84 (14.16)	1.15 (14.06)	–1.0 (11.80)	3.0 (13.52)
Between-group difference, mean (95% CI)	–2.09 (–3.32 to –0.86)		–4.27 (-6.76 to –1.78)	
P value	0.0008[b]		0.0008[c]	
Proportion of patients with a ≥ 7.5-point worsening in MSIS-29 physical impact score				
n (%)	171 (19)	213 (23)	Post-hoc analysis was performed	

	DECIDE		SELECT	
	DAC 150 mg (N = 919)	**IFN beta-1a 30 µg (N = 922)**	**DAC 150 mg (N = 201)**	**PL (N = 196)**
Odds ratio (DAC/IFN beta-1a) (95% CI)	0.76 (0.60 to 0.95)		for this outcome	
P value	0.0176			
SF-12 physical component score				
Change from baseline, mean (SD)	NR		1.2 (7.32)	–0.4 (7.03)
Between-group difference, mean (95% CI)			NR	
P value			0.0116	
SF-12 mental component score				
Change from baseline, mean (SD)	NR		0.7 (9.58)	–1.4 (9.24)
Between-group difference, mean (95% CI)			NR	
P value			0.0118	
EQ-5D				
Change in VAS score from baseline (SD)	2.69 (18.12)	0.33 (18.00)	2.9 (13.26)	–1.8 (13.22)
P value	0.0006[b]		< 0.0001[c]	
Change in summary health index from baseline (SD)	0.028 (0.1763)	0.004 (0.1942)	0.01 (0.178)	–0.04 (0.195)
P value	0.0048[b]		0.0091[c]	
MSFC z score				
Change from baseline, median (25th, 75th percentile)	0.091 (–0.096 to 0.287)	0.055 (–0.136 to 0.240)	NR	
Between-group difference, mean (95% CI)	NR			
P value	0.0007[b]			
MRI results				
Number of new or newly enlarging T2 hyperintense lesions[h]				
Adjusted mean at study end point (95% CI)	Week 96: 4.31 (3.85 to 4.81) N = 864	Week 96: 9.44 (8.46 to 10.54) N = 841	Week 52: 2.42 (1.96 to 2.99) N = 199	Week 52: 8.13 (6.65 to 9.94) N = 195
% reduction between groups (95% CI)	54.4 (46.9 to 60.8)		70.23 (59.94 to 77.88)	
P value	< 0.0001[b]		< 0.0001[c]	
Number of new Gd-enhancing lesions				
Mean at study end point (SD)	Week 96: 0.4 (1.41) N = 900	Week 96: 1.0 (2.82) N = 909	Week 52: 0.3 (0.86) N = 199	Week 52: 1.4 (2.29) N = 195
OR (95% CI)	0.25 (0.20 to 0.32)		0.15 (0.09 to 0.25)	
P value	< 0.0001[b]		< 0.0001[c]	
Whole-brain volume[i]				
% change, mean (SD)	Change from week 24 to week 96: –0.518 (0.3958) N = 899	Change from week 24 to week 96: –0.556 (0.4267) N = 907	Change from baseline to week 52: -0.79 (0.832)	Change from baseline to week 52: –0.74 (0.904)

	DECIDE		SELECT	
	DAC 150 mg (N = 919)	**IFN beta-1a 30 µg (N = 922)**	**DAC 150 mg (N = 201)**	**PL (N = 196)**
			N = 198	N = 194
P value	< 0.0001[b]		0.3263[c]	

ANCOVA = analysis of covariance; ARR = annualized relapse rate; CI = confidence interval; CSR = Clinical Study Report; DAC = daclizumab; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions questionnaire; Gd = gadolinium; HR = hazard ratio; HRQoL = health-related quality of life; IFN = interferon; MRI = magnetic resonance imaging; MSFC = Multiple Sclerosis Functional Composite; MSIS-29 = Multiple Sclerosis Impact Scale-29; n = number of patients with event; N = number of patients; NR = not reported; OR = odds ratio; *P* = probability; PL = placebo; SD = standard deviation; SF-12 = Short Form (12) Health Survey; VAS = visual analogue scale.

[a] In both SELECT and DECIDE, treatment-group differences were compared using a negative binomial regression model adjusted for the number of relapses in the one-year (in SELECT) or three-year interval (DECIDE) before study entry, baseline EDSS, and age. History of prior IFN beta-1a use was also adjusted in DECIDE.

[b] Comparison versus IFN beta 1a.

[c] Comparison versus placebo.

[d] Estimated from the Cox proportional hazards model. Covariates included were number of relapses in the one year before study entry, baseline EDSS, and age.

[e] The difference between treatment groups in confirmed disability progression was assessed using a Cox proportional hazards model, adjusted for baseline EDSS and baseline age. History of prior IFN beta-1a use was also adjusted in DECIDE.

[f] Treatment-group differences in EDSS change from baseline to week 52 were analyzed using ANCOVA, adjusted for baseline EDSS score.

[g] The treatment effect on the change from baseline to week 52 in the MSIS-29 physical score was analyzed using an ANCOVA model adjusting for the baseline score. History of prior IFN beta use and baseline age were also adjusted in DECIDE.

[h] Treatment effects on the number of new T2 lesions at week 52 were analyzed using a negative binomial regression model adjusting for the baseline number of T2 lesions.

[i] The percentage change in whole-brain volume between baseline and week 52 was estimated using the SIENNA method, and group differences were tested using an ANCOVA model adjusting for baseline brain volume.

Source: CSRs for DECIDE[38] and SELECT.[39]

3.7 Harms

Only those harms identified in the review protocol are reported in the following (see 2.2.1, Protocol).

3.7.1 Adverse Events

In DECIDE, the proportion of patients who experienced a treatment-emergent AE was similar between DAC 150 mg (91%) and placebo (91%) at study end point (weeks 96 to 144). The majority of patients with AEs had events that were mild to moderate in severity. The most common AEs in both treatment groups were MS relapse (33% versus 47% for IFN), nasopharyngitis (25% versus 21% for IFN), headache (17% versus 19% for IFN), upper respiratory tract infection (16% versus 13% for IFN), pyrexia (11% versus 15%), urinary tract infection (10% versus 11%), injection-site pain (10% versus 11% for IFN), and influenza-like illness (10% versus 38% for IFN). In general, a higher frequency of patients treated with DAC experienced infection-related AEs, while a higher proportion of patients treated with IFN beta-1a reported MS relapse and influenza-like illness.

In SELECT, the proportion of patients who experienced a treatment-emergent AE was similar between DAC 150 mg (73%) and placebo (79%) at week 52. The majority of patients with AEs had events that were mild to moderate in severity. The most commonly reported AEs with DAC included: MS relapse (23% versus 38% for placebo), nasopharyngitis (14% versus 15% for placebo), headache (10% versus 10% for placebo), and upper respiratory tract infection (9% versus 7% for placebo).

3.7.2 Serious Adverse Events

In the two studies, the occurrence of SAEs was not common when MS relapses were excluded.

In DECIDE, there was a higher frequency of SAEs in the DAC group (24%) compared with the IFN beta-1a group (21%) at the end of the study (weeks 96 to 144). Excluding MS relapse, SAEs were reported in 15% of the DAC group and in 10% of the IFN beta-1a group. Patients in the DAC group were more likely to report an SAE of infections, blood/lymphatic system disorder, and skin disorder. The numbers of patients experiencing a psychiatric disorder were similar between DAC and IFN beta-1a. The frequency of serious events of depression (three patients with DAC versus two patients with IFN beta-1a) and suicide-related SAEs (suicidal ideation: one patient versus one patient; suicidal attempt: zero versus two patients; completed suicide: zero versus one patient; depression suicidal: one patient versus zero) were similar between DAC and IFN beta-1a.

In SELECT, the number of patients experiencing an SAE was lower with DAC 150 mg (15%) compared with placebo (26%) at week 52. After excluding MS relapse, the frequency of SAE was 7% in the DAC 150 mg group and 6% in the placebo group.

3.7.3 Withdrawal Due to Adverse Events

In DECIDE, more patients in the DAC group (15%) discontinued the treatment due to an AE compared with the IFN beta-1a group (12%) over 96 to 144 weeks. After excluding MS relapse, the proportion of patients who discontinued the treatment due to an AE was still higher in the DAC group (14%) compared with the IFN beta-1a group (9%). Patients in the DAC group were more likely to discontinue the treatment due to skin disorders (5%) or abnormal "investigations" (5%, i.e., increased hepatic enzyme), while patients in the IFN beta-1a group were more likely to withdraw the treatment due to nervous system disorders (3%), or general disorders/administration site conditions (1%).

In SELECT, a total of 3% of patients in the DAC 150 mg group discontinued study treatment due to an AE compared with less than 1% of patients in the placebo group over 52 weeks. Patients in the DAC group were more likely to discontinue the treatment due to skin disorders or abnormal "investigations" (increased hepatic enzyme) compared with the placebo group.

3.7.4 Mortality

In DECIDE, five deaths were reported: one in the DAC group and four in the IFN beta-1a group. In the DAC group, one patient with an acute exacerbation of MS that involved the brainstem and loss of the ability to swallow died from aspiration pneumonia and septicemia after the patient withdrew from the study and four months after the patient's last dose of DAC. In the IFN beta-1a group, the four deaths were secondary to acute myocardial infarction, peritonitis, completed suicide, and metastatic cancer of the pancreas. None of the deaths were considered by the investigators to be related to study treatment. In SELECT, after completion of the treatment period, one patient treated with DAC 150 mg who was recovering from a serious rash died due to ischemic colitis and psoas abscess. [redacted]

3.7.5 Notable Harms

In DECIDE, more patients treated with DAC 150 mg experienced elevated liver enzymes compared with those treated with IFN beta-1a (alanine transaminase [ALT] ≥ 3 times upper limit of normal [ULN]: 9% versus 8%; ALT > 5 times ULN: 6% versus 3%; aspartate transaminase [AST] ≥ 3 times ULN: 7% versus 4%; AST > 5 times ULN: 4% versus 2%). The proportion of patients who experienced depression was 8% in the DAC group compared with 6% in the IFN beta-1a group. Treatment with DAC 150 mg was associated with higher frequency of serious infection and more cases of lymphadenopathy, compared with IFN beta-1a.

In SELECT, the frequency of increased liver enzymes was higher in the DAC group compared with placebo group (ALT > 3 to 5 times ULN: 3% versus 3%; ALT > 5 to 20 times ULN: 3% versus < 1%; AST ≥ 3 to 5 times ULN: < 1% versus 0; AST > 5 to 20 times ULN: 2% versus < 1%). The proportion of patients who experienced depression was 5% in the DAC group compared with less than 1% in the placebo group.

Progressive multifocal leukoencephalopathy (PML) was not observed in either study.

TABLE 8: HARMS; SAFETY SET

	DECIDE		SELECT	
	DAC 150 mg (N = 919)	**IFN beta-1a 30 µg (N = 922)**	**DAC 150 mg (N = 208)**	**PL (N = 204)**
Overall AEs, n (%)				
Patients with > 0 AEs	838 (91)	842 (91)	151 (73)	161 (79)
Common AEs (≥ 10%)				
MS relapse	299 (33)	432 (47)	47 (23)	77 (38)
Nasopharyngitis	226 (25)	197 (21)	30 (14)	31 (15)
Headache	159 (17)	175 (19)	20 (10)	21 (10)
Upper respiratory tract infection	149 (16)	124 (13)	18 (9)	14 (7)
Pyrexia	104 (11)	134 (15)	7 (3)	2 (< 1)
Injection-site pain	96 (10)	102 (11)	–	–
Urinary tract infection	96 (10)	98 (11)	9 (4)	9 (4)
Influenza-like illness	88 (10)	346 (38)	6 (3)	6 (3)
SAEs, n (%)				
Patients with > 0 SAEs	221 (24)	194 (21)	32 (15)	53 (26)
Patients with > 0 SAEs excluding MS relapse	142 (15)	88 (10)	15 (7)	12 (6)
Most common SAEs				
Infections/infestations	40 (4)	15 (2)	6 (3)	0
Neoplasms	14 (2)	11 (1)	1 (< 1)	1 (< 1)
Blood/lymphatic system disorders	12 (1)	2 (< 1)	0	1 (< 1)
Psychiatric disorders	6 (< 1)	8 (< 1)	1 (< 1)	0
Nervous system disorders	109 (12)	131 (14)	20 (10)	45 (22)
Gastrointestinal disorders	11 (1)	6 (< 1)	3 (1)	1 (< 1)
Hepatobiliary disorders	7 (< 1)	4 (< 1)	2 (< 1)	1 (< 1)
Skin/subcutaneous tissue disorders	14 (2)	1 (< 1)	2 (< 1)	0
Injury, poisoning, procedural complications	9 (< 1)	8 (< 1)	1 (< 1)	2 (< 1)
WDAEs, n (%)				
WDAEs	142 (15)	112 (12)	6 (3)	2 (< 1)
WDAEs (excluding MS relapse)	131 (14)	84 (9)	NR	
Reasons				
Infections/infestations	5 (< 1)	3 (< 1)	1 (< 1)	0
Neoplasms	4 (< 1)	8 (< 1)	0	1 (< 1)
Blood/lymphatic system disorders	8 (< 1)	3 (< 1)	NR	
Psychiatric disorders	1 (< 1)	6 (< 1)	NR	
Nervous system disorders	14 (2)	32 (3)	0	0
Skin/subcutaneous tissue disorders	43 (5)	7 (< 1)	3 (1)	0
Investigations	45 (5)	35 (4)	3 (1)	1 (< 1)
Gastrointestinal disorders	3 (< 1)	1 (< 1)	NR	
Hepatobiliary disorders	7 (< 1)	3 (< 1)	0	0

	DECIDE		SELECT	
	DAC 150 mg (N = 919)	**IFN beta-1a 30 µg (N = 922)**	**DAC 150 mg (N = 208)**	**PL (N = 204)**
Skin/subcutaneous tissue disorders	43 (5)	7 (< 1)	3 (1)	0
General disorders and administration safe	7 (< 1)	13 (1)	NR	
Deaths				
Number of deaths, n (%)	1 (0.1)	4 (0.4)	1 (0.5)	0
Reasons	Aspiration pneumonia and septicemia following an acute MS exacerbation	Acute MI, peritonitis, completed suicide, and metastatic cancer of the pancreas	Ischemic colitis and psoas abscess	
Notable harms				
Depression	75 (8)	57 (6)	10 (5)	3 (1)
ALT increased	≥ 3 ULN: 87 (9)	≥ 3 ULN: 76 (8)	> 3-5 ULN: 7 (3)	> 3-5 ULN: 6 (3)
ALT increased	> 5 ULN: 53 (6)	> 5 ULN: 30 (3)	> 5-20 ULN: 6 (3)	> 5-20 ULN: 1 (< 1)
AST increased	≥ 3 ULN: 63 (7)	≥ 3 ULN: 34 (4)	> 3-5 ULN: 1 (< 1)	> 3-5 ULN: 0
AST increased	> 5 ULN: 37 (4)	> 5 ULN: 14 (2)	> 5-20 ULN: 5 (2)	> 5-20 ULN: 1 (< 1)
Serious infections	40 (4)	15 (2)	6 (3)	0
Lymphadenopathy	47 (5)	7 (< 1)	0	0

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; CSR = Clinical Study Report; DAC = daclizumab; IFN = interferon; MI = myocardial infarction; MS = multiple sclerosis; NR = not reported; PL = placebo; SAE = serious adverse event; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.
Source: CSRs for DECIDE[38] and SELECT.[39]

4. DISCUSSION

4.1 Summary of Available Evidence

Two manufacturer-sponsored, multi-centre, randomized, DB studies, DECIDE (N = 1,841) and SELECT (N = 621) were included in this review. DECIDE enrolled patients from North America, including Canada (1%). The studies evaluated the efficacy and safety of DAC 150 mg once every four weeks compared with IFN beta-1a (Avonex) 30 µg once weekly or placebo in adult patients with RRMS, with or without prior DMTs for MS. The primary outcome in both trials was the ARR. The treatment duration was 96 weeks to 144 weeks in DECIDE and 52 weeks in SELECT. At the end of the treatment period, patients could enter the extension studies of DECIDE and SELECT, where the efficacy and safety were followed up to 6.5 years.

Both studies were generally of adequate design to ensure internal validity. One limitation of the available evidence is the uncertainty in the clinical significance for patient-reported outcomes. There are limited head-to-head trial data comparing DAC 150 mg to other active treatments. The manufacturer submitted an indirect treatment comparison (ITC) analysis to evaluate the comparative efficacy of DAC 150 mg to other currently available DMTs in patients with RRMS. Another ITC was identified through literature review (APPENDIX 7: SUMMARY OF INDIRECT TREATMENT COMPARISONS).

4.2 Interpretation of Results

4.2.1 Efficacy

The primary end point of the two included studies was achieved. In DECIDE, the ARR was statistically significantly lower for patients on DAC compared with those on IFN beta-1a with a reduction of 45% over 96 weeks to 144 weeks. In SELECT, the ARR was statistically significantly lower for patients on DAC compared with those on placebo with a reduction of 54% over 52 weeks. The between-group differences were considered clinically meaningful according to the clinical expert consulted for this review. Multiple sensitivity analyses of the primary end point were performed to explore the impact of various covariates and assess the robustness of the primary analysis. The results of sensitivity analyses were consistent with the primary analysis conducted in the ITT population. Subgroup analyses were also performed to examine the effect from the study drug based on various patient's baseline demographic or disease characteristics. Note that no subgroup analyses were pre-specified for the CDR review. The results of subgroup analyses were generally consistent with those of the overall population. [redacted] The sample sizes for each treatment group is relatively small for the region 1 subgroup and may to some extent explain the finding. The manufacturer reported that the *P* value for the likelihood ratio statistic for interaction was 0.2613, indicating no statistically significant interaction of this subgroup. Nevertheless, DECIDE was the only study that enrolled patients from Canada and the US and therefore the lack of a statistically significant finding for the primary outcome for these countries means the generalizability of the results to these populations is somewhat uncertain. The clinical expert involved in the review noted that the baseline demographic and disease characteristics of patients enrolled in both studies were, overall, similar to those seen in clinical practice. [redacted] The US FDA medical review noted that the "completion rate was lower for patients from the US and Canada. Fewer patients from the US and Canada in Study 301 were treatment-naive, which

may have influenced the completion rate. However there is no indication that these differences affected the treatment effect and therefore the results appear to be applicable to the population if MS patients in the US."[35] The lack of confirmatory evidence from phase III RCTs similarly designed to DECIDE means it is unclear to what extent this finding will apply to the RRMS population in Canada.

The Health Canada indication for DAC indicates it should be used second-line or later. Most patients enrolled in SELECT and almost half of those enrolled in DECIDE were MS treatment-naive. The subgroup analysis based on prior MS therapy (see APPENDIX 4: DETAILED OUTCOME DATA) implies that the magnitude of relative reduction in ARR with DAC versus placebo or IFN may be somewhat larger among treatment-naive patients as compared with the patients who had received prior MS therapies. The subgroups were likely underpowered in SELECT to detect differences between DAC and placebo, and no interaction tests were reported for comparisons between subgroups. Therefore, there is no concrete efficacy evidence to indicate the place in therapy for DAC. As discussed later, the Health Canada indication (as well as that from other regulators) is largely driven by the safety profile of DAC.

Disability progression is another important clinical outcome because MS is one of the major causes of disability in young adults. In SELECT, over 52 weeks, treatment with DAC 150 mg was associated with a 57% reduction in the risk of three-month confirmed disability progression compared with placebo, and the difference was statistically significant. In DECIDE, treatment with DAC 150 mg was associated with a 16% reduction in three-month confirmed disability progression; however, the between-group difference did not reach statistical significance. The six-month confirmed disability progression was also measured in both studies, and the differences between DAC and placebo, or between DAC and IFN beta-1a, were statistically significant. It is noteworthy that the three– and six-month confirmed disability progression in SELECT and the six-month disability progression in DECIDE were tertiary and/or supportive end points; therefore, they were not included in the sequential closed testing procedure. Since the purpose of this procedure was to control for potentially inflated type I error rate, the results need to be interpreted with caution. Although DAC may result in fewer patients with worsening of their disability, there were no data regarding sustained disability improvement, which is also an important clinical outcome.

In SELECT and DECIDE, the following MRI outcomes (relevant to this review) were measured between treatment groups: new and enlarging T2 hyperintense lesion count, T2 hyperintense lesion volume, Gd-enhancing lesions, and whole-brain volume. These are conventional MRI outcomes that are widely used to monitor treatment effects in clinical trials of MS. Their roles as a surrogate for clinical outcomes such as relapses and disability progression in RRMS have been investigated in previous research but inconsistent conclusions were drawn (APPENDIX 5: VALIDITY OF OUTCOME MEASURES). Compared with placebo or IFN beta-1a, patients treated with DAC had fewer numbers of new or newly enlarging T2 hyperintense lesions and fewer numbers of new Gd-enhancing lesions. The MRI results from the two studies suggest that most comparisons show less deterioration (reduced focal and destructive areas of brain inflammation in RRMS patients from baseline) in the DAC group compared with placebo or IFN beta-1a.

A number of scales or questionnaires were measured in the included studies to explore the clinical benefits of the study drug on patient-reported outcomes, such as generic HRQoL assessment tools (i.e., EQ-5D, SF-12) or disease-specific questionnaires (i.e., EDSS, MSIS-29, and MSFC). For many of these outcomes, even though statistical significance has been achieved for between-group differences, the clinical relevance may still remain uncertain due to the lack of an MCID, or the scale has not been well validated in the study population. The European Medicines Agency (EMA)'s guidance to industry on the clinical investigation of medicinal products for the treatment of MS notes similar concerns regarding the

limited evidence validating patient-reported outcomes measures for the MS patient population, and that "specific recommendations on specific scales cannot be made."[47] In addition, there were no specific patient-reported outcomes directly measuring either fatigue or productivity (i.e., patients' capacity to participate in school or work). Therefore, there remains uncertainty regarding the comparative effects of DAC on patient-reported outcomes. A description of these scales is provided in APPENDIX 5: VALIDITY OF OUTCOME MEASURES. According to the manufacturer's comments on this CDR review, fatigue and productivity are difficult to measure in the context of an RCT because both outcomes have multiple confounding factors. It is also noteworthy that there are questions with a physical/mental fatigue component in the MSIS-29, as well as questions related to life with limitations in social and leisure activities or cutting down the amount of time spent on work or other daily activities.[48]

Patients who had completed the 52-week SELECT were eligible to enter the 52-week extension phase (Study 205MS202, also known as SELECTION).[49] Patients were re-randomized to receive the following treatments: DAC 150 mg SC for a total of 13 doses, DAC 300 mg SC for 13 doses, five doses placebo followed by eight doses DAC 150 mg SC, or five doses placebo followed by eight doses DAC 300 mg SC. The findings suggested that measures of MS disease activity, such as ARR, were similar in the extension phase and SELECT. In patients who began to receive DAC 150 mg in Study 202 after being on placebo in SELECT, reduction in MS disease activity measures (i.e., ARR) were apparent in the second year. EXTEND is the ongoing, open-label extension study of DECIDE and was performed to assess the long-term (up to five-year) safety and efficacy of DAC 150 mg every four weeks in patients with RRMS. The interim safety analysis included 1,203 patients. The patients on IFN beta-1a in DECIDE switched to DAC 150 mg every four weeks (IFN beta-1a plus DAC 150 mg; 597 patients), while those patients already on DAC 150 mg every four weeks (DAC 150 mg plus DAC 150 mg; 606 patients) continued their previous regimen. Patients in the IFN beta-1a plus DAC 150 mg group experienced a decreased ARR in the open-label extension, while the ARR in patients in the DAC 150 mg plus DAC 150 mg group remained similar to that of DECIDE. The overall safety profile was determined to be consistent in EXTEND with that of DECIDE. The lack of an appropriate control group makes it difficult to interpret the results from the two extension studies. Therefore, there remains considerable uncertainty of the comparative effects of DAC beyond what was observed versus placebo and IFN in the reviewed RCTs. Details of this extension study are presented in APPENDIX 6: SUMMARY OF OTHER STUDIES.

The manufacturer provided an ITC to evaluate the comparative efficacy and safety of DAC versus currently available DMTs for RRMS.[16] A second ITC (by Tramacere et al.)[50] was identified in a supplemental literature search for this review. While many of the same studies were included in both ITCs, results from these two analyses were somewhat different with respect to efficacy outcomes, such as ARR. The manufacturer–provided ITC indicated that DAC statistically significantly reduced the ARR versus IFN beta-1a 30 mcg once weekly, IFN beta-1a 44 mcg three times a week, IFN beta-1b 250 mcg every other day, glatiramer acetate 20 mg once daily, glatiramer acetate 40 mg three times a week, and teriflunomide 14 mg once daily. Conversely, Tramacere et al. reported no statistically significant differences between DAC and these drugs for reducing the ARR. Significant clinical heterogeneity among the included clinical trials and uncertainty as to whether or not transitivity was satisfied were key limitations of both ITCs. Therefore, given the degree of uncertainty in the relative treatment effect estimates, there is insufficient evidence to determine if there is a meaningful clinical difference between DAC and other DMTs for the treatment of RRMS, particularly in the population specified in the Health Canada–approved indication for DAC. Details of the critical appraisal and summary are presented in APPENDIX 7: SUMMARY OF INDIRECT TREATMENT COMPARISONS.

4.2.2 Harms

The overall AE rates were similar between DAC and placebo in SELECT, and between DAC and IFN beta-1a in DECIDE. After excluding MS relapse, the most common AEs among patients treated with DAC included nasopharyngitis, headache, and upper respiratory tract infection, while influenza-like illness was more frequently reported in the IFN beta-1a group in DECIDE.

Although the overall frequency of AEs appeared similar between DAC and placebo or IFN, there appear to be signals for potential serious harms associated with DAC. SAEs occurred at a similar frequency to IFN in DECIDE and at a lower frequency versus placebo in SELECT. However, after excluding MS relapse, there were 5% more patients with an SAE with DAC (15%) versus IFN (10%). Serious infections/infestations, skin disorders, and liver injury were more likely to be reported in the DAC groups compared with placebo or IFN beta-1a. The frequency of depression and suicide–related SAEs (suicidal ideation/suicidal attempt/completed suicide/depression suicidal) were less than 1% in both DAC and IFN beta-1a groups in DECIDE. Nonetheless, the product monograph currently contains a warning regarding depression and suicide being potentially related to DAC.[18] The use of DAC was also associated with a higher frequency of lymphadenopathy. PML was not reported in either study during the one to three years of treatment. In the extension study of SELECT, the number of patients with at least one AE, and the number of SAEs and WDAEs at the end of the 52-week (year 2) treatment period were similar across treatment groups, and were consistent with the safety profile observed in the placebo-controlled phase.

Both Health Canada and the US FDA expressed considerable concerns over the safety profile of DAC.[35,37] Despite the fact that SELECT and DECIDE included patients with mixed treatment histories and neither study was designed to provide evidence as to the place in therapy for DAC, both regulators restricted use of DAC to second-line (Health Canada), third-line (FDA), or later (both) therapy because of the potential serious harms with DAC. Based on pooled safety analyses (combined AEs from SELECT, DECIDE, SELECT and DECIDE extensions, one multiple-dose clinical pharmacology study [Study 302 and its extension], and the 120-day Safety Update Report [cut-off date was November 14, 2014]), the Health Canada reviewer noted that two of five deaths that occurred in patients treated with DAC (one autoimmune hepatitis in a patient treated with DAC 300 mg and one infectious complication of a serious cutaneous reaction in a patient with DAC 150 mg) might be drug-related. The warnings and precautions section of the DAC product monograph includes information related to these two deaths. The warnings and precautions section also contains a note regarding the potential for DAC to cause severe liver injury, including life-threatening events, liver failure, and autoimmune hepatitis. Health Canada and the FDA recommend assessing serum transaminases and bilirubin before starting DAC, and monitoring and evaluating transaminase and bilirubin levels monthly during treatment and up to six months after the last dose.[18,51] The EMA has the same recommendation, but limits monitoring to only four months after the last dose of DAC.[52] During an opportunity to comment on a draft of the Clinical Review report, the manufacturer stated that DAC is only available through a controlled distribution program (Biogen ONE Support Program) in Canada to mitigate the risk of severe liver injury. In this program, only registered prescribers and pharmacies are able to prescribe and dispense the product. DAC can only be dispensed as one injection per month to the registered patients who have been informed about the risks of treatment with DAC and who are adherent with monthly liver function monitoring.[18,48] DAC is contraindicated in patients with pre-existing hepatic disease or hepatic impairment, including ALT or AST at least two times the ULN, and in patients with a history of autoimmune hepatitis or other autoimmune condition involving the liver.

In the two ITC analyses, the safety outcome assessments were limited and the comparative safety of DAC to the other DMTs is uncertain.

4.3 Potential Place in Therapy[1]

MS patients are categorized into two broad, overlapping groups: relapsing and progressive forms. Each group has similar and unique needs. The current first-line and second-line DMTs are used for relapsing forms of MS, including patients with progressive disease with superimposed relapses.

No therapies are currently approved by Health Canada for purely progressive forms of MS. DAC has not been studied for progressive MS and is unlikely to fill this unmet need.

DMTs for relapsing MS can be broadly categorized clinically as modestly effective at preventing relapses and progression (IFNs, glatiramer acetate, teriflunomide, dimethyl fumarate), moderately effective (fingolimod), and highly effective (natalizumab, alemtuzumab).

The unmet need for relapsing patients is sustained improvement of disability. This can occur spontaneously in approximately 10% to 15% of untreated patients (placebo cohorts) and patients treated with IFN over two years.[53] Longer-term prospective data with alemtuzumab (and possibly with natalizumab) demonstrated high rates of improvement.[54] There is no data to suggest that DAC will improve disability (i.e., result in sustained improvement in EDSS score at three months or at six months).

MS patients may be willing to sacrifice convenience and safety if there is greater efficacy.[55] In terms of DMTs with a similar efficacy for preventing relapses (modest to moderate efficacy), these range in terms of convenience, from daily to bi-weekly SC injection, and daily oral administration. DAC is administered as a monthly SC injection, which could be more convenient for some patients. However, with a self-administered therapy, it could be easy for patients to forget to take their treatment and therefore real-world adherence to treatment is uncertain.

DAC could be an option for patients with a contraindication to fingolimod, such as cardiac disease, which is not common in a relatively young MS population. There does not appear to be any additional benefit with DAC in terms of a lower risk of unusual infections. However, there is a concerning risk of serious infections (4% for DAC versus 2% for IFN beta-1a IM in DECIDE, death secondary to iliopsoas abscess in SELECT). Nor is there a benefit in risk of liver toxicity. While no progressive multifocal leukoencephalopathy cases have been reported, one would not expect this drug to be completely without risk for PML. There may be some interest in using this therapy to de-escalate natalizumab patients who are at risk for PML (serum JC virus antibody–positive). Currently, fingolimod or alemtuzumab are the favoured alternatives in practice.

As a second-line therapy, DAC will probably be considered for the rare patient who does not tolerate fingolimod or does not want natalizumab because of the risk of PML. The monthly blood monitoring could negate the convenience of monthly injections. Many physicians will be concerned about the additional burden required to monitor patients on DAC.

In summary, DAC will be an option for a small number of patients who cannot tolerate any other modest-efficacy therapy, and for those who are not comfortable with the risks associated with the higher-efficacy therapies. The potential main benefit of this drug, compared with others, is the convenience of dosage, but this may be countered by concerns of adherence and monitoring burden.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

5. CONCLUSIONS

In two DB RCTs in patients with RRMS, DAC was associated with a lower rate of relapse and delayed disability progression (sustained for three months and six months) versus placebo and IM interferon beta-1a. The effects of DAC on patient-reported outcomes, such as HRQoL and function, are uncertain. After treatment, the numbers of Gd-enhancing lesions and new/enlarging T2-weighted lesions observed on MRI scans were statistically significantly reduced in the DAC group, compared with placebo or IFN beta-1a.

With respect to safety, the overall incidence of AEs was similar between DAC and IFN beta-1a or placebo. However, there were more SAEs reported in the DAC group, primarily due to infections. The use of DAC was also associated with higher frequency of serious hepatic AEs and skin disorders. The comparative safety of DAC and other medications for RRMS is uncertain due to the lack of long-term head-to-head trials.

There was insufficient evidence, associated with a high degree of uncertainty, from ITCs regarding the comparative efficacy and safety of DAC and other DMTs for RRMS.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input
One patient group supplied input for this submission.

The Multiple Sclerosis Society of Canada (MS Society) is a national voluntary organization that supports multiple sclerosis (MS) research and provides services related to MS for patients and their families and caregivers. The MS Society received educational grants between 2015 and 2016 from the following pharmaceutical companies: Bayer, Biogen, EMD Serono, Novartis, Pfizer, Genzyme – A Sanofi Company, Allergan, and Teva Neuroscience. All contributions are subject to policies that prevent any control or influence by the donor on the society's decision-making.

No conflicts of interest were declared in the preparation of this submission.

2. Condition-Related Information
Information was obtained from a bilingual (English and French) online survey posted between November 1, 2016 and November 14, 2016 using various sources (including social media, e-newsletters, and email). In addition, information was also obtained from publicly available information. Seventy-six per cent of survey respondents were female, 95% were patients with MS, and 95% of respondents identified as having relapsing-remitting MS (RRMS) (although other types of MS were still represented and included secondary-progressive MS and primary-progressive MS). The ages of respondents ranged from fewer than 20 years of age to 65 and older, with most respondents being between the ages of 35 and 54. The length of diagnosis varied between fewer than two years to more than 20 years, with the highest number having been diagnosed between two and 10 years prior.

MS is an unpredictable and often disabling disease of the central nervous system (CNS) whereby the myelin sheath surrounding the axons is damaged and there is an interrupted or loss of normal nerve impulse flow along the axons. The most commonly diagnosed form of MS is the relapse-remitting form (85% to 95% of patients) which is characterized by attacks of bouts of inflammation in the CNS followed by full or near recovery. About 50% of these patients will develop secondary-progressive MS within 10 to 20 years of the initial diagnosis and this form is characterized by fewer or no attacks but advanced disability. The remaining proportion of patients is diagnosed with primary-progressive MS, which is characterized by steady worsening of disease, of which their MS is not preceded by the relapse-remitting form. MS is most commonly diagnosed between the ages of 15 and 40 but can occur at any age. It is more common in women than men and is more prevalent in Northern Hemisphere countries, with the highest prevalence in Canada.

Due to the aforementioned natural history of the disease, patients with MS most commonly experience fatigue, difficulty walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain. In addition, patients can also experience issues with balance, sexual dysfunction, spasticity, tremor, weakness, and difficulties with speaking and swallowing. Medication side effects also present problems in patients. Unique issues are encountered by the patients due to the fact that diagnosis and symptoms occur during the peak times for schooling, employment, and family-building. Due to the episodic nature of the disease and how much it can affect quality of life (QoL), many patients are unable

to maintain full-time employment status or attend school (or their schooling is adversely affected), and their bouts of inflammation can seriously affect their ability to participate in physical activities, recreational life, interpersonal relationships, and can interfere with family commitments.

Caregivers can also be severely affected by their loved ones having MS as they are normally instrumental and responsible for the overall management of the disease, especially when the disability is severe. The role of the caregiver can range from providing emotional and physical support and administering medications to performing all household duties and helping the patients with personal care (e.g., feeding, dressing, etc.). As one caregiver expressed it: "I consider my father a dependent, he needs support for daily living and I am there for him daily. This makes working and caring for my children more challenging, emotionally, physically, and financially." In addition, caregivers are usually responsible for transportation to and from medical appointments. All of these aspects can ultimately affect the daily lives of the caregiver.

3. Current Therapy-Related Information

Eleven Health Canada–approved disease-modifying therapies (DMTs) are available to Canadians for the relapsing form of MS, although there is no standard defined DMT. These DMTs have been shown to reduce annual relapse rates between 30% and 70% (depending on the drug) and also are effective in slowing disability progression and reducing number of new or enhanced lesions. Symptoms are also managed with medications, corticosteroid therapy, and complementary or alternative therapies. In addition, some non-medication therapies used to treat MS symptoms include physiotherapy, physical therapy, and other types of rehabilitation. Side effects from medications are generally well managed with over-the-counter medications and changes to patient lifestyles (e.g., more rest).

While DMTs are generally well tolerated, if one patient cannot tolerate one, they switch to another. Patients highlighted that they would like more DMTs to become available so they can find one that best suits them. One patient said: "There is always someone who can benefit from a different therapy and we should have as many as possible to choose from since the benefits of treatment vary so much from person to person. Drug therapies are the difference between life and death in my opinion. You want to have as normal a life as possible and that usually isn't possible without treatment."

4. Expectations About the Drug Being Reviewed

While most patients who responded (97%) did not have any experience with daclizumab (DAC) beta, only one patient indicated that they had any desire to switch to it should it become available. Adverse effects associated with DAC beta include fatigue, headache, nausea, rash, musculoskeletal disorders, allergic reactions, infections, elevated liver enzymes, heart problems, and reduced platelet number.

Of the three currently available subsequent (or second-line) DMTs, one is an oral medication (sphingosine 1-phosphate receptor [S1PR] modulator), while the other two are monoclonal antibodies requiring intravenous infusions. All three carry the potential risk of progressive multifocal leukoencephalopathy (PML), a rare and potentially fatal brain infection. Patients believe that DAC beta will alleviate two significant gaps related to these current subsequent therapies for MS, the first being that the patient does not need to travel to a specialized infusion clinic for treatment and the second being that there is no increased risk of PML.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 25, 2017
Alerts:	Monthly search updates until May 17, 2017 (date of CDEC meeting)
Study Types:	randomized controlled trials; controlled clinical trials
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
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#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(152923-56-3 or CUJ2MVI71Y).rn,nm.
2	(Anti-TAC or DAC HYP or Daclizumab* or dacliximab* or dacluzimab* or Ro 24-7375 or Rr024 7375 or zenapzx* or zenepax* or UNII-CUJ2MVI71Y or Zenapax* or Zinbryta* or "bib 019" or biib019).ti,ab,ot,hw,rn,nm,kf.
3	1 or 2
4	3 use pmez
5	*daclizumab/
6	(Anti-TAC or DAC HYP or Daclizumab* or dacliximab* or dacluzimab* or Ro 24-7375 or Rr024 7375 or zenapzx* or zenepax* or UNII-CUJ2MVI71Y or Zenapax* or Zinbryta* or "bib 019" or biib019).ti,ab,kw.
7	5 or 6
8	7 use oemezd
9	4 or 8
10	9 not conference abstract.pt.
11	remove duplicates from 10
12	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.
13	Randomized Controlled Trial/
14	exp Randomized Controlled Trials as Topic/
15	"Randomized Controlled Trial (topic)"/
16	Controlled Clinical Trial/
17	exp Controlled Clinical Trials as Topic/
18	"Controlled Clinical Trial (topic)"/
19	Randomization/
20	Random Allocation/
21	Double-Blind Method/
22	Double Blind Procedure/
23	Double-Blind Studies/
24	Single-Blind Method/
25	Single Blind Procedure/
26	Single-Blind Studies/
27	Placebos/
28	Placebo/
29	Control Groups/
30	Control Group/
31	(random* or sham or placebo*).ti,ab,hw,kf,kw.
32	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
33	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
34	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
35	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
36	allocated.ti,ab,hw.
37	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
38	or/12-37
39	11 and 38
40	Multiple Sclerosis, Relapsing-Remitting/ or multiple sclerosis/
41	(relapsing remitting adj2 multiple sclerosis).ti,ab,sh,hw,ot,kf.
42	(remitting relapsing adj2 multiple sclerosis).ti,ab,sh,hw,ot,kf.
43	((relapsing remitting adj2 ms) or (remitting relapsing adj2 ms)).ti,ab,sh,hw,ot,kf.
44	((exacerbat* or disseminated or insular or secondary progressive or primary progressive or progressive relapsing) adj2 (sclerosis or ms)).ti,ab,sh,hw,ot,kf.

MULTI-DATABASE STRATEGY	
#	**Searches**
45	(rrms or encephalomyelitis disseminat*).ti,ab,sh,hw,ot,kf.
46	acute relapsing multiple sclerosis.ti,ab,sh,hw,ot,kf.
47	or/40-46
48	47 use pmez
49	Multiple Sclerosis/
50	(relapsing remitting adj2 multiple sclerosis).ti,ab,kw.
51	(remitting relapsing adj2 multiple sclerosis).ti,ab,kw.
52	((relapsing remitting adj2 ms) or (remitting relapsing adj2 ms)).ti,ab,kw.
53	((exacerbat* or disseminated or insular or secondary progressive or primary progressive or progressive relapsing) adj2 (sclerosis or ms)).ti,ab,kw.
54	(rrms or encephalomyelitis disseminat*).ti,ab,kw.
55	acute relapsing multiple sclerosis.ti,ab,kw.
56	or/49-55
57	56 use oemezd
58	48 or 57
59	11 and 58
60	39 or 59

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	January 2017
Keywords:	Zinbryta (daclizumab)
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Radue EW, Sprenger T, Vollmer T, Giovannoni G, Gold R, Havrdova E, et al. Daclizumab high-yield process reduced the evolution of new gadolinium-enhancing lesions to T1 black holes in patients with relapsing-remitting multiple sclerosis. Eur J Neurol. 2016 Feb;23(2):412-5.	Inappropriate study design (post-hoc analysis)
Phillips G, Guo S, Bender R, Havrdova E, Proskorovsky I, Vollmer T. Assessing the impact of multiple sclerosis disease activity and daclizumab HYP treatment on patient-reported outcomes: Results from the SELECT trial. Mult Scler Relat Disord. 2016 Mar;6:66-72.	Inappropriate study design (post-hoc analysis)
Havrdova E, Giovannoni G, Stefoski D, Forster S, Umans K, Mehta L, et al. Disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with daclizumab high-yield process in the SELECT study. Mult Scler. 2014 Apr;20(4):464-70.	Inappropriate study design (post-hoc analysis)
Kappos L, Havrdova E, Giovannoni G, Khatri BO, Gauthier SA, Greenberg SJ, et al. No evidence of disease activity in patients receiving daclizumab versus intramuscular interferon beta-1a for relapsing-remitting multiple sclerosis in the DECIDE study. Mult Scler [Internet]. 2016 Dec 1	Inappropriate study design (post-hoc analysis)
Gold R, Radue EW, Giovannoni G, Selmaj K, Havrdova E, Stefoski D, et al. Safety and efficacy of daclizumab in relapsing-remitting multiple sclerosis: 3-year results from the SELECTED open-label extension study. BMC Neurol [Internet]. 2016 Jul 26 [cited 2017 Feb 1];16:117.	Inappropriate study design (extension study)
Giovannoni G, Gold R, Selmaj K, Havrdova E, Montalban X, Radue EW, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECTION): a multicentre, randomized, double-blind extension trial. Lancet Neurol. 2014 May;13(5):472-81.	Inappropriate study design (extension study)

APPENDIX 4: DETAILED OUTCOME DATA

No subgroup analyses were pre-specified in the review protocol; the clinical expert involved in the review helped develop the review protocol. The following subgroup data based on previous multiple sclerosis (MS) therapy is provided as additional context.

[redacted]

In DECIDE, for patients had a history of interferon (IFN) use, [redacted]. For patients who were IFN-naive, [redacted]

In SELECT, for patients with prior MS therapy, [redacted] For patients who were MS treatment-naive, [redacted]

TABLE 9: ANNUALIZED RELAPSE RATE — SUBGROUP ANALYSIS (BASED ON USE OF PRIOR MS THERAPY)

	DECIDE		SELECT	
	DAC 150 mg (N = 919)	**IFN beta-1a 30 µg (N = 922)**	**DAC 150 mg (N = 201)**	**PL (N = 196)**
Prior IFN beta use				
Yes, n (%)	[redacted]	[redacted]	NR	
ARR (95% CI)	[redacted]	[redacted]		
No, n (%)	[redacted]	[redacted]		
ARR (95% CI)	[redacted]	[redacted]		
Prior immunomodulatory therapy for MS, excluding steroids				
Yes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
ARR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
ARR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

ARR = annualized relapse rate; CI = confidence interval; CSR = Clinical Study Report; DAC = daclizumab; IFN = interferon; MS = multiple sclerosis; n = number of patients with event; N = number of patients; NR = not reported; PL = placebo.
Source: CSRs for DECIDE[38] and SELECT.[39]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the characteristics of the following outcome measures, including their validity, reliability, and minimal clinically important difference (MCID):

- Expanded Disability Status Scale (EDSS)
- EuroQol 5-Dimensions questionnaire (EQ-5D)
- Multiple Sclerosis Functional Composite (MSFC)
- Short Form (12) Health Survey (SF-12)
- MRI outcomes
- Multiple Sclerosis Impact Scale (MSIS-29).

Findings

EDSS

The EDSS is an ordinal scale used to measure disability in multiple sclerosis (MS). It relies on identification of eight functional systems (FSs) (plus "other"). These are pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. Each FS is graded separately on a scale of 0 (normal) to either 5 or 6.[43] The EDSS score is a composite ranging from 0 to 10 (in increments of 0.5) that incorporates FS grades as well as the degree of functional disability and ambulation (Table 10). Scores from 0 to 4.5 represent normal ambulation, while scores of 5 and above represent progressive loss of ambulatory ability.

The distribution of EDSS scores among MS patients is typically biphasic, accumulating around two to three points, and six to seven points, indicating that patients do not stay equally long at each step of the scale. There are many criticisms of the EDSS, including the fact that it has only modest intra-rater reliability, low reproducibility, poor assessment of upper limb and cognitive function, and lacks linearity.[56-59] Other flaws include that it is an arbitrary scale with limited and discrete levels of disability, that it relies heavily on evaluation of motor function and the ability to walk, and that it requires a subjective evaluation of disability using a parametric scale.

In published literature,[60] the MCID was determined to be a 1.0 point change when the score was between the EDSS zero and 5.5 range, while it was determined that this value decreased to a 0.5-point change when the EDSS score was between the 5.5 and 8.5 range.

TABLE 10: SCORING OF EXPANDED DISABILITY STATUS SCALE

	Normal Neurological Exam (All Grade 0 in Functional Systems; Cerebral Grade 1 Acceptable)
1	No disability, minimal signs in one FS (i.e., grade 1, excluding cerebral grade 1).
1.5	No disability, minimal signs in more than one FS (more than one grade 1, excluding cerebral grade 1).
2.0	Minimal disability in one FS (one FS grade 2; other 0 or 1).
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory.
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relative severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 metres.

	Normal Neurological Exam (All Grade 0 in Functional Systems; Cerebral Grade 1 Acceptable)
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 metres.
5.0	Ambulatory without aid or rest for about 200 metres; disability severe enough to impair full daily activities (e.g., to work full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding specifications for step 4.0.)
5.5	Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding those for step 4.0.)
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 metres with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 metres without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
7.0	Unable to walk beyond about 5 metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone.)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+.)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair; but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems.)
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions. (Usual FS equivalents are combinations, generally 4+ in several systems.)
9.0	Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+.)
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+.)
10.0	Death due to MS.

FS = functional system; MS = multiple sclerosis.

EQ-5D

The EQ-5D is a generic quality of life (QoL) instrument that may be applied to a wide range of health conditions and treatments.[44,45] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[44,45] The second part is a 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores fewer than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 100 are assigned to the health states "dead" and "perfect health," respectively. The MCID for the EQ-5D ranges from 0.033 to 0.074.[61]

Validity in MS: No studies specifically validating EQ-5D in patients with MS were identified. As with any generic health-related quality of life (HRQoL) instrument, there is the possibility that items important to patients with a specific disease may be missed by the EQ-5D, or that the instrument may lack sufficient sensitivity to detect clinically important changes. A recent Canadian study reported that the EQ-5D identified only four of 10 domains identified as important by patients with MS; the missed domains included fatigue, sports, social life, relationships, cognition, and balance. Furthermore, the instrument over-estimated utility scores compared with a disease-specific measure.[62]

MSFC

The MSFC is a measure of MS disability that was developed in 1994 by a task force convened by the US National Multiple Sclerosis Society.[63,64] The MSFC assesses different clinical dimensions: arm (9-Hole Peg Test [9HPT], which measures time to insert and remove nine pegs), leg (Timed 25-Foot Walk [T25-FW], which measures time to walk 25 feet), and cognition (Paced Auditory Serial Addition Test [PASAT] 3, which measures a number of correct additions). The raw scores for each item are transformed into z scores in order to achieve a common metric, in standard deviation units. A z score represents the number of SDs a patient's test result is higher ($z > 0$) or lower ($z < 0$) than the average test result ($z = 0$) of the reference population. The mean and standard deviation from test results at the baseline visit for all patients in each study was used as the reference population values to create the z scores for each component of the composite. The z score is calculated by subtracting the mean of the reference population from the test result and then dividing this by the standard deviation of the reference population. For T25-FW and 9HPT, a higher test result means the patient worsened from baseline. For PASAT 3, a higher test result means that the patient improved from baseline. In order to ensure that all measures are in the same direction, a transformation is necessary. In creating the composite outcome measure, it was decided that a higher test result would indicate improvement from baseline.[64]
Psychometric properties and MCID in MS patients are provided in the following:

- *Test-retest reliability*: Intra-class coefficients of 0.87 to 0.96 have been reported.[63]
- *Construct validity*: MSFC scores were lower in more disabled patients (–0.4 in primary-progressive MS, –0.3 in secondary-progressive MS versus + 0.42 in relapsing-remitting MS).[63]
- *Convergent validity (correlation with EDSS)*: A study by Ozakbas et al. (N = 38) found a significant correlation between EDSS and MSFC. In looking at individual components, the EDSS had the lowest correlation (correlation coefficient for bivariate analysis $[r] = 0.31$) with the PASAT, and the authors suggested that this might confirm the observation of poor assessment of cognitive function by ++++++EDSS. The strongest correlation was between EDSS and T25WT ($r = 0.84$) followed by 9HPT ($r = 0.51$) (which was only moderately correlated); again, this was consistent with the observation of poor assessment of upper limb function by EDSS.

- *MCID*: A 20% change in scores on T25-FW and 9HPT, and a 0.5 standard deviation change on PASAT 3, are considered clinically meaningful; however, a clinically meaningful value for overall MSFC score has not been determined.[63]

SF-12

The SF-12 is a multi-item generic HRQoL questionnaire that was developed from the Short Form (36) Health Survey (SF-36).[65] It has been used in clinical trials to study the impact of chronic disease on HRQoL but can be used for patients of any age, with any disease, and for any treatment since it involves general health concepts.[66] The SF-12 is composed of the physical component summary score and the mental component summary score, which measure the physical and psychological burden of disease, respectively.[65] Scores range between 0 and 100, with higher scores indicating better HRQoL.[65]

Like the SF-36, the SF-12 measures eight health domains. The eight individual domains include: general health (which measures the patient's perception of their overall health), vitality (whereby fatigue and energy levels are assessed), bodily pain (which measures both the frequency of pain and how much pain interferes with normal functioning), social functioning (which measures how much a patient's illness affects social functioning), physical functioning (the extent to which daily life is affected), role physical (which measures limitations in roles due to problems with physical health), mental health (measures psychological distress), and role emotional (which assesses role limitation due to emotional issues).[66] The 12 items that make of up the SF-12 are derived from the eight domains and include the following:

- general health — one item
- vitality — one item
- bodily pain — one item
- social functioning — one item
- physical functioning — two items
- role physical — two items
- mental health — two items
- role emotional — two items.[66]

The SF-12 has been shown to have 90% of the variance of the full SF-36.[64] Moderate reliability for the SF-12 was obtained in one study whereby generic QoL assessments were compared with MS-specific QoL assessments (MSIS-29 and Patient Determined Disease Steps) in patients with various types of MS.[65] In this study, the physical and mental components of the SF-12 were strongly correlated with the physical and mental components of the MSIS-29, respectively. This provides further evidence regarding the validity of the SF-12 in patients with MS.[65]

No MCID for the SF-12 was identified for patients with MS.

MRI Outcomes

MRI techniques play an important role in the diagnosis of MS. In addition, they are valuable in monitoring treatment response and predicting disease progression. However, the correlation between the burden of lesions observed on MRI scans and the clinical manifestations of the disease remains controversial.[67-69]

In CARE-MS-II, the following MRI outcomes were measured between treatment groups: new and enlarging T2 hyperintense lesion count, T2 hyperintense lesion volume, and gadolinium (Gd)-enhancing lesions. These are conventional MRI outcomes that are widely used to monitor treatment effects in

clinical trials of MS. Their roles as a surrogate for clinical outcomes such as relapses and disability progression in RRMS have been investigated in previous research. Findings from systematic reviews and large randomized controlled trials (RCTs) reporting the correlations between the treatment effect on relapses and disability progression and the treatment effect on MRI lesions are presented in Table 11. In these studies, RRMS patients received interferon, cladribine, fingolimod, placebo, or no drug treatment. The correlations between MRI outcomes and clinical outcomes (relapses and disability progression) varied across studies.

TABLE 11: SUMMARY OF CORRELATIONS BETWEEN MRI OUTCOMES AND CLINICAL OUTCOMES

	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
Sormani 2013[70]	31 RCTs of all available DMTs for RRMS, published from 2008 to 2012	Number of MRI lesions (new or enlarging T2 lesions; or Gd-enhancing lesions) ARR: number of relapses divided by patient-years MRI effect: ratio between the average number of MRI lesions per patient in the experimental group and in the control group REL effect: ratio between the relapse rate in the experimental group and in the control group R^2: used to assess the goodness of fit for a regression equation in which the treatment effect on relapses was predicted by MRI results	Data from 31 RCTs were used in deriving regression equation. $R^2 = 0.71$, suggesting a good degree of prediction of REL effect using MRI effect.	The effect of a treatment on relapses can be accurately predicted by the effect of that therapy on MRI lesions.
Sormani 2010[71]	3 RCTs enrolling RRMS patients: – Cladribine vs. placebo – Fingolimod vs. placebo – Fingolimod vs. interferon Follow-up: 12 months to 24 months	MRI effect: ratio between the average number of new and enlarging T2 lesions/patient in the experimental group and in control group REL effect: ratio between the ARR in the experimental group and in the control group DIS effect: ratio between % of patients with disability progression (≥ 1 point on EDSS at month 3) in experimental and control group Regression equations from previous meta-analyses were used to predict the drug effect on relapse (REL effect) and disability progression (DIS effect) based on MRI effect	92% of observed effects of oral drugs (cladribine and fingolimod) on clinical outcomes resulted close to those predicted by MRI active lesions. From the regression lines provided in the article, 10 out of 12 observed that effects on the clinical variables were very close to those predicted by the lines.	MRI markers were able to predict treatment effects on clinical end points in RRMS patients treated with novel oral drugs.

	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
Sormani 2010[72]	The PRISMS study enrolling 560 RRMS patients: subcutaneous interferon vs. placebo Follow-up: 2 years	PTE on relapses that was accounted for by the effect of treatment on the MRI marker	New T2 lesions and relapses were significantly correlated: compared with placebo, interferon significantly ↓ new T2 lesion number by 60% over 2 years, and the number of relapses ↓ by 30%. PTE on relapses accounted for by the effect of treatment on new T2 MRI lesions was 53% in RRMS patients. A pooled PTE of 62% was found when meta-analysis was performed on data from PRISMS and 2 other trials of disease-modifying drugs.	The study provides evidence that new T2 MRI lesion count is a surrogate for relapses in MS patients treated with interferon or drugs with similar mechanism of action.
Kappos 1999[73]	Patients in natural-course studies or who were treated with placebo or observed in the pre-treatment phase of controlled clinical trials 77% of the patients had RRMS; 23% had secondary-progressive MS Follow-up: 6 months to 24 months	Change in disability: assessed by EDSS Relapse MRI data	Relapse rate in the first year was predicted with moderate ability by mean number of Gd-enhancing lesions: RR 1.13, *P* = 0.023. The mean of Gd-enhancing lesion counts in the first 6 monthly scans was weakly predictive of EDSS change after 1 year (OR 1.34, *P* = 0.082) and 2 years (OR 1.65, *P* = 0.049).	Gd-enhancing MRI was not a strong predictor of the development of cumulative impairment or disability.

ARR = annual relapse rate; DIS = disability; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MRI = magnetic resonance imaging; MS = multiple sclerosis; OR = odds ratio; *P* = probability; PTE = proportion of treatment effect; R^2 = coefficient of determination; REL = relapse; RCT = randomized controlled trial; RR = relative risk; RRMS = relapsing-remitting multiple sclerosis.

MSIS-29

The MSIS-29 is a 29-item questionnaire that was developed at the Neurological Outcome Measures Unit of the Institute of Neurology/National Hospital for Neurology and Neurosurgery in London, England.[74]

This 29-item, self-reported questionnaire is used to measure both the physical and psychological impact of MS on affected individuals. The physical component assesses 20 items (one through 20), while the psychological component assesses nine items (21 through 29).[60,74,75] Symptoms for each item are rated on a five-point Likert scale, added, and then transformed to a zero to 100 scale.[75,76] Lower scores are indicative of independence while higher scores are indicative of a larger amount of compromise. Physical scores range from 20 to 100, which represent best to worst functioning, respectively, while the psychological scores range from five to 45, which correspond to best and worst, respectively.[76]

In order to assess the validity and reliability of the MSIS-29, Riazi et al.[77] examined the MSIS-29 along with three other self-reported measures (Functional Assessment of Multiple Sclerosis [FAMS], SF-36, and the 12-item General Health Questionnaire [GHQ-12]) in 58 patients admitted to a hospital rehabilitation unit with confirmed MS. They also assessed the EDSS for each patient. The authors determined that the MSIS-29 met the standard criteria for being a reliable and valid measurement, with similar results obtained in the hospital setting when compared with the community setting.[77] In addition, they noted that the MSIS-29 had minimal floor-to-ceiling effects and the physical scores spanned the full range of scores; however, lower-than-expected correlations were observed between the MSIS-29 and the physical component of the SF-36 and EDSS. Limitations associated this study included a relatively small sample size.[77] In contrast to this, moderately good correlations were observed in Costelloe et al. between changes in the MSIS-29 physical score and changes in the EDSS scores in the ranges of zero to 8.5 and 5.5 to eight, whereas the correlation was weaker between the two with EDSS changes in the range of zero to five.[60]

In a sample of 245 patients who were generally older (mean age of 47 years) and who had more established MS disease (mean duration of 14 years), Hobart et al.[78] ascertained that the MSIS-29 physical scale had large effect sizes, was able to detect change in patients in the rehabilitation unit and in patients on steroids better than other effect measures (SF-36, FAMS, and GHQ-12), and had the greatest differential responsiveness across samples. That being said, the authors observed that the psychological scale was not as responsive as the GHQ-12 overall.[78]

Using receiver operating characteristic curve curves in a population of patients (n = 214) with a range of MS disability (EDSS scores ranging from zero to 8.5 and MSIS-29 scores ranging from zero to 99), Costelloe et al.[60] determined that a minimal change of eight points on the MSIS-29 physical is clinically significant.

Conclusion

A summary of the characteristics of five instruments was provided; two measured disability (with EDSS and MFSC) and three measured HRQoL (including EQ-5D, SF-36, and MSIS-29). In addition, the correlation between MRI outcomes and clinical outcomes such as relapses and progression in disability in RRMS patients were examined.

With respect to the reliability and validity of the instruments:

- MFSC shows good construct validity but is only moderately correlated to EDSS.
- The reliability and validity of EQ-5D has not been determined in MS patients specifically.
- SF-12 has good internal consistency reliability and test-retest reliability was low to high, depending on the dimension. Construct validity was good for physical-type dimensions.

- MSIS-29 is a valid and reliable tool that is responsive across sample types, has large effect sizes, is able to detect change, and whose changes in the physical scale correlates moderately well with changes in the EDSS scores in the range of zero to 8.5 and 5.5 to 8.

No MCID was available for the SF-12 with regard to patients with MS. In addition, while not specific for patients with MS, the reported MCID for the EQ-5D has ranged from 0.033 to 0.074. A 20% change in scores on T25-FW and 9HPT, and a 0.5 standard deviation change on the PASAT 3 are considered clinically meaningful in MSFC; however, an MCID for overall MSFC score has not been determined. It appears as though the MCID for the MSIS-29 physical score is eight points; however, no MCID with regard to its overall score was identified.

Findings from the studies investigating the correlations of MRI outcomes and clinical outcomes suggested that conventional MRI scans may be a tool for predicting disease relapses and disability progression for patients with RRMS; however, the correlations between MRI outcomes and clinical outcomes were not consistent across studies.

APPENDIX 6: SUMMARY OF OTHER STUDIES

1. Objective

To summarize the efficacy and safety results of the 52-week extension study of the SELECT trial and the interim analysis of EXTEND (an open-label extension of DECIDE).[34] The following summary is based on unpublished data from the extension trial 205MS202 (hereafter termed Study 202), the Clinical Study Report for SELECT[49], and the CADTH Common Drug Review (CDR) submission (Clinical Summary) for EXTEND.[34]

2. Findings

Study Design

Study 202 was a multi-centre, randomized, double-blind (DB) extension study that sought to evaluate the long-term efficacy and safety of daclizumab (DAC) monotherapy for patients with relapsing-remitting multiple sclerosis (RRMS) who had completed the 52-week SELECT study. Patients were randomized based on their original treatment allocation in Study 201:

- Patients in the placebo group in SELECT were randomized 1:1 to receive either DAC 150 mg subcutaneously (SC) every four weeks (total of 13 doses) (termed "placebo [PL] plus DAC 150 mg") or DAC 300 mg SC every four weeks (total of 13 doses).
- Patients in the DAC 150 mg SC group in SELECT were randomized 1:1 to receive either placebo SC every four weeks (total of five doses) followed by DAC 150 mg SC every four weeks (total of eight doses) (termed "DAC 150 mg plus washout") or DAC 150 mg SC every four weeks (total of 13 doses) (termed "DAC 150 mg for two years").

For the purposes of this review, patients who were originally randomized to DAC 300 mg SC every four weeks will not be presented, nor will those randomized to receive DAC 300 mg SC in Study 202.

Populations that were used for the efficacy analysis included the following:

- The intention-to-treat (ITT) population consisted of all patients randomized in Study 202 and received study treatment (excluding patients from Site 903).
- The per-protocol (PP) population was a subset of the ITT population that excluded 75 patients for whom the time between the last dose of study treatment in Study 201 and the first dose in Study 202 was 56 days or longer.
- The safety population consisted of all patients randomized in Study 202 who received study treatment.

No formal statistics were performed to assess significance in Study 202. Instead, analyses were descriptive in nature.

The EXTEND study is the ongoing, open-label extension study of DECIDE and was performed to assess the long-term (up to five years) safety and efficacy of DAC 150 mg every four weeks in patients with RRMS. Patients on interferon (IFN) beta-1a in DECIDE switched to DAC 150 mg every four weeks, while those patients already on DAC 150 mg every four weeks continued their previous regimen. The interim analysis was performed using data through either January 11, 2016 (for patients who were enrolled in the pre-filled pen [PFP] substudy, which was only available at certain sites) or September 10, 2015 (for patients not enrolled in the PFP substudy). The PFP substudy was performed to observe treatment-related adverse events (AEs) associated with injection using the pen.

Results

SELECT extension study: Of the 577 patients who completed SELECT, 517 patients were randomized to and received treatment in Study 202. As stated previously, this review will only report on patients who received DAC 150 mg (not those patients who received DAC 300 mg). Of note: 18 patients from Site 903 were excluded in the efficacy analysis as the site was closed due to protocol violations. In patients who received DAC 150 mg for two years, 88% (n = 72) completed treatment, with the most common reasons for discontinuation being withdrawn consent (9%) and AEs (2%). In the DAC 150 mg plus washout group, 86% completed treatment with 8% and 5% of patients discontinuing due to AEs and withdrawal of consent, respectively. For patients in the PL plus DAC 150 mg group, 89% of patients completed treatment with 5% and 4% of patients discontinuing due to withdrawal of consent and AEs, respectively. Table 12 outlines the patient disposition in detail.

EXTEND extension study: The safety analysis included 1,203 patients from DECIDE, of which 597 switched from IFN beta-1a to DAC 150 mg every four weeks (IFN beta-1a plus DAC 150 mg) and 606 patients continued with their original DAC 150 mg every four weeks regimen (DAC 150 mg plus DAC 150 mg). There was a substudy performed at certain sites whereby patients received six consecutive doses of DAC 150 mg every four weeks with a PFP [n = 97]. Of these patients, 91% (n = 88) completed the six doses, while 9% (n = 9) withdrew from the study (AEs: n = 5; withdrawn consent: n = 3; other: n = 1). Six PFP doses were received by 84% (n = 81) of patients. Injection-site AEs occurred in 10% of patients, with mean (standard deviation) visual analogue scale (VAS) scores of 1.7 (2.5) and 1.6 (2.3) after the first and fourth injections, respectively.

TABLE 12: PATIENT DISPOSITION THROUGHOUT EXTENSION STUDY 202[A] AND THE EXTEND STUDY

SELECT	Extension Study Treatment Arms		
	PL + DAC 150 mg	**DAC 150 mg + Washout**	**DAC 150 mg for 2 Years**
Randomized, n (%)	84 (100)	85 (100)	82 (100)
Completed treatment, n (%)	75 (89)	73 (86)	72 (88)
Discontinued treatment, n (%)	9 (11)	12 (14)	10 (12)
AE	3 (4)	7 (8)	2 (2)
Withdrew consent	4 (5)	4 (5)	7 (9)
Investigator decision	1 (1)	0	0
Non-compliance	0	0	1 (1)
Other	1 (1)	1 (1)	0
Completed treatment phase, n (%)	77 (92)	76 (89)	75 (91)
Study withdrawals during treatment phase, n (%)	7 (8)	9 (11)	7 (9)
AE	1 (1)	3 (4)	1 (1)
Withdrew consent	5 (6)	4 (5)	6 (7)
Investigator decision	1 (1)	1 (1)	0
Other	0	1 (1)	0
EXTEND	**IFN beta-1a + DAC 150 mg**	**DAC 150 mg + DAC 150 mg**	**PFP[b]**
Entered, N = 1,203	597	606	97

AE = adverse event; CDR = CADTH Common Drug Review; CSR = Clinical Study Report; DAC = daclizumab; IFN = interferon; n = number of patients with event; N = number of patients; PFP = pre-filled pen; PL = placebo.

[a] Results exclude Site 903.

[b] Received six consecutive doses of DAC 150 mg every four weeks in PFP (subgroup study).

Source: CSR 205MS202[49] and the CDR submission (Clinical Summary) for EXTEND[34].

Patient Characteristics

The baseline characteristics were obtained and reported on from the baseline of the extension study (Study 202) and were reported from the safety population. Mean ages in the three treatment arms of interest ranged between 36.2 and 38.2 years (standard deviation between 8.8 and 9.8 years), with the majority of patients being white (range 95% to 99%). In addition, more patients were female in all three relevant treatment arms (range 62% to 69%).

With regard to multiple sclerosis (MS) disease history (in the PP population), more patients in the PL plus DAC 150 mg group had one or two relapses during Study 201 (27% and 7%, respectively) when compared with the other two treatment arms (DAC 150 mg plus washout with 14% and 5%, respectively, and DAC 150 mg for two years with 17% and 2%, respectively). The mean number of gadolinium (Gd)-enhancing lesions at baseline were lower in patients had previously received DAC 150 mg in Study 201 (range 0.2 ([standard deviation of 0.4] to 0.4 [standard deviation of 1.1] in the DAC 150 mg for two years and DAC 150 mg plus washout groups, respectively) when compared with the PL plus DAC 150 mg group (1.2 [standard deviation of 2.5]). The mean number of T2 hyperintense lesions were similar across treatment arms (mean range of 44.3 to 45.3 [standard deviation ranging between 35.0 and 38.9]). Detailed patient characteristics and MS history at baseline are provided in Table 13.

TABLE 13: PATIENT CHARACTERISTICS AND MS HISTORY AT BASELINE OF EXTENSION STUDY 202

	Extension Study Treatment Arms		
	PL + DAC 150 mg	**DAC 150 mg + Washout**	**DAC 150 mg for 2 Years**
Patient characteristics — Safety population			
N (%)	**86 (100)**	**86 (100)**	**86 (100)**
Age (years)			
Mean (SD)	38.2 (9.8)	36.8 (8.8)	36.2 (9.3)
Median (min., max.)	38.5 (20, 56)	37.5 (20, 54)	36.5 (20, 55)
Sex, n (%)			
Male	33 (38)	27 (31)	33 (38)
Female	53 (62)	59 (69)	53 (62)
Race, n (%)			
White	82 (95)	85 (99)	83 (97)
Asian	4 (5)	1 (1)	3 (3)
MS history — Per-protocol population[a]			
N (%)	**84 (100)**	**64 (100)**	**65 (100)**
Total number of relapses during Study 201, n (%)			
0	55 (65)	52 (81)	53 (82)
1	23 (27)	9 (14)	11 (17)
2	6 (7)	3 (5)	1 (2)
Time since last relapse (months)			
Mean (SD)	6.03 (3.12)	4.33 (3.65)	6.42 (3.70)
Total number of GD lesions at baseline, n (%)			
0	52 (62)	50 (78)	55 (85)
1 to 4	23 (27)	11 (17)	10 (15)
5 to 8	4 (5)	1 (2)	0
9 to 12	1 (1)	0	0
13 to 16	1 (1)	0	0

	Extension Study Treatment Arms		
	PL + DAC 150 mg	**DAC 150 mg + Washout**	**DAC 150 mg for 2 Years**
Missing	3 (4)	2 (3)	0
Mean (SD)	1.2 (2.5)	0.4 (1.1)	0.2 (0.4)
Total number of T2 hyperintense lesions at baseline, n (%)			
0	0	1 (2)	0
1 to < 40	46 (55)	35 (55)	35 (54)
40 to < 80	25 (30)	15 (23)	22 (34)
80 to < 120	5 (6)	7 (11)	5 (8)
120 to < 160	4 (5)	4 (6)	2 (3)
≥ 160	1 (1)	0	1 (2)
Missing	3 (4)	2 (3)	0
Mean (SD)	44.4 (36.4)	44.3 (38.9)	45.3 (35.0)
Total volume of T1 hypointense lesions (mm^3) at baseline			
n	81	62	65
Mean (SD)	2,260.50 (3,313.89)	1,691.41 (2,500.89)	2,838.41 (4,042.85)
Total lesion volume of T2 hyperintense lesions (mm^3) at baseline			
n	81	65	65
Mean (SD)	7,774.40 (9,264.90)	7,016.86 (8,582.19)	8,764.05 (10,460.81)
Normalized brain volume (mL) at week 24 of Study 201 (SELECT)			
n	83	63	64
Mean (SD)	1,504.46 (88.65)	1,513.18 (87.59)	1,480.08 (87.57)
Number of doses received			
n	86	86	86
Mean (SD)	11.8 (2.9)	11.6 (3.1)	11.7 (2.8)
Concomitant mediations taken by ≥ 10% of patients in any treatment group in Study 202[b], n (%)			
Patients taking any concomitant medications	58 (67)	69 (80)	58 (67)
Methylprednisolone	17 (20)	24 (28)	14 (16)
Paracetamol	15 (17)	12 (14)	10 (12)
Omeprazole	7 (8)	12 (14)	7 (8)
Ibuprofen	7 (8)	8 (9)	10 (12)
Baclofen	13 (15)	7 (8)	6 (7)

CSR = Clinical Study Report; DAC = daclizumab; GD = gadolinium; max. = maximum; min. = minimum; MS = multiple sclerosis; n = number of patients with event; N = number of patients; PL = placebo; SD = standard deviation.
[a] Unless stated otherwise.
[b] Not a full list.
Source: CSR 205MS202[49].

Clinical Efficacy Outcomes

Study 202

The annualized relapse rate (ARR) with accompanying 95% confidence intervals was lowest in the DAC 150 mg for two years group (ARR of 0.198 [standard deviation of 0.111 to 0.354]), followed by the PL plus DAC 150 mg (ARR of 0.219 [standard deviation of 0.137 to 0.351]) and DAC 150 mg plus washout (ARR of 0.323 [standard deviation of 0.203 to 0.515]) groups. The estimated proportion of patients who relapsed in Study 202 was 16.0%, 18.6%, and 24.9% in the DAC 150 mg for two years, PL plus DAC 150 mg, and DAC 150 mg plus washout groups, respectively.

Confirmed disability progression was defined as greater than or equal to a 1.0-point increase on the Expanded Disability Status Scale (EDSS) during year 2 from the Study 202 baseline, EDSS score greater than or equal to 1.0 that was sustained for three months, greater than or equal to a 1.5-point increase on the EDSS during year 2 from the Study 202 baseline, or EDSS score of zero that was sustained for three months. A cut-off of 74 days was used to determine sustained progression for three months. The proportion of patients with confirmed disability progression at three months was lowest in the PL plus DAC 150 mg group (5%), followed by the DAC 150 mg plus washout and DAC 150 mg for two years groups (both with 9%).

MRI end points were analyzed using descriptive statistics. The mean numbers of new lesions observed at week 52 of Study 202 were 0.1 (standard deviation of 0.4), 0.2 (standard deviation of 0.6), and 0.3 (standard deviation of 1.5) in the PL plus DAC 150 mg, DAC 150 mg plus washout, and DAC 150 mg for two years groups, respectively. The mean numbers of new or newly forming T2 hyperintense lesions at week 52 of Study 202 were 2.0 (standard deviation of 3.7), 4.3 (standard deviation of 8.9),a and 1.4 (standard deviation of 503) in the PL plus DAC 150 mg, DAC 150 mg plus washout, and DAC 150 mg for two years groups, respectively. With regard to whole-brain volume, the percentage change from baseline to week 52 of Study 202 was –0.760 (standard deviation of 0.873), –0.830 (standard deviation of 0.770), and –0.682 (standard deviation of 0.948) in the PL plus DAC 150 mg, DAC 150 mg plus washout, and DAC 150 mg for two years groups, respectively.

Detailed efficacy end point results are presented in Table 14.

EXTEND

Patients in the IFN beta-1a plus DAC 150 mg group experienced a decreased ARR from 0.317 to 0.152 in the open-label extension, while the ARR in patients in the DAC 150 mg plus DAC 150 mg group remained similar to that of DECIDE (0.195 in DECIDE and 0.156 in EXTEND).

With regard to 24-week confirmed disability progression (observing the combined DECIDE/EXTEND period), patients who received DAC 150 mg every four weeks up to week 168 had a 21% relative risk reduction when compared with patients who switched from IFN beta-1a (P = 0.047).

TABLE 14: CLINICAL EFFICACY END POINTS OF EXTENSION STUDY 202 (PER-PROTOCOL POPULATION)

Outcomes	Extension Study Treatment Arms					
	PL + DAC 150 mg		DAC 150 mg + Washout		DAC 150 mg for 2 Years	
	Year 1 (201)	Year 2 (202)	Year 1 (201)	Year 2 (202)	Year 1 (201)	Year 2 (202)
Per-protocol, N (%)	84 (100)		64 (100)		65 (100)	
ARR (95% CI)[a]	0.399 (0.287 to 0.555)	0.219 (0.137 to 0.351)	0.216 (0.131 to 0.356)	0.323 (0.203 to 0.515)	0.169 (0.094 to 0.302)	0.198 (0.111 to 0.354)
Relapsing patients, %[b]	32.1	18.6	18.8	24.9	15.4	16.0
CDP3M						
Patients who progressed, n (%[b])	8 (10)	4 (5)	2 (3)	6 (9)	3 (5)	6 (9)
MRI — Gd-enhancing lesions, mean (SD)						
Baseline lesions (Study 201)	1.7 (4.6)		1.9 (3.3)		1.8 (2.8)	
New lesions (week 52 — Study 201)	1.2 (2.4)		0.4 (1.1)		0.2 (0.4)	
New lesions (week 52 — Study 202)	0.1 (0.4)		0.2 (0.6)		0.3 (1.5)	
MRI — T2 hyperintense lesions, mean (SD)						
New/newly enlarging lesions (week 52 — Study 201)	7.3 (7.8)		5.0 (12.5)		2.0 (4.0)	
Total lesions (baseline — Study 201)	44.4 (36.4)		44.3 (38.9)		45.3 (35.0)	
New/newly enlarging lesions (week 52 — Study 202)	2.0 (3.7)		4.3 (8.9)		1.4 (5.3)	
MRI — Total lesion volume of T2 hyperintense lesions (mm^3), mean (SD)						
Change from baseline to week 52 (Study 202)	–829.14 (1,716.26)		–167.17 (1,747.13)		–548.70 (1,281.97)	
Percentage change from baseline to week 52 (Study 202)	–7.75 (21.95)		–0.78 (22.24)		–4.90 (25.94)	
MRI — Total volume of T1 hypointense lesions (mm^3), mean (SD)						
Change from baseline to week 52 (Study 202)	–78.65 (642.08)		–127.94 (735.56)		–353.89 (516.93)	
Percentage change from baseline to week 52 (Study 202)	–3.99 (35.54)		–5.51 (49.97)		–13.89 (18.09)	
MRI — Whole-brain volume (mL)						
Percentage change from baseline to week 52 (Study 201), mean (SD)	–0.703 (0.873)		–0.830 (0.770)		–0.682 (0.948)	
Subject years followed — adjusted rate (Study 201) (95% CI)	–0.705 (–0.895 to –0.515)		–0.856 (–1.074 to –0.638)		–0.628 (–0.846 to –0.411)	
Percentage change from baseline[c] to week 52	–0.760 (0.873)		–0.830 (0.770)		–0.682 (0.948)	

Outcomes	Extension Study Treatment Arms					
	PL + DAC 150 mg		DAC 150 mg + Washout		DAC 150 mg for 2 Years	
	Year 1 (201)	Year 2 (202)	Year 1 (201)	Year 2 (202)	Year 1 (201)	Year 2 (202)
(Study 202), mean (SD)						
Subject years followed — adjusted rate (Study 202) (95% CI)	–0.705 (–0.895 to –0.515)		–0.856 (–1.074 to –0.638)		–0.628 (–0.846 to –0.411)	

ARR = annualized relapse rate; CDP3M = confirmed disability progression for three months; CI = confidence interval; CSR = Clinical Study Report; DAC = daclizumab; Gd = gadolinium; INEC = Independent Neurology Evaluation Committee; MRI = magnetic resonance imaging; n = number of patients with event; N = number of patients; PL = placebo; SD = standard deviation.

[a] "The primary analysis of the ARR was based on INEC-confirmed relapses (Section 9.5.2.1.1), and it included data from all subjects in the per-protocol population until the end of the treatment period, a switch to alternative MS medication, or withdrawal from the study" (p. 105).[49]

[b] Estimated proportion.

[c] Baseline was the beginning of Study 202.

Source: CSR 205MS202.[49]

Patient-Reported Outcomes

Patient-reported outcomes were assessed in the PP population. Mean changes in the EuroQol 5-Dimensions questionnaire (EQ-5D) global VAS from baseline to week 52 were 0.92 (standard deviation of 18.27), 1.90 (standard deviation of 17.45), and 3.01 (standard deviation of 10.35) in the PL plus DAC 150 mg, DAC 150 mg plus washout, and DAC 150 mg for two years groups, respectively. The highest scores in the EQ-5D at week 52 were observed in the DAC 150 mg for two years group (75.77 [standard deviation of 19.69]); hence, patients in this group felt they were doing better. Mean changes in the Short Form (12) Health Survey (SF-12) physical component summary score from baseline to week 52 was 0.48 (standard deviation of 7.80), 0.81 (standard deviation of 7.17), and 1.41 (standard deviation of 5.78), while the mean changes in the SF-12 mental component summary score were –0.66 (standard deviation of 9.87), –0.68 (standard deviation of 9.72), and 1.28 (standard deviation of 9.57) in the PL plus DAC 150 mg, DAC 150 mg plus washout, and DAC 150 mg for two years groups, respectively. The largest improvement in both the SF-12 physical and mental scores was observed in the DAC 150 mg for two years group. Mean changes in the Multiple Sclerosis Impact Scale (MSIS)-29 physical score were 1.17 (standard deviation of 14.81), –0.51 (standard deviation of 13.84), and 0.55 (standard deviation of 11.23), while the mean changes in the MSIS-29 psychological scores were –1.51 (standard deviation of 18.38), 0.95 (standard deviation of 15.62), and –2.10 (standard deviation of 16.57) in the PL plus DAC 150 mg, DAC 150 mg plus washout, and DAC 150 mg for two years groups, respectively. Details regarding the patient-reported outcomes are presented in Table 15.

TABLE 15: PATIENT-REPORTED OUTCOMES OF EXTENSION STUDY 202 (PER-PROTOCOL POPULATION)

Outcomes	Extension Study Treatment Arms		
	PL + DAC 150 mg	DAC 150 mg + Washout	DAC 150 mg for 2 Years
Per-protocol, N (%)	84 (100)	64 (100)	65 (100)
EQ-5D global (VAS), mean (SD)			
Study 201 baseline	69.80 (18.84)	66.84 (18.20)	73.47 (17.73)
Study 202 baseline	69.26 (21.89)	72.29 (16.49)	75.41 (18.31)
Study 202 week 52	71.21 (21.60)	68.42 (21.19)	75.77 (19.69)
Changes from baseline[a] — baseline Study 202	–0.26 (15.31)	5.60 (15.62)	2.55 (11.12)
Changes from baseline[a] — week 52 Study 202	0.92 (18.27)	1.90 (17.45)	3.01 (10.35)
SF-12 PCS, mean (SD)			
Study 201 baseline	42.22 (9.60)	41.92 (9.73)	43.77 (9.69)
Study 202 baseline	42.29 (10.66)	43.50 (9.51)	43.69 (9.35)
Study 202 week 52	42.66 (10.40)	43.01 (9.27)	45.12 (9.43)
Changes from baseline[a] — baseline Study 202	0.16 (7.42)	1.68 (7.04)	–0.20 (6.56)
Changes from baseline[a] — week 52 Study 202	0.48 (7.80)	0.81 (7.17)	1.41 (5.78)
SF-12 MCS, mean (SD)			
Study 201 baseline	45.83 (9.84)	45.18 (11.54)	46.68 (10.34)
Study 202 baseline	44.74 (10.54)	45.73 (10.50)	48.05 (11.16)
Study 202 week 52	45.21 (10.50)	44.82 (9.91)	48.12 (9.97)
Changes from baseline[a] — baseline Study 202	–0.98 (8.36)	0.57 (9.91)	1.46 (9.51)
Changes from baseline[a] — week 52 Study 202	–0.66 (9.87)	–0.68 (9.72)	1.28 (9.57)
MSIS-29 physical score, mean (SD)			
Study 201 baseline	28.47 (23.53)	25.62 (20.69)	22.30 (17.56)
Study 202 baseline	30.21 (26.77)	24.91 (19.49)	24.33 (19.53)
Study 202 week 52	29.66 (24.90)	24.88 (18.71)	22.82 (19.11)
Changes from baseline[a] — baseline Study 202	1.74 (14.69)	–0.66 (11.23)	2.03 (11.84)
Changes from baseline[a] — week 52 Study 202	1.17 (14.81)	–0.51 (13.84)	0.55 (11.23)
MSIS-29 psychological score, mean (SD)			
Study 201 baseline	31.76 (24.35)	28.09 (21.45)	26.81 (20.61)
Study 202 baseline	31.90 (24.54)	27.22 (20.51)	26.53 (22.98)

Outcomes	Extension Study Treatment Arms		
	PL + DAC 150 mg	DAC 150 mg + Washout	DAC 150 mg for 2 Years
Study 202 week 52	30.38 (24.01)	28.49 (17.87)	24.75 (21.41)
Changes from baseline[a] — baseline Study 202	0.14 (13.83)	–0.89 (14.50)	–0.33 (15.4)
Changes from baseline[a] — week 52 Study 202	–1.51 (18.38)	0.95 (15.62)	–2.10 (16.57)

CSR = Clinical Study Report; DAC = daclizumab; EQ-5D = EuroQol 5-Dimensions questionnaire; MCS = mental component summary; MSIS-29 = Multiple Sclerosis Impact Scale-29; N = number of patients; PCS = physical component summary; PL = placebo; SD = standard deviation; SF-12 = Short Form (12) Health Survey; VAS = visual analogue scale.
[a] Change from Study 201 baseline.
Source: CSR 205MS202[49].

Safety

Study 202

With regard to patients in the PL plus DAC 150 mg group, 71% (n = 61) of patients experienced at least one AE. In addition, 81% (n = 70) and 66% (n = 57) of patients experienced at least one AE in the DAC 150 mg plus washout and DAC 150 mg for two years groups, respectively. The most common AEs were MS relapse (incidence ranging between 16% and 30%), followed by nasopharyngitis (ranging between 12% and 14%), and upper respiratory tract infection (ranging between 7% and 10%). The proportion of patients experiencing at least one serious adverse event (SAE) ranged between 17% and 21%, with MS relapse being the most common (incidence ranging between 10% and 14%). Treatment discontinuations due to AEs ranged between 2% and 8% and there were no deaths in these three treatment groups. Detailed safety results are provided in Table 16.

EXTEND

With regard to patients in the IFN beta-1a plus DAC 150 mg group, treatment-emergent SAEs (other than MS relapse) at a median of 18 months were observed in 9% of patients. This compares to the 10% of patients (exposed to IFN beta-1a at a median of 26 months in DECIDE) who experienced treatment-emergent SAEs. The overall safety profile was determined to be consistent in both EXTEND and DECIDE.

TABLE 16: SAFETY RESULTS OF EXTENSION STUDY 202

Outcomes	Extension Study Treatment Arms		
	PL + DAC 150 mg	DAC 150 mg + Washout	DAC 150 mg for 2 Years
Safety set, N (%)	86 (100)	86 (100)	86 (100)
Patients with ≥ 1 AE	61 (71)	70 (81)	57 (66)
AEs occurring in ≥ 5% of patients, n (%)			
MS relapse	16 (19)	26 (30)	14 (16)
Nasopharyngitis	12 (14)	11 (13)	10 (12)
URTI	6 (7)	7 (8)	9 (10)
Headache	5 (6)	5 (6)	3 (3)
Pharyngitis	5 (6)	4 (5)	5 (6)
Rash	3 (3)	5 (6)	4 (5)
Oral herpes	5 (6)	6 (7)	1 (1)
ALT increased	2 (2)	3 (3)	4 (5)
Fatigue	5 (6)	2 (2)	3 (3)

Outcomes	Extension Study Treatment Arms		
	PL + DAC 150 mg	DAC 150 mg + Washout	DAC 150 mg for 2 Years
Viral RTI	3 (3)	5 (6)	1 (1)
UTI	3 (3)	5 (6)	3 (3)
Diarrhea	4 (5)	1 (1)	5 (6)
Bronchitis	4 (5)	2 (2)	2 (2)
Allergic dermatitis	1 (1)	4 (5)	3 (3)
Influenza	2 (2)	4 (5)	4 (5)
Gamma-glutamyl transferase increased	2 (2)	2 (2)	4 (5)
Anemia	0	4 (5)	2 (2)
Influenza-like illness	2 (2)	4 (5)	0
Patients with ≥ 1 SAE	15 (17)	18 (21)	15 (17)
MS relapse	9 (10)	12 (14)	9 (10)
Anemia	0	0	1 (1)
Drug hypersensitivity	0	0	1 (1)
Hepatic steatosis	0	1 (1)	0
WDAE, n (%)			
Treatment	3 (3)	7 (8)	2 (2)
Study	2 (2)	3 (3)	2 (2)
Deaths	0	0	0

AE = adverse event; ALT = alanine transaminase; CSR = Clinical Study Report; DAC = daclizumab; MS = multiple sclerosis; n = number of patients with event; N = number of patients; PL = placebo; RTI = respiratory tract infection; SAE = serious adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.
Source: CSR 205MS202.[49]

Critical Appraisal

The main limitations inherent to this extension study were the lack of a control group and the lack of power necessary to perform meaningful statistics. While the investigators sought to maintain the blinding (all patients and health care providers were blinded), all patients (regardless of their original group allocation of placebo, DAC 150 mg, or DAC 300 mg administered every four weeks in SELECT) were allocated to receive either DAC 150 mg or DAC 300 mg, thereby precluding any ability to ascertain statistical and clinical significance between treatment and control groups. In addition, while 90% of patients who completed SELECT enrolled into the extension study, there were smaller numbers of patients (when compared with that of the main trial) in each of the six separate treatment groups (three that included the administration of DAC 150 mg and three that included the administration of DAC 300 mg). The small sample sizes per group does not provide a lot of confidence associated with the long-term administration of DAC 150 mg every four weeks or in patients who have had a washout period and then resume with DAC 150 mg every four weeks.

3. Summary

It appears that measures of MS disease activity (e.g., ARR, estimated proportion of relapses, the number of Gd-enhancing lesions on MRI, and whole-brain volume [mL]) in Study 202 were similar to those at the end of SELECT. There was a decrease in ARR in the EXTEND study in patients continuing to receive DAC 150 mg every four weeks. Likewise, the safety profile for DAC in Study 202 resembled that observed in SELECT, while those in EXTEND were similar to DECIDE. However, the lack of a comparator group and the smaller cohort of patients receiving DAC 150 mg every four weeks for two years (n = 65) (SELECT) makes interpretation of the longer-term data very difficult. Therefore, it is uncertain what the long-term potential benefits and harms associated with DAC are.

APPENDIX 7: SUMMARY OF INDIRECT TREATMENT COMPARISONS

A1.1 Introduction

A1.1.1 Background

Given the absence of head-to-head studies that have compared daclizumab (DAC) beta against other relevant disease-modifying therapies (DMTs) used to treat relapsing-remitting multiple sclerosis (RRMS), the objective of this appendix was to summarize and critically appraise the evidence available regarding the comparative efficacy and safety of DAC beta versus the interferon (IFN) betas (pegylated [peg], 1a, 1b), glatiramer acetate, dimethyl fumarate, fingolimod, teriflunomide, natalizumab, and alemtuzumab through indirect treatment comparison (ITC) using network meta-analysis (NMA) methodology.

A1.1.2 Methods

Adult patients with a confirmed diagnosis of RRMS were evaluated in this review. Two ITCs were assessed: the unpublished ITC submitted by the manufacturer[50] and a published ITC by Tramacere et al.[16] that was identified in a separate literature search.

A1.2 Description of Identified ITCs

The manufacturer submitted an ITC[50] that sought to observe the relative clinical efficacy and safety of DAC beta 150 mg administered every four weeks to all approved DMTs that have been approved at the European Union (EU)–approved dosage regimen for patients with RRMS. The manufacturer performed a systematic review in order to identify relevant studies to be included in the ITC. While their list was long in terms of desired outcomes, they were only able to include the annualized relapse rate (ARR), confirmed disability progression at three and six months, any serious adverse events (SAEs), and any cause of treatment discontinuations in their ITC. Details regarding the inclusion criteria for the manufacturer-submitted ITC are presented in Table 17.

Tramacere et al.[16] performed an ITC in order to compare the benefit and acceptability of IFN beta-1b, IFN beta-1a (Avonex, Rebif), glatiramer acetate, mitoxantrone, peg-IFN beta-1a, dimethyl fumarate, fingolimod, natalizumab, teriflunomide, alemtuzumab, ocrelizumab, laquinimod, daclizumab, azathioprine, and immunoglobulins for the treatment of patients with RRMS. In addition, they sought to ascertain the ranking of these treatments according to their benefit and acceptability. Details regarding the inclusion criteria for the Tramacere et al. ITC are presented in Table 17.

TABLE 17: INCLUSION CRITERIA FOR THE MANUFACTURER-SUBMITTED ITC AND TRAMACERE ET AL.

	Manufacturer's ITC	Tramacere et al.
Patient population	• Adults ≥ 18 years with a confirmed diagnosis of RRMS or RES RRMS	• Adults ≥ 18 years of age with RRMS according to the Poser or McDonald diagnostic criteria
Intervention	• Daclizumab (Zinbryta)	Included the following irrespective of dose and licensing: • IFN beta-1a (Avonex, Rebif) • IFN beta-1b • Peg-IFN beta-1a • Glatiramer acetate • Natalizumab
Comparators[a]	• IFN beta-1a (Avonex) 30 mcg once weekly • Peg-IFN beta-1a (Plegridy) 125 mcg q.2.w. • IFN beta-1a 22 mcg or 44 mcg (Rebif) • IFN beta-1b (Betaseron) 250 mcg q.o.d.	

	Manufacturer's ITC	Tramacere et al.
	• Glatiramer acetate (Copaxone) 20 mg q.d. (or 40 mg t.i.w.[b]) • Dimethyl fumarate (Tecfidera) 240 mg b.i.d. • Fingolimod (Gilenya) 0.5 mg q.d. • Teriflunomide (Aubagio) 14 mg q.d. • Natalizumab (Tysabri) 300 mg q.4.w. • Alemtuzumab (Lemtrada) 12 mg q.d. • Ocrelizumab[b] • Cladribine (Leustat)[c] • Standard of care (± placebo)	• Mitoxantrone • Fingolimod • Teriflunomide • Dimethyl fumarate • Alemtuzumab • Daclizumab • Ocrelizumab • Laquinimod[d] • Azathioprine • Immunoglobulins
Outcomes	***Clinical outcomes:*** • ARR • CDP sustained for 3 months • CDP sustained for 6 months • Annualized steroid-treated relapse rate • Change in EDSS score from baseline • Proportion of patients with relapse • Proportion of patients remaining relapse-free • QoL: SF-36, global VAS, MSIS • Health utility: EQ-5D, EQ VAS ***Tolerability outcomes:*** • Discontinuations due to any cause • Discontinuations due to AEs ***Safety outcomes:*** • Any AEs • Any SAEs • Mortality • Any other AEs occurring in ≥ 5% in at least one treatment group	***Efficacy outcomes:*** *Primary outcome:* • Clinical benefit as measured according to the following: ○ Proportion of new relapses[e] over 12, 24, and 36 months after randomization or at study end ○ Disability worsening[f] over 24 or 36 months after randomization or at study end • Acceptability as measured by discontinuations due to AEs ***Secondary outcome:*** • Total SAEs
Study design	Published or unpublished prospective RCTs	RCTs > 6 months in duration

AE = adverse event; b.i.d. = twice daily; CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions questionnaire; EQ VAS = EuroQol Visual Analogue Scale; ITC = indirect treatment comparison; IFN = interferon; MS = multiple sclerosis; MSIS = Multiple Sclerosis Impact Score; peg = pegylated; q.2.w. = once every two weeks; q.4.w. = once every four weeks; q.d. = once daily; q.o.d. = every other day; QoL = quality of life; RCT = randomized controlled trial; RES = rapidly evolving severe; RRMS = relapsing-remitting multiple sclerosis; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; t.i.w. = three times a week; VAS = visual analogue scale.

[a] European approved dosage.

[b] At the time of this review, ocrelizumab is under review by Health Canada.

[c] Not approved for treating MS in Canada.

[d] Not available in Canada.

[e] "A relapse is defined as newly developed or recently worsened symptoms of neurologic dysfunction that last for at least 24 hours, occurring in the absence of fever or other acute diseases and separated in time from any previous episode by more than 30 days" (p. 24).[16]

[f] "Worsening is defined as at least a one-point EDSS increase or a 0.5-point increase if the baseline EDSS was greater than or equal to 5.5, confirmed during two subsequent neurological examinations separated by at least a six-month interval free of attacks" (p. 24).[16]

Sources: Manufacturer-submitted ITC[50] and Tramacere et al.[16]

A1.2.1 Review and Appraisal of ITCs

A1.2.2 Review of Manufacturer-Submitted ITC[50]

Study Eligibility and Selection Process

The manufacturer submitted an ITC based on a systematic review that compared DAC beta 150 mg every four weeks with all DMTs and their respective dosage regimens that were approved in Europe; these included IFN beta-1a 30 mcg once weekly, IFN beta-1a 22 mcg (and 44 mcg) three times a week, peg-IFN beta-1a 125 mcg every two weeks, IFN beta-1b 250 mcg every other day, glatiramer acetate 20 mg once daily or 40 mg three times per week, teriflunomide 14 mg once daily, dimethyl fumarate 240 mg twice daily, fingolimod 0.5 mg once daily, natalizumab 300 mg every four weeks, and alemtuzumab 12 mg once daily. The objective and rationale for performing this ITC were presented clearly. The European dosage regimens all corresponded to those approved by Health Canada. A systematic search of randomized controlled trials (RCTs) was performed by searching multiple electronic databases in addition to searching for existing systematic reviews, protocols, Health Technology Assessments, guidance, and guidelines in the full area of both RRMS and secondary-progressive MS. However, only those studies that focused on RRMS were included in the ITC, with studies that examined cladribine or ocrelizumab not being included (as, at the time of performing this ITC, they had not yet been approved in Europe). The original searches for this review were performed in October 2014 and were followed by two additional updates, one in November 2015 and the other in February 2016.

A full list of the outcomes of interest for the systematic literature review was outlined in Table 17. For dichotomous outcomes, sufficient data to calculate the odds ratio or risk ratio were extracted (including number of patients achieving the outcome per study group, total number of patients per study group, analysis population used [true intention-to-treat (ITT), modified ITT, per-protocol (PP), and unknown]). For rate outcomes, the authors attempted to extract sufficient data to calculate the risk ratio, and the annualized relapse rate (ARR) per arm was extracted as the total number of relapses and total number of patient-years of follow-up. Other information related to relapses — such as the reported risk ratio or number of patients with zero, one, two, three, or greater than or equal to four relapses — were also extracted, where available. Finally, for time-to-event outcomes (e.g., disability progression) the authors attempted to extract the hazard ratio with 95% confidence intervals if available. With regard to the systematic review, two independent reviewers assessed titles and abstracts and potentially relevant articles were retrieved for full-text review. Eligible articles were selected based on the inclusion and exclusion criteria provided by the manufacturer, with discrepancies resolved through discussion and/or a third reviewer. Data extraction was also performed in duplicate, with any discrepancies resolved through discussion or a third reviewer.

The NMA did not include all of the aforementioned outcomes listed; instead only the ARR and confirmed disability progression at three and six months were included as efficacy outcomes. Safety end points that were included in the NMA analysis included any SAEs and treatment discontinuation due to any cause. The ITC attempted to examine outcomes at one and two–year follow-up times; however, there were discrepancies in these times between studies. Studies were therefore included in the analysis if their follow-up times for one year were reported at either 11 (48 weeks) or 12 months (52 weeks), while those studies reporting outcomes ranging from 22.2 months (96 weeks) to 24.9 months (108 weeks) were included for the two-year follow-up time point. A protocol modification in May 2015 allowed for other time points than 12 or 24 months to be considered for the ARR, as this outcome was presented as relapses per patient year (and there were discrepancies between studies). Complete lists of included and excluded studies, along with reasons for exclusion if applicable, were also provided.

Methodological quality of the included studies was assessed using the Cochrane Collaboration risk of bias tool, with results presented narratively and in tabular form. In addition, the authors discussed the study and patient baselines characteristics in detail. Head-to-head meta-analyses were performed using a frequentist random-effects model and accompanying forest plots per outcome, along with sensitivity analyses, were provided. In addition, fixed effects models were performed in a sensitivity analysis to observe whether results were similar between the two models. Statistical heterogeneity in the direct head-to-head meta-analyses was ascertained using the I^2 statistic, whereas clinical heterogeneity was ascertained in the assessment of both study and patient characteristics of the included studies.

ITC Methods

The inclusion of studies into the ITC NMA was conducted in two stages: the first stage comprised including studies based on the inclusion criteria (Table 17), while in the second stage the authors considered inclusion based on the homogeneity of the trials (if trials were sufficiently homogeneous to be compared), the similarity of the trials (in this case the authors examined diagnostic criteria, age of patients, proportion of male versus female patients, the Expanded Disability Status Scale [EDSS] scores, disease duration, number of relapses before enrolment, and proportion of previously treated patients), and their consistency. The base-case analysis focused on the overall RRMS population as each study reported them.

The NMA was performed using a Bayesian approach and the gemtc package. A burn-in of 50,000 simulations was performed, along with a further run of 50,000 simulations in order to obtain parameter estimates. Model convergence was assessed using the Brooks-Gelman-Rubin statistic and model fit was assessed using the residual deviance and the deviance information criterion (DIC). A random-effects model was chosen for the primary analysis with a fixed-effect model run to ensure transparency in the process. The odds ratio (SAEs and treatment discontinuations due to any cause), HRs (disability progression confirmed at three and six months), and RRs (ARRs) were reported and accompanied by their 95% credible intervals for the Bayesian analysis or 95% confidence intervals for the frequentist method. With regard to the primary analysis of ARR, pooled data from studies that reported randomized outcome data for follow-up periods of greater than 12 months were utilized as the authors felt it reasonable to combine data across multiple time points for this outcome (time-to-event outcome).

In order to ascertain whether the Bayesian methods were sensitive to the choice of priors, the authors performed multiple sensitivity analyses using alternative prior distributions; these included uniform distributions with different ranges (uniform [0, 0.5], uniform [0, 1], uniform [0, 3], and uniform [0, 5]). For the purposes of this review (while multiple subgroup analyses were performed), only those subgroups that pertained to the requirements or were of particular interest will be mentioned. The subgroup analyses of interest that were performed (or were planned to be performed) included patients who were non-responders to previous treatment, treatment-naive patients (those not receiving previous DMTs), treatment-experienced patients (those defined as having received prior DMTs), and used the 144-week end of study for DECIDE to observe any possible changes between year one and year two values. Heterogeneity in the NMA was assessed based on an evaluation of study design and patient characteristics, with only those studies that were considered similar enough to combine being included in the final networks. Inconsistency for the NMAs was ascertained by an assessment of whether the networks presented with any closed loops and then, in those networks, inconsistency was assessed using node splitting. With regard to the handling of missing data, missing values were calculated using the available data and standard methods.

TABLE 18: SELECT STUDY CHARACTERISTICS FOR STUDIES INCLUDED IN THE INDIRECT TREATMENT COMPARISON

Study ID	N	Treatment Arms	Randomized Patients[a]	Diagnosis Criteria	Age (Years)	EDSS	Previous Relapse
ADVANCE	1,512	Peg-IFN beta-1a 125 mcg q.4.w.	500	McDonald 2005	18 to 65	0 to 5.0	≥ 2 in previous 3 years with ≥ 1 within past 12 months
		Peg-IFN beta-1a 125 mcg q.2.w.	512				
		PL	500				
AFFIRM	942	NAT 300 mg q.4.w.	627	McDonald	18 to 50	0 to 5.0	> 1 in 12 months before study
		PL	315				
BEYOND	2,244	GA 20 mg q.d.	448	McDonald	18 to 55	0 to 5.0	≥ 1 in year before study
		IFN beta-1b 250 mcg q.o.d.	897				
		IFN beta-1b 500 mcg q.o.d.	899				
Bornstein (1987)	50	GA 20 mg q.d.	25	Poser	20 to 35	0 to 6.0	≥2 exacerbations in 2 years before admission
		PL	25				
BRAVO	1,331	IFN beta-1a 30 mcg q.w.	447	McDonald 2005	18 to 55	0 to 5.5	≥ 1 in previous year, 2 in previous 2 years, or 1 in previous 1 to 2 years and 1 or more Gd-enhancing lesions in the previous year
		PL	450				
		Laquinimod 0.6 mg q.d.	434				
Calabrese (2012)	165	GA, 20 mg q.d.	55	McDonald 2005	18 to 55	0 to 5.0	NR
		IFN beta-1a 30 mcg q.w. weekly	55				
		IFN beta-1a 44 mcg t.i.w.	55				
CAMMS223	334	IFN beta-1a 44 mcg t.i.w.	111	McDonald	NR	0 to 3.0	≥ 2 clinical episodes during previous 2 years
		ALM 12 mg q.d.	113				
		ALM 24 mg q.d.	110				
CARE-MS I	581	IFN beta-1a 44 mcg t.i.w.	195	McDonald 2005	18 to 50	0 to 3.0	≥ 2 in previous 2 years and ≥ 1 in previous year
		ALM 12 mg q.d.	386				
CARE-MS-II	840	IFN beta-1a 44 mcg t.i.w.	231	McDonald 2005	18 to 50	0 to 3.0	≥ 2 attacks in previous 2 years with ≥ 1 in previous year
		ALM 12 mg q.d.	436				
		ALM 24 mg q.d.	173				
CombiRx	509	GA 20 mg q.d.	259	Other	18 to 60	0 to 5.5	≥ 2 exacerbations in prior 3 years, where 1 exacerbation could be an MRI change
		IFN beta-1a 30 mcg q.w.	250				
CONFIRM	1,430	DMF 240 mg b.i.d., q.o.d.	362	McDonald 2005	18 to 55	0 to 5.0	≥ 1 in previous 12 months or ≥ 1 Gd-enhancing lesion 0 to 6 weeks before randomization
		DMF 240 mg t.i.d.	345				
		GA 20 mg q.d.	360				
		PL	363				

Study ID	N	Treatment Arms	Randomized Patients[a]	Diagnosis Criteria	Age (Years)	EDSS	Previous Relapse
Copolymer I Study	251	GA 20 mg q.d.	125	Poser	18 to 45	0 to 5.0	Onset of relapse > 1 year before randomization
		PL	126				
DECIDE	1,841	DAC 150 mg q.4.w.	919	McDonald 2005	18 to 55	0 to 5.0	≥ 1 clinical relapse in the 12 months before randomization OR ≥ 1 clinical relapses and 1 or more new MRI lesions (Gd-enhancing and/or T2 hyperintense lesion) within the previous 2 years.
		IFN beta-1a 30 mcg q.w.	922				
DEFINE	1,237	DMF 240 mg b.i.d.	411	McDonald 2005	18 to 55	0 to 5.0	≥ 1 within 12 months before randomization or a brain MRI scan, obtained within 6 weeks before randomization, that showed ≥ 1 Gd-enhancing lesion
		DMF 240 mg t.i.d.	416				
		PL	410				
Etemadifar (2006)	90	IFN beta-1a 30 mcg q.w.	30	Poser	15 to 50	0 to 5.0	≥ 2 within 2-year period to treatment
		IFN beta-1a 44 mcg t.i.w.	30				
		IFN beta-1b 250 mcg q.o.d.	30				
EVIDENCE	677	IFN beta-1a 30 mcg q.o.d.	338	Poser	NR	0 to 5.5	≥ 2 exacerbations of MS in prior 2 years
		IFN beta-1a 44 mcg t.i.w.	339				
FREEDOMS	1,272	Fingolimod 0.5 mg q.d.	425	McDonald 2005	18 to 55	0 to 5.5	≥ 1 in previous year or ≥ 2 in previous 2 years
		Fingolimod 1.25 mg q.d.	429				
		PL	418				
FREEDOMS II	1,083	Fingolimod 0.5 mg q.d.	358	McDonald 2005	18 to 55	0 to 5.5	≥ 1 in previous year or ≥ 2 in previous 2 years
		Fingolimod 1.25 mg q.d.	370				
		PL	355				
GALA	1,404	GA 40mg t.i.w.	943	McDonald 2005	18 to 55	0 to 5.5	1 in 12 months before screening, 2 in 24 months before screening, or 1 between 12 and 24 months before screening
		PL	461				
Gobbi (2013)	19	IFN beta-1b 250 mcg q.o.d.	9	McDonald 2005	18 to 60	NR	Free from relapses and disability progression for at least 6 months and no Gd-enhancing lesions on baseline MRI
		NAT 300 mg q.4.w.	10				
IFNB MS study	372	IFN beta-1b 250 mcg q.o.d.	124	Poser	18 to 50	0 to 5.5	≥ 2 acute exacerbations during previous 2 years
		IFN beta-1b 50 mcg q.o.d.	125				
		PL	123				
INCOMIN	188	IFN beta-1a 30 mcg q.w.	92	Poser	18 to 50	1 to 3·5	2 during preceding 2 years
		IFN beta-1b 250 mcg q.o.d.	96				
MSCRG	301	IFN beta-1a 30 mcg q.w.	158	Poser	18 to 55	1.0 to 3.5	≥ 2 within previous 3 years
		PL	143				

Study ID	N	Treatment Arms	Randomized Patients[a]	Diagnosis Criteria	Age (Years)	EDSS	Previous Relapse
PRISMS	560	IFN beta-1a 44 mcg t.i.w.	184	Schumacher	NR	0 to 5.0	≥ 2 in preceding 2 years
		IFN beta-1a 22 mcg t.i.w.	189				
		PL	187				
REGARD	764	GA 20 mg q.d.	378	McDonald	18 to 60	0 to 5.5	≥ 1 in preceding 12 months
		IFN beta-1a 44 mcg t.i.w.	386				
SELECT	621	DAC 150mg q.4.w.	208	McDonald 2005	18 to 55	0 to 5.0	≥ 1 relapse within the 12 months before randomization
		DAC 300mg q.4.w.	209				
		PL	204				
TEMSO	1,088	TER 7 mg q.d.	366	McDonald	18 to 55	0 to5.5	≥ 2 in previous 2 years or 1 during preceding year
		TER 14 mg q.d.	359				
		PL	363				
TENERE	324	IFN beta-1a 44 mcg t.i.w.	104	McDonald 2005	≥ 18	0 to 5.5	NR
		TER 7 mg q.d.	109				
		TER 14 mg q.d.	111				
TOWER	1,169	TER 7 mg q.d.	408	McDonald 2005	18 to 55	0 to 5.5	≥ 1 in previous year or ≥ 2 in previous 2 years
		TER 14 mg q.d.	372				
		PL	389				
TRANS-FORMS	1,292	IFN beta-1a 30 mcg q.w.	435	McDonald 2005	18 to 55	0 to 5.0	≥ 1 during previous year or ≥ 2 during previous 2 years
		Fingolimod 0.5 mg q.d.	431				
		Fingolimod 1.25 mg q.d.	426				

ALM = alemtuzumab; b.i.d. = twice daily; DAC = daclizumab; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; Gd = gadolinium; ITC = indirect treatment comparison; IFN = interferon; MRI = magnetic resonance imaging; MS = multiple sclerosis; N = number of patients; NAT = natalizumab; NR = not reported; OR = odds ratio; peg = pegylated; PL = placebo; q.2.w. = once every two weeks; q.4.w. = once every four weeks; q.d. = once daily; q.o.d. = every other day; q.w. = once weekly; TER = teriflunomide; t.i.d. = three times a day; t.i.w. = three times a week.

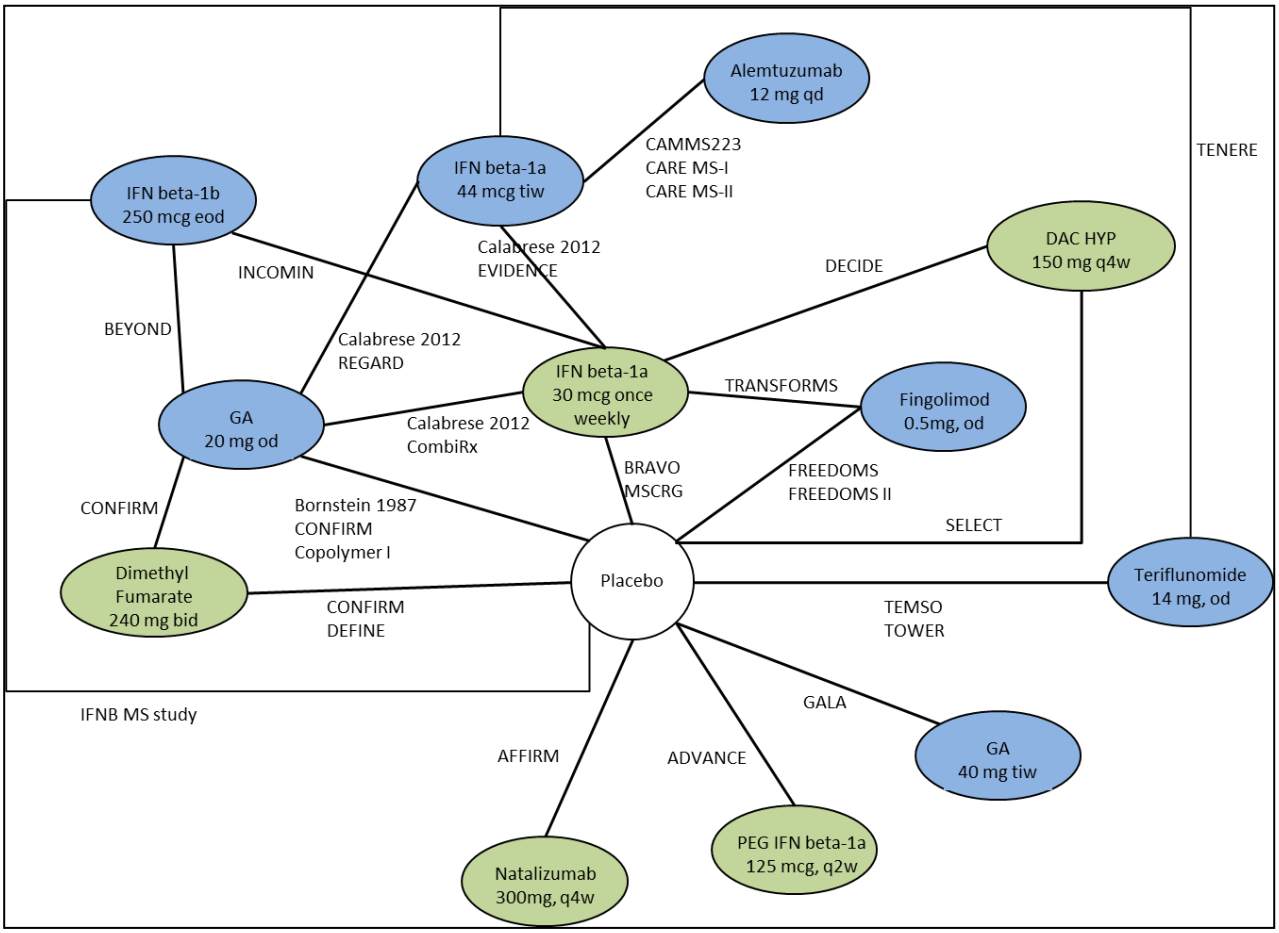
[a] Not necessarily those treated.

Source: Manufacturer-submitted ITC.[50]

Evidence Networks

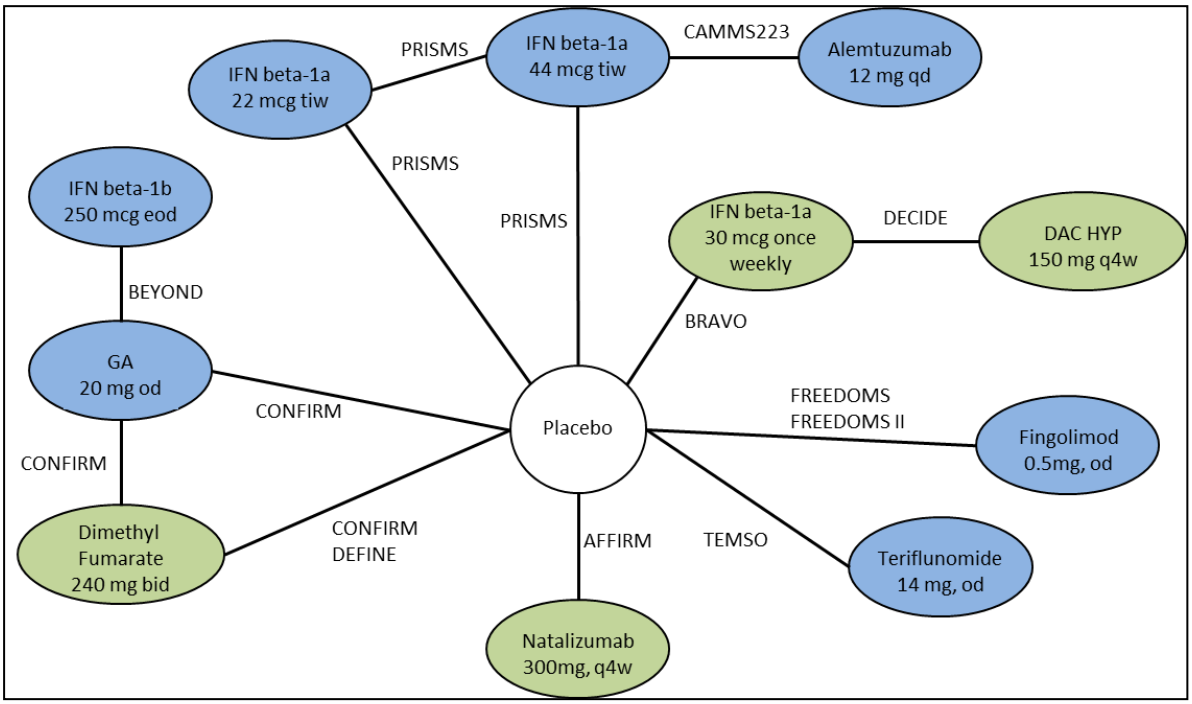
Evidence networks were presented separately for each outcome of interest. These are presented in Figure 2 through Figure 6.

FIGURE 2: OVERALL NETWORK FOR THE ANNUALIZED RELAPSE RATE



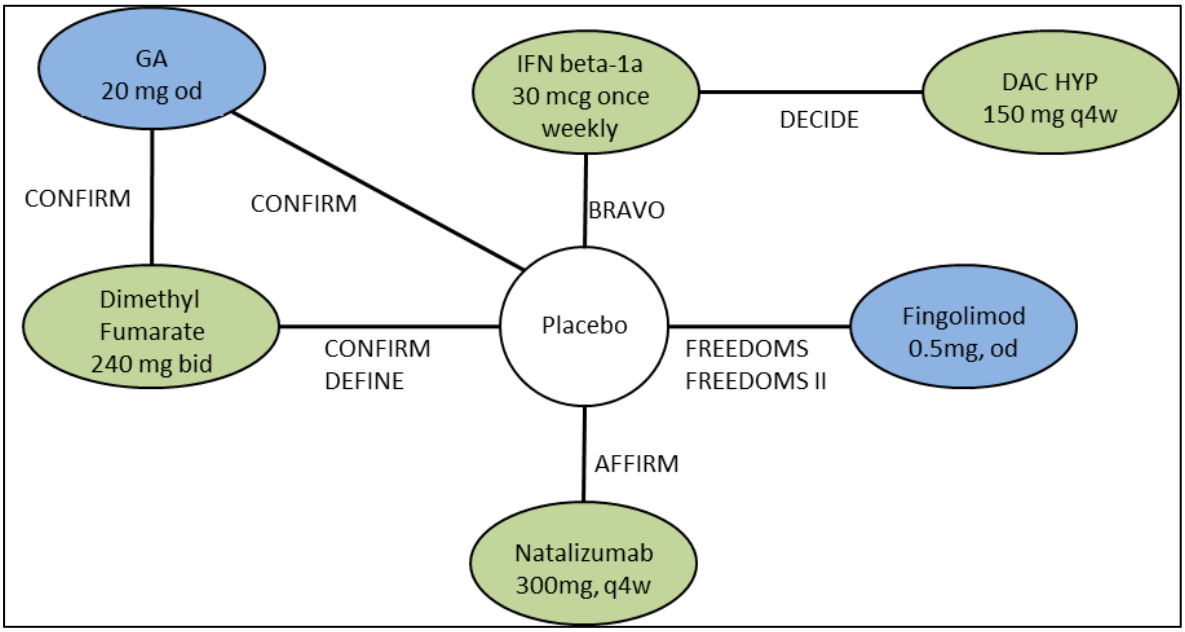
b.i.d. = twice daily; DAC = daclizumab; eod = every other day; GA = glatiramer acetate; ITC = indirect treatment comparison; IFN = interferon; MS = multiple sclerosis; od = once daily; peg = pegylated; q.2.w. = once every two weeks; q.4.w. = once every four weeks; t.i.w. = three times a week.
Source: Manufacturer-submitted ITC.[50]

FIGURE 3: OVERALL NETWORK FOR DISABILITY PROGRESSION CONFIRMED AFTER THREE MONTHS



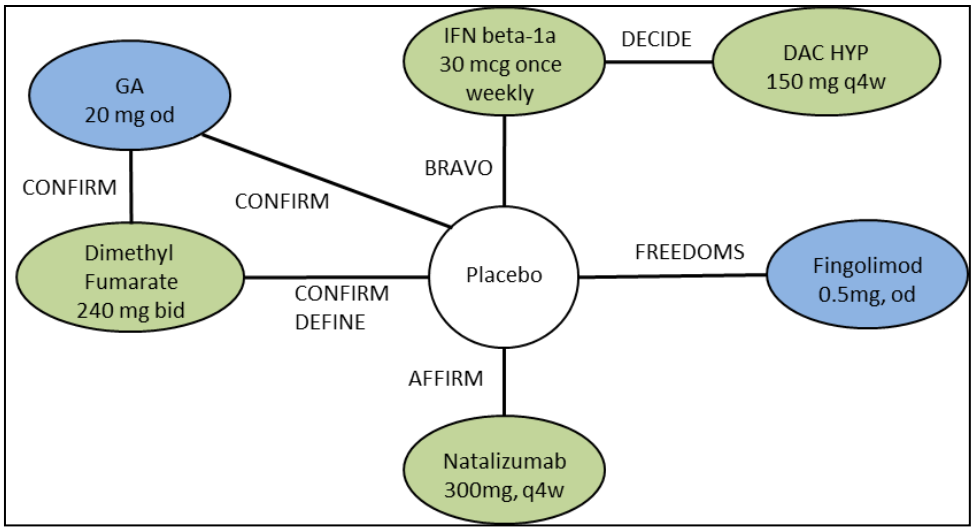
b.i.d. = twice daily; DAC = daclizumab; eod = every other day; GA = glatiramer acetate; HYP = high yield process; ITC = indirect treatment comparison; IFN = interferon; od = once daily; q.4.w. = once every four weeks; t.i.w. = three times a week.
Source: Manufacturer-submitted ITC.[50]

FIGURE 4: OVERALL NETWORK FOR DISABILITY PROGRESSION CONFIRMED AFTER SIX MONTHS



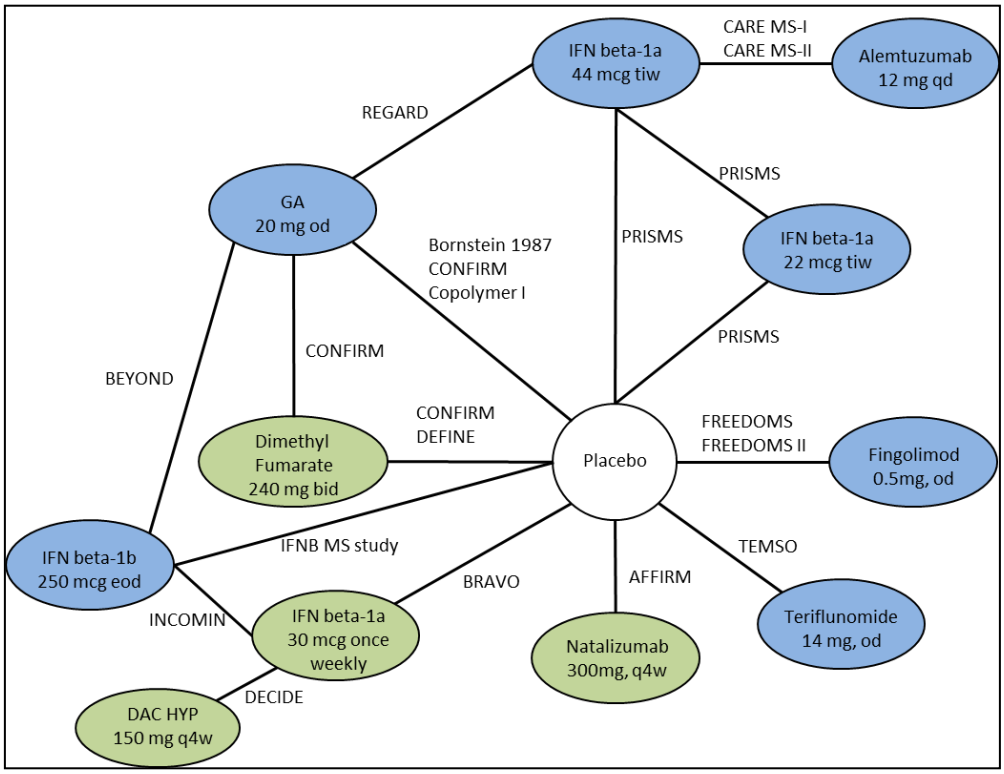
b.i.d. = twice daily; DAC = daclizumab; GA = glatiramer acetate; HYP = high yield process; ITC = indirect treatment comparison; IFN = interferon; od = once daily; q.4.w. = once every four weeks; q.d. = once daily.
Source: Manufacturer-submitted ITC.[50]

FIGURE 5: OVERALL NETWORK FOR ANY SERIOUS ADVERSE EVENT AT 24 MONTHS



b.i.d. = twice daily; DAC = daclizumab; GA = glatiramer acetate; HYP = high yield process; ITC = indirect treatment comparison; IFN = interferon; od = once daily; q.4.w. = once every four week.
Source: Manufacturer-submitted ITC.[50]

FIGURE 6: OVERALL NETWORK FOR TREATMENT DISCONTINUATION DUE TO ANY CAUSE



b.i.d. = twice daily; DAC = daclizumab; GA = glatiramer acetate; HYP = high yield process; ITC = indirect treatment comparison; IFN = interferon; MS = multiple sclerosis; od = once daily; q.4.w. = once every four weeks; t.i.w. = three times a week.
Source: Manufacturer-submitted ITC.[50]

Results

Study and Patient Characteristics

A total of 30 studies were included in the mixed treatment comparison (MTC) for the analysis of ARR, while 27 studies were eligible for the inclusion in the analysis of other outcomes. With regard to study comparisons, one study compared the efficacy and safety of peg-IFN 125 mcg every two weeks to placebo (ADVANCE), two studies compared natalizumab 300 mg every four weeks against either placebo or IFN beta-1b 250 mcg every other day (AFFIRM, Gobbi 2013), seven studies compared glatiramer acetate 20 mg once daily to various comparators (IFN beta-1b 250 mcg every other day [BEYOND], placebo [Bornstein 1987, Coploymer I study], IFN beta-1a 30 mcg once weekly [Calabrese 2012, CombiRx], or IFN beta-1a 44 mcg twice per week [REGARD]), one study compared glatiramer acetate 40 mg three times a week to placebo (GALA), five studies compared IFN beta-1a 30 mcg once weekly to various comparators (placebo [BRAVO, MSCRG], IFN beta-1b 250 mcg every other day [INCOMIN], IFN beta-1a 44 mcg three times a week and IFN beta-1b 250 mcg every other day [Etemadifar 2006], or only beta-1a 44 mcg three times a week [EVIDENCE]), three studies compared alemtuzumab 12 mg once daily to IFN beta-1av 44 mcg three times a week (CAMMS223, CARE-MS-I, CARE-MS-II), two studies compared DAC beta 150 mg every four weeks to various comparators (IFN beta-1a 30 mcg once weekly [DECIDE] or placebo [SELECT]), two studies compared dimethyl fumarate 240 mg twice daily to various comparators (glatiramer acetate 20 mg once daily and placebo [CONFIRM], or placebo alone [DEFINE]), three studies compared fingolimod 0.5 mg once daily to various comparators (placebo [FREEDOMS, FREEDOMS II] or IFN beta-1a 30 mcg once weekly [TRANSFORMS]), one studies compared IFN beta-1b 250 mcg every other day to placebo (IFNB MS study), one study compared IFN beta-1a 22 mcg three times a week to both IFN beta-1a 44 mcg three times a week and placebo (PRISMS), and three studies compared teriflunomide 14 mg once daily to various comparators (placebo [TEMSO, TOWER] or IFN beta-1a 44 mcg three times a week [TENERE]).

Risk of bias was assessed using the Cochrane risk of bias tool. Nine of the included trials were rated as having a low risk of bias (AFFIRM, BEYOND, CONFIRM, DECIDE, FREEDOMS, FREEDOMS II, GALA, SELECT, TOWER). The major potential source of bias in the trials was insufficient blinding, with approximately a third of studies not adequately blinding the patients, caregivers, and/or assessors (Bornstein 1987, BRAVO, CAMMS223, CARE MS-I, CARE MS-II, Etemadifar 2006, EVIDENCE, Gobbi 2013, INCOMIN, REGARD, TENERE, TRANSFORMS). Selective outcome reporting was a potential source of bias in four of the included studies (CARE MS-II, Gobbi 2013, MSCRG, TEMSO). The authors were unable to rate at least one of the seven domains in the majority of trials.

Numerous patient characteristics were provided. The total number of patients enrolled in the studies ranged between 19 and 1,841, with trial group patient numbers ranging between nine and 992. The mean patient age was between 30 and 40 years (with the standard deviation ranging between 1.2 and 10.6), with the exception of Etemadifar 2006 and Gobbi 2013, where the mean age was below 30 years and a median age in one group was 43, respectively. The proportion of female patients in the included studies ranged between 65% and 75%, with the exception of Bornstein 1987 (less than 65%), CAMMS223 (64% female), Etemadifar 2006 (greater than 75% in two out of three arms), FREEDOMS II (greater than 75%), Gobbi 2013 (less than 65%), and INCOMIN (less than 65% in one group). When reported, all trials included patients with mean baseline EDSS scores between one and three (standard deviation ranging between 0.7 and 1.4). The authors had difficulty assessing the duration of disease due to the varying definitions between studies. Twelve studies reported time since first MS symptoms while eight studies reported time since confirmed MS diagnosis. In addition, some studies did not specify which definition they used or did not report disease duration at all (Table 19). Disease duration as reported by the manufacturer ranged between 1.2 years (in BRAVO) and 12 years (in Gobbi 2013).

The authors of the MTC did note the considerable heterogeneity in the disease duration and hence included all the studies regardless of the clinical heterogeneity in this characteristic. Previous relapses were assessed based on the number of relapses in the previous year before enrolment; however, several studies only reported relapses over the previous two years. Therefore, the manufacturer estimated that the number of relapses in the previous year as half of the number over the previous two years in these situations. In addition to some trials not reporting on previous treatment, different trials had different inclusion criteria based on their previous treatment. Baseline patient characteristics are provided in Table 19.

TABLE 19: BASELINE CHARACTERISTICS FOR STUDIES INCLUDED IN THE INDIRECT TREATMENT COMPARISON

Study ID	Treatment Arms	Total, N	Males, n (%) Females, n (%)	Age in Years, Mean (SD)	Mean EDSS Score (SD)	Disease Duration, Years (SD) (Time Since…)	Relapses[a], Mean (SD)	Previous Treatment, n (%)
ADVANCE	Peg-IFN beta-1a 125 mcg q.2.w.	512	151 (29) 361 (71)	36.9 (9.8)	2.47 (1.26)	6.9 (6.6) (First MS symptoms)	1.6 (0.67)	Yes = 39 (8) No = 473 (92.4)
	PL	500	142 (29) 358 (71)	36.3 (9.7)	2.44 (1.18)	6.3 (6.3) (First MS symptoms)	1.6 (0.67)	Yes = 35 (7) No = 465 (93)
AFFIRM	NAT 300 mg q.4.w.	627	178 (28) 449 (72)	35.6 (8.5)	2.3 (1.2) 2 (0 to 6)[b]	5 (0 to 34)[b] (First MS symptoms)	1.53 (0.91)	Yes = 53 (8.5) No = 574 (91.5)
	PL	315	104 (33) 211 (67)	36.7 (7.8)	2.3 (1.2) 2 (0 to 6)[b]	6 (0 to 33)[b] (First MS symptoms)	1.5 (0.77)	Yes = 26 (8.3) No = 289 (91.7)
BEYOND	GA 20 mg q.d.	448	142 (32) 306 (68)	35.2 (NR) 35 (27 to 43)[c]	2.28 (NR) 2 (1.5 to 3)[c]	5.1 (NR) 3 (1 to 7)[c] (MS diagnosis)	1.6 (NR) 1 (1 to 2)[c]	Treatment-experienced patients were excluded.
	IFN beta-1b 250 mcg q.o.d.	897	270 (30) 627 (70)	35.8 (NR) 35 (28 to 43)[c]	2.35 (NR) 2 (1.5 to 3)[c]	5.3 (NR) 3 (1 to 7)[c] (MS diagnosis)	1.6 (NR) 1 (1 to 2)[c]	
Bornstein (1987)	GA 20 mg q.d.	25	11 (44) 14 (56)	30 (NR)	NR	4.9 (NR) (Unclear)	2 years: 3.8 (Unclear average)	NR
	PL	25	10 (40) 15 (60)	31 (NR)	NR	6.1 (NR) (Unclear)	2 years: 3.9 (Unclear average)	
BRAVO	IFN beta-1a 30 mcg q.w.	447	140 (31.3) 307 (68.7)	38.5 (30.3-45.9)[c]	2.5 (1.5 to 3.5)[c]	1.4 (0.3 to 4.7)[c] (MS diagnosis)	1 (1 to 2)[c]	Prior DMT for MS at any time before study entry, including mitoxantrone, immunoglobulin, IgG, GA, IFN beta drugs, meglumine acridonacetate, azathioprine.
	PL	450	129 (28.7) 321 (71.3)	37.5 (30.3 to 45.4)[c]	2.5 (1.5 to 3.5)[c]	1.2 (0.3 to 4)[c] (MS diagnosis)	1 (1 to 2)[c]	

Study ID	Treatment Arms	Total, N	Males, n (%) Females, n (%)	Age in Years, Mean (SD)	Mean EDSS Score (SD)	Disease Duration, Years (SD) (Time Since…)	Relapses[a], Mean (SD)	Previous Treatment, n (%)
Calabrese (2012)	GA 20 mg q.d.	48	13 (27.1) 35 (72.9)	38.9 (10.2)	2.1 (Range: 1 to 5)	5.5 (range: 0-9) (Unclear)	NR	NR
	IFN beta-1a 30 mcg q.w.	47	15 (32) 32 (68)	34.8 (9.6)	1.9 (Range: 1 to 5)	5.3 (range: 0 to 8) (Unclear)	NR	
	IFN beta-1a 44 mcg t.i.w.	46	14 (30.5) 32 (69.5)	35.9 (9.1)	1.9 (Range: 1 to 5)	5.7 (range: 0 to 9) (Unclear)	NR	
CAMMS223	IFN beta-1a 44 mcg t.i.w.	111	40 (36) 71 (64)	32.8 (8.8) 31 (18 to 60)[b]	1.9 (0.81) 2 (0 to 3.5)[b]	NR	NR	Previous treatment with DMT was an exclusion criterion.
	ALM 12 mg q.d.	112	39 (35.5) 71 (64.5)	31.9 (8) 31 (18 to 49)[b]	2 (0.73) 2 (0 to 3)[b]	NR	NR	
CARE-MS I	IFN beta-1a 44 mcg t.i.w.	187	65 (35) 122 (65)	33.2 (8.5)	2 (0.8) 2 (0 to 3.5)[b]	2 (1.3) 1.5 (0.2 to 5)[b] (First MS symptoms)	1.8 (0.8) 2 (0 to 5)[b] 2 years: 2.4 (0.85)	Key exclusion criteria were previous MS DMT (apart from corticosteroids), and previous immunosuppressive, investigational, or mAb therapy.
	ALM 12 mg q.d.	376	132 (35) 243 (65)	33 (8)	2 (0.8) 2 (0 to 4)[b]	2.1 (1.4) 1.7 (0.1 to 5.2)[b] (First MS symptoms)	1.8 (0.8) 2 (0 to 5)[b]	
CARE-MS-II	IFN beta-1a 44 mcg t.i.w.	202	71 (35) 131 (65)	35.8 (8.77)	2.7 (1.21) 2.5 (0 to 6)[b]	4.7 (2.86) 4.1 (0.4 to 10.1)[b] (First MS symptoms)	1.5 (0.75) 1 (0 to 4)[b]	At least one relapse while on IFN beta or GA after at least 6 months of treatment was an inclusion criterion.
	ALM 12 mg q.d.	426	145 (34) 281 (66)	34.8 (8.36)	2.7 (1.26) 2.5 (0 to 6.5)[b]	4.5 (2.68) 3.8 (0.2 to 14.4)[b] (First MS symptoms)	1.7 (0.86) 1 (0 to 5)[b]	

Study ID	Treatment Arms	Total, N	Males, n (%) Females, n (%)	Age in Years, Mean (SD)	Mean EDSS Score (SD)	Disease Duration, Years (SD) (Time Since…)	Relapses[a], Mean (SD)	Previous Treatment, n (%)
CombiRx	GA 20 mg q.d.	259	74 (28.6) 185 (71.4)	39 (9.5)	1.9 (1.2)	1 (2.9) (First MS symptoms)	1.6 (0.7)	NR
	IFN beta-1a 30 mcg q.w.	250	77 (30.8) 173 (69.2)	37.6 (10.2)	2.0 (1.2)	1.4 (4.0) (First MS symptoms)	1.7 (0.9)	
CONFIRM	DMF 240 mg b.i.d.	359	114 (32) 245 (68)	37.8 (9.4)	2.56 (1.2)	4.9 (5.1) (MS diagnosis)	1.3 (0.6)	Any prior approved DMT including exposure to IFN beta-1a, IFN beta-1b, NAT, or GA. Patients may also have received other non-approved therapies for MS.
	GA 20 mg q.d.	350	103 (29) 247 (71)	36.7 (9.1)	2.57 (1.22)	4.4 (4.7) (MS diagnosis)	1.4 (0.6)	
	PL	363	112 (31) 251 (69)	36.9 (9.2)	2.59 (1.17)	4.8 (5) (MS diagnosis)	1.4 (0.8)	
Copolymer I Study	GA, 20 mg q.d.	125	37 (29.6) 88 (70.4)	34.6 (6)	2.8 (1.2)	7.3 (4.9) (Unclear)	2 years: 2.9 (1.3)	NR
	PL	126	30 (23.8) 96 (76.2)	34.3 (6.5)	2.4 (1.3)	6.6 (5.1) (Unclear)	2 years: 2.9 (1.1)	
DECIDE	DAC 150 mg q.4.w.	919	294 (32) 625 (68)	36.4 (9.36)	2.48 (1.21)	4.2 (5.0) (MS diagnosis)	1.5 (0.72)	Number of patients who took any prior MS therapy, including IFN beta-1a, IFN beta-1b, or GA.
	IFN beta-1a 30 mcg q.w.	922	295 (32) 627 (68)	36.2 (9.32)	2.54 (1.26)	4.1 (4.7) (MS diagnosis)	1.6 (0.75)	
DEFINE	DMF 240 mg b.i.d.	410	114 (28) 296 (72)	38.1 (9.1)	2.4 (1.29)	5.6 (5.4) (MS diagnosis)	1.3 (0.7)	Previous use of approved medications for MS (including IFN beta-1a, IFN beta-1b, GA, and NAT); patients may have received ≥ 1 prior therapy for MS. Patients may have received other non-approved therapies for MS.
	PL	408	102 (25) 306 (75)	38.5 (9.1)	2.48 (1.24)	5.8 (5.8) (MS diagnosis)	1.3 (0.7)	

Study ID	Treatment Arms	Total, N	Males, n (%) Females, n (%)	Age in Years, Mean (SD)	Mean EDSS Score (SD)	Disease Duration, Years (SD) (Time Since…)	Relapses[a], Mean (SD)	Previous Treatment, n (%)
Etemadifar (2006)	IFN beta-1a 30 mcg q.w.	30	6 (20) 24 (80)	28.1 (1.2)	1.9 (1.1)	2.9 (2.3) (Unclear)	2 (0.8)	NR
	IFN beta-1a 44 mcg t.i.w.	30	7 (23) 23 (77)	27.4 (1.2)	2.1 (1)	3 (2.2) (Unclear)	2.4 (1)	
	IFN beta-1b 250 mcg q.o.d.	30	9 (30) 21 (70)	29.9 (1.4)	1.9 (0.7)	3.7 (2.3) (Unclear)	2.2 (0.7)	
EVIDENCE	IFN beta-1a 30 mcg q.w.	338	86 (25.4) 252 (74.6)	37.4 (range: 18 to 55)	2.3 (NR) 2 (NR)[b]	6.7 (NR) 4.1 (NR)[b] (Unclear)	2 years: 2.6 (NR) 2 years: 2 (NR)[b]	NR
	IFN beta-1a 44 mcg t.i.w.	339	85 (25.1) 254 (74.9)	38.3 (range: 18-55)	2.3 (NR) 2 (NR)[b]	6.5 (NR) 4 (NR)[b] (Unclear)	2 years: 2.6 (NR) 2 years: 2 (NR)[b]	
FREEDOMS	Fingolimod 0.5 mg q.d.	425	129 (30.4) 296 (69.6)	36.6 (8.8) 36 (18 to 55)[b]	2.3 (1.3) 2 (0 to 5.5)[b]	8 (6.6) 6.6 (0 to 35)[b] (First MS symptoms)	1.5 (0.8) 1 (0 to 5)[b]	Previous IFN beta or GA.
	PL	418	120 (28.7) 298 (71.3)	37.2 (8.6) 37 (18 to 55)[b]	2.5 (1.3) 2 (0 to 5.5)[b]	8.1 (6.4) 7 (0 to 32)[b] (First MS symptoms)	1.4 (0.7) 1 (0 to 6)[b]	
FREEDOMS II	Fingolimod 0.5 mg q.d.	358	83 (23) 75 (77)	40.6 (8.4) 41 (18 to 55)[b]	2.4 (1.3) 2 (0 to 6.5)[b]	10.4 (8) 8.6 (0 to 49)[b] (First MS symptoms)	1.4 (0.9) 1 (0 to 6)[b]	Previous treatment with any IFN beta-1a, IFN beta-1b, GA, or NAT.
	PL	355	67 (19) 288 (81)	40.1 (8.4) 40 (19 to 55)[b]	2.4 (1.3) 2 (0 to 6)[b]	10.6 (7.9) 9.2 (0 to 40)[b] (First MS symptoms)	1.5 (0.9) 1 (0 to 7)[b]	

Study ID	Treatment Arms	Total, N	Males, n (%) Females, n (%)	Age in Years, Mean (SD)	Mean EDSS Score (SD)	Disease Duration, Years (SD) (Time Since…)	Relapses[a], Mean (SD)	Previous Treatment, n (%)
GALA	GA 40mg t.i.w.	943	302 (32) 641 (68)	37.4 (9.4)	2.8 (1.2)	7.7 (6.7) (First MS symptoms)	1.3 (0.6)	Prior DMT treatment; type of DMT not defined.
	PL	461	148 (32.1) 313 (67.9)	38.1 (9.2)	2.7 (1.2)	7.6 (6.4) (First MS symptoms)	1.3 (0.6)	
Gobbi (2013)	IFN beta-1b 250 mcg q.o.d.	9	6 (67) 3 (33)	39 (24 to 48)[b]	3 (1.5 to 3.5)[b]	12 (2 to 23)[b] (Unclear)	2 years: 1 (0.5 to 2.5)[b]	Prior therapy before run-in with NAT: • GA, n = 1 (11%) • IFN beta-1a IM, n = 1 (11%) • IFN beta-1a SC, n = 2 (22%) • IFN beta-1b, n = 4 (44%).
	NAT 300 mg q.4.w.	10	4 (40) 6 (60)	43 (20 to 60)[b]	3 (1.5 to 3.5)[b]	10 (5 to 17)[b] (Unclear)	2 years: 1.3 (0.5 to 2.5)[b]	
IFNB MS study	IFN beta-1b 250 mcg q.o.d.	124	38 (30.6) 86 (69.4)	35.2 (SE: 0.6)	3 (SE: 0.1)	4.7 (SE: 0.4) (MS diagnosis)	2 years: 3.4 (SE: 0.2)	NR
	PL	123	35 (28.5) 88 (71.5)	36 (SE: 0.6)	2.8 (SE: 0.1)	3.9 (SE: 0.3) (MS diagnosis)	2 years: 3.6 (SE: 0.1)	
INCOMIN	IFN beta-1a 30 mcg q.w.	92	35 (38) 57 (62)	34.9 (7.9)	1.96 (0.7)	6.7 (5.4) (Unclear)	NR	NR
	IFN beta-1b 250 mcg q.o.d.	96	30 (31) 66 (69)	38.8 (7.1)	1.97 (0.7)	5.9 (4.2) (Unclear)	NR	
MSCRG	IFN beta-1a, 30 mcg, q.w.	158	40 (25) 118 (75)	36.7 (7.16)	2.4 (0.75)	6.6 (NR) (MS diagnosis)	1.2 (0.63)	Administered within 60 days before the first day of injection of study medication. Medications used by at least 10% of group included many drugs.[d]
	PL	143	40 (28) 103 (72)	36.9 (7.65)	2.3 (0.84)	6.4 (NR) (MS diagnosis)	1.2 (0.6)	
PRISMS	IFN beta-1a 22 mcg t.i.w.	189	62 (33) 127 (67)	34.8 (29.3 to 39.8)[c]	2.5 (1.2)	5.4 (3 to 11.2)[c] (Unclear)	2 years: 3 (1.1)	NR
	IFN beta-1a 44 mcg	184	63 (34)	35.6 (28.4	2.5 (1.3)	6.4 (2.9 to 10.3)[c]	2 years: 3 (1.1)	

Study ID	Treatment Arms	Total, N	Males, n (%) Females, n (%)	Age in Years, Mean (SD)	Mean EDSS Score (SD)	Disease Duration, Years (SD) (Time Since…)	Relapses[a], Mean (SD)	Previous Treatment, n (%)
	t.i.w.		121 (66)	to 41)[c]		(Unclear)		
	PL	187	47 (25) 140 (75)	34.6 (28.8 to 40.4)[c]	2.4 (1.2)	4.3 (2.4 to 8.4)[c] (Unclear)	2 years: 3 (1.3)	
REGARD	GA 20 mg q.d.	378	106 (28) 272 (72)	36.8 (9.5)	2.33 (1.31) 2 (NR)[b]	NR	NR	Steroid treatment in the previous 6 months.
	IFN beta-1a 44 mcg t.i.w.	386	119 (31) 267 (69)	36.7 (9.8)	2.35 (1.28) 2 (NR)[b]	NR	NR	
SELECT	DAC 150mg q.4.w.	208	68 (33) 140 (67)	35.3 (8.94)	2.8 (1.15)	4.5 (4.96) (MS diagnosis)	1.4 (0.73)	Number of patients with prior use of approved RRMS treatments: • IFN beta-1b, n = 20 (10%) • IFN beta-1a, n = 15 (7%) • GA, n = 9 (4%) • NAT, n = 2 (1%) • Mitoxantrone, n = 0 (0%).
	PL	204	76 (37) 128 (63)	36.6 (9.02)	2.7 (1.17)	4.1 (5.26) (MS diagnosis)	1.3 (0.6)	
TEMSO	TER 14 mg q.d.	359	104 (29) 255 (71)	37.8 (8.2)	2.67 (1.24)	8.7 (6.7) 7.2 (NR)[b] (First MS symptoms)	1.3 (0.7) 2 years: 2 (NR)[b]	Use of DMT in previous 2 years, including IFN beta-1a, IFN beta-1b, and GA. Patients may have received more than 1 previous therapy.
	PL	363	88 (24.2) 275 (75.8)	38.4 (9)	2.68 (1.34)	8.6 (7.1) 6.3 (NR)[b] (First MS symptoms)	1.4 (0.7) 2 years: 2 (NR)[b]	
TENERE	IFN beta-1a 44 mcg t.i.w.	104	33 (31.7) 71 (68.3)	37 (10.6)	2 (1.2)	7.7 (7.6) (First MS symptoms)	1.2 (1.0)	Use of DMT in previous 2 years, including: • IFN beta-1a

Study ID	Treatment Arms	Total, N	Males, n (%) Females, n (%)	Age in Years, Mean (SD)	Mean EDSS Score (SD)	Disease Duration, Years (SD) (Time Since…)	Relapses[a], Mean (SD)	Previous Treatment, n (%)
	TER, 14 mg, q.d.	111	33 (29.7) 78 (70.3)	36.8 (10.3)	2.3 (1.4)	6.6 (7.6) (First MS symptoms)	1.4 (0.8)	• IFN beta-1b • GA. Patients may have received more than 1 DMT.
TOWER	TER 14 mg q.d.	372	114 (31) 258 (69)	38.2 (9.4)	2.71 (1.35)	8.18 (6.73) (First MS symptoms)	1.4 (0.7)	Use of MS medication in the previous 2 years, including: • IFN beta-1a • IFN beta-1b • GA. Patients may have received more than 1 prior medication.
	PL	389	116 (30) 273 (70)	38.1 (9.1)	2.69 (1.36)	7.64 (6.7) (First MS symptoms)	1.4 (0.8)	
TRANS-FORMS	IFN beta-1a 30 mcg q.w.	435	140 (32.2) 295 (67.8)	36 (8.3) 36 (18 to 55)[b]	2.19 (1.26) 2 (0 to 5.5)[b]	7.4 (6.3) 6 (0 to 40)[b] (First MS symptoms)	1.5 (0.8) 1 (0 to 6)[b]	Any prior therapy, defined as any IFN beta, GA, or NAT. Patients may have received more than 1 prior therapy.
	Fingolimod 0.5 mg q.d.	431	149 (34.6) 282 (65.4)	36.7 (8.8) 37 (18 to 55)[b]	2.24 (1.33) 2 (0 to 5.5)[b]	7.5 (6.2) 6 (0 to 34)[b] (First MS symptoms)	1.5 (1.2) 1 (0 to 20)[b]	

ALM = alemtuzumab; b.i.d. = twice daily; DAC = daclizumab; DMF = dimethyl fumarate; DMT = disease-modifying therapy; GA = glatiramer acetate; ITC = indirect treatment comparison; IFN = interferon; IgG = immunoglobulin; IM = intramuscular; mAb = monoclonal antibody; MS = multiple sclerosis; n = number of patients with event; N = number of patients; NAT = natalizumab; NR = not reported; peg = pegylated; PL = placebo; q.2.w. = once every two weeks; q.4.w. = once every four weeks; q.d. = once daily; q.o.d. = every other day; q.w. = once weekly; SC = subcutaneous; SD = standard deviation; SE = standard error; TER = teriflunomide; t.i.w. = three times a week.

[a] Relapses in previous year.

[b] Median (range).

[c] Median (Interquartile range).

[d] Included were ascorbic acid, nicotinamide, riboflavin, thiamine hydrochloride, retinol, ergocalciferol, folic acid, panthenol, paracetamol, ibuprofen, amantadine, acetylsalicylic acid, baclofen, pyridoxine hydrochloride, tocopherol, vitamins, and calcium pantothenate.

Source: Manufacturer-submitted ITC.[50]

Efficacy Results

ARR

Twenty-eight studies were included in this network (Figure 2), with four studies reporting ARR after 12 months and 20 studies reporting ARR after 24 months. In addition, four studies reported ARR at follow-up times that were different from the 12- or 24-month marks (CAMMS223: 36 months; CombiRx: 36 months; TENERE: approximately 14 months or 15 months; TOWER: approximately 18 months or 19 months). Statistically significant reductions in the risk of relapse in favour of DAC beta 150 mg every four weeks were observed when compared with IFN beta-1a 30 mcg once weekly (risk ratio of 0.561 [CrI of 0.455 to 0.691]), IFN beta-1a 44 mcg three times per week (risk ratio of 0.695 [CrI of 0.526 to 0.936]), IFN beta-1b 250 mcg every other day (risk ratio of 0.696 [CrI of 0.528 to 0.931]), glatiramer acetate 20 mg once daily (risk ratio of 0.722 [CrI of 0.567 to 0.976), glatiramer acetate 40 mg three times a week (risk ratio of 0.690 [CrI of 0.485 to 0.976], and teriflunomide 14 mg once daily (risk ratio of 0.615 [CrI of 0.458 to 0.829]) in the overall population. Results were statistically significantly in favour of alemtuzumab 12 mg once daily when compared with DAC beta 150 mg once every four weeks for a reduction in the risk of relapse (risk ratio of 1.592; CrI of 1.129 to 2.308). ARR results from the random-effects model NMA are provided in Table 20.

The fixed-effect (FE) model was performed as a sensitivity analysis and the DIC was lower than that of the random-effects (RE) model (DIC FE was 48.52; DIC RE was 49.84); however, the differences were small enough that it did not alter the conclusions. Due to the fact that there were 15 treatment comparisons with the potential for inconsistency, node splitting to test for inconsistency was performed. The authors found no evidence of inconsistency between the direct and indirect assessments of ARR in the overall network (data not shown).

Subgroup analyses were performed as outlined a priori in the methods. The authors ascertained that there were only two populations that reported data in the relevant population of non-responders (FREEDOMS, SELECT). Using the Bucher method, the authors indirectly compared DAC beta 150 mg every four weeks with fingolimod 0.5 mg once daily (with placebo as the common comparator) and determined that there was no statistically significant difference between treatments in the risk of relapse in the non-responder population (rate ratio of 1.276, confidence interval of 0.420 to 3.872). With regard to the treatment-naive population, it was determined that eight studies could be included in the network (ADVANCE, CONFIRM, DECIDE, DEFINE, FREEDOMS, SELECT, TEMSO, TRANSFORMS); however, the results of the NMA were relative to placebo and therefore not pertinent to report in this review. With regard to the previously treated population, it was determined that eight studies could be included in this network (ADVANCE, CONFIRM, DECIDE, DEFINE, FREEDOMS, SELECT, TEMSO, TRANSFORMS); however, the results of the NMA were relative to placebo and therefore not pertinent to report in this review. In addition, the manufacturer performed a sensitivity analysis to determine any differences between the year 1 and year 2 results using the 144-week data for DECIDE and determined that there was no substantial change in the results.

As the base-case analysis for ARR involved pooled data measured at different time points, the authors performed a sensitivity analysis that included studies with ARR measured at 24 months. The results were comparable to those that involved the overall network and there were no differences that altered the interpretation of the evidence (data not shown).

Disability Progression Confirmed After Three Months (CDP3M)

Eleven studies were included in the CDP3M network (Figure 3). No statistically significant risk of disability progression confirmed after three months was observed when comparing DAC beta 150 mg every four weeks to any other treatment in the network in the overall population. CDP3M results from the random-effects model NMA are provided in Table 20.

When the FE model was performed in a sensitivity analysis, the DIC was lower than that of the RE model (DIC FE was 23.42; DIC RE was 24.59), which was most likely due to the small number of studies included. Sensitivity analyses using a range of prior distributions (uniform [0, 0.5], uniform [0, 3], and uniform [0, 5]) to account for the small number of studies were performed to assess any difference that may have occurred using the prior distribution for the base-case analysis (uniform [0, 1]). The estimated HRs were similar or identical to the base-case analysis results when performing the analysis with the alternate prior distributions (results not shown); therefore, the authors maintained that the uniform (0, 1) prior distribution was sufficient.

The authors noted that there was substantial uncertainty with all of the estimated treatment effects for CDP3M, most likely due to the small number of studies that informed the network. Inconsistency could not be assessed as there were only two closed loops that were formed by a single three-arm study. In addition, a priori subgroup analyses could not be performed due to differences in when the follow-up data were obtained or the lack of subgroup data.

Disability Progression Confirmed After Six Months (CDP6M)

Seven studies were included in the CDP6M network (Figure 4). No statistically significant risk of disability progression confirmed after six months was observed when comparing DAC beta 150 mg every four weeks to any other treatment in the network in the overall population. CDP6M results from the random-effects model NMA are provided in Table 20.

A sensitivity analysis was performed using a FE model and the DIC was lower than that of the RE model (DIC FE was 12.67; DIC RE was 14.12), which was most likely due to the small number of studies included. As in the case of the CDP3M, other sensitivity analyses using a range of prior distributions (uniform [0, 0.5], uniform [0, 3], and uniform [0, 5]) were performed to assess any difference that may have occurred using the prior distribution for the base-case analysis (uniform [0, 1]); mainly to account for the small number of studies. The estimated HRs were similar or identical to the base-case analysis results when performing the analysis with the alternate prior distributions (results not shown); therefore, the authors maintained that the uniform (0, 1) prior distribution was sufficient.

The authors noted that there was substantial uncertainty with all of the estimated treatment effects for CDP3M, most likely due to the small number of studies that were included in each treatment comparison in the network. All but two comparisons (dimethyl fumarate versus placebo and fingolimod versus placebo) were informed by a single study each. Inconsistency was not assessed as there was only one closed loop in the network and this was due to one three-armed study. In addition, a priori subgroup analyses could not be performed due to the differences in when the follow-up data were obtained or the lack of subgroup data.

TABLE 20: CLINICAL EFFICACY RESULTS OF NETWORK META-ANALYSIS FOR THE MANUFACTURER-SUBMITTED ITC

Treatment	Outcomes[b]		
	ARR RR (95% CrI)	CDP3M HR (95% CrI)	CDP6M HR (95% CrI)
DAC 150 mg q.4.w. relative to:			
IFN beta-1a 30 mcg q.w.	**0.561 (0.455, 0.691)**	0.842 (0.377, 1.863)	0.731 (0.323, 1.640)
IFN beta-1a 44 mcg t.i.w.	**0.695 (0.526, 0.936)**	1.006 (0.241, 4.251)	–
Peg-IFN beta-1a 125 mcg q.2.w.	0.702 (0.479, 1.029)	–	–
IFN beta-1b 250 mcg q.o.d.	**0.696 (0.528, 0.931)**	0.683 (0.134, 3.368)	–
IFN beta-1a 22 mcg t.i.w.	–	0.914 (0.223, 3.807)	–
GA 20 mg q.d.	**0.722 (0.567, 0.942)**	0.716 (0.174, 2.880)	0.571 (0.136, 2.417)
GA 40 mg t.i.w.	**0.690 (0.485, 0.976)**	–	–
TER 14 mg q.d.	**0.615 (0.458, 0.829)**	0.884 (0.215, 3.679)	–
DMF 240 mg b.i.d.	0.912 (0.669, 1.240)	0.900 (0.242, 3.297)	0.752 (0.202, 2.921)
Fingolimod 0.5 mg q.d.	0.976 (0.734, 1.309)	0.808 (0.222, 2.964)	0.792 (0.211, 2.958)
NAT 300 mg q.4.w.	1.432 (0.983, 2.096)	1.068 (0.259, 4.397)	1.151 (0.274, 4.912)
ALM 12 mg q.d.	**1.592 (1.129, 2.308)**	2.662 (0.463, 15.132)	0.530 (0.163, 1.761)
Measures of model fit			
Total residual deviance (mean) RE	34.22	12.46	7.16
Total residual deviance (mean) FE	36.53	12.40	6.67
DIC RE	34.22	24.59	14.12
DIC FE	36.53	23.42	12.67

ALM = alemtuzumab; ARR = annualized relapse rate; b.i.d. = twice daily; CDP3M = disability progression confirmed after three months; CDP6M = disability progression confirmed after six months; CrI = credible interval; DAC = daclizumab; DIC = deviance information criterion; DMF = dimethyl fumarate; FE = fixed effect; GA = glatiramer acetate; HR = hazard ratio; ITC = indirect treatment comparison; IFN = interferon; NAT = natalizumab; peg = pegylated; q.2.w. = once every two weeks; q.4.w. = once every four weeks; q.d. = once daily; q.o.d. = every other day; q.w. = once weekly; RE = random effects; RR = rate ratio; TER = teriflunomide; t.i.w. = three times a week.
Note: Statistically significant results are bolded.
[a] Random-effects model.
[b] Overall population assessed.
Source: Manufacturer-submitted ITC.[50]

Safety Results

An overview of adverse events (AEs) and SAEs (including and excluding MS relapse as an SAE) was provided by the authors for each study. With regard to any AE, the proportion of patients in one treatment group that experienced at least one AE ranged from 62% to 98%. No NMA was performed on the AEs. In patients experiencing an SAE that included MS relapse, the proportion of patients in one treatment group that experienced at least one SAE ranged from 5% to 26%; however, many studies did not report on the proportion of SAEs that included MS relapse. In patients experiencing an SAE that excluded MS relapse, the proportion of patients in one treatment group who experienced at least one SAE ranged from 0% to 16%. The definition of treatment discontinuation due to AEs differed between studies, with some indicating that they discontinued the study due to an AE while others discontinued treatment due to an AE. Regardless, the proportion of discontinuations due to AEs in one of the treatment arms ranged from 0% to 21.2%. An overview of AEs, SAEs, and discontinuations due to AEs is provided in Table 21.

TABLE 21: OVERVIEW OF ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND DISCONTINUATIONS

Study ID	Treatment Arms	Follow-Up (Months)	Total Number of Patients Analyzed	Any SAE Excluding MS Relapse		Any SAE Including MS Relapse		Any AE		Treatment Discontinuation Due to AEs			
				Events (n)	%	Events (n)	%	Events (n)	%	Events (n)	Total Number Analyzed	%	Outcome Definition
ADVANCE	Peg-IFN beta-1a 125 mcg q.2.w.	11	512	24	5	55	11	481	94	25	512	5	Discontinued study due to AE
	PL		500	23	5	76	15	417	83	7	500	1	
AFFIRM	NAT 300 mg q.4.w.	24	627	82	13	119	19	596	95	15	627	2	Discontinued study due to AE
	PL		312	34	11	75	24	300	96	6	315	2	
BEYOND	GA 20 mg q.d.	24	445	57	13	NR	NR	NR	NR	8	448	1.8	Discontinued study due to AE
	IFN beta-1b 250 mcg q.o.d.		888	100	11	NR	NR	NR	NR	13	897	1.4	
Bornstein (1987)	GA 20 mg q.d.	–	–	–	–	–	–	–	–	–	–	–	–
	PL												
BRAVO	IFN beta-1a 30 mcg q.w.	24	442	34	8	34	8	362	82	26	447	5.8	Discontinued study due to AE
	PL		449	52	12	54	12	314	70	19	450	4.2	
Calabrese (2012)	GA 20 mg q.d.	–	–	–	–	–	–	–	–	–	–	–	–
	IFN beta-1a 30 mcg q.w.												
	IFN beta-1a 44 mcg t.i.w.												
CAMMS223	IFN beta-1a 44 mcg t.i.w.	–	–	–	–	–	–	–	–	–	–	–	–
	ALM 12 mg q.d.												
CARE-MS I	IFN beta-1a 44 mcg t.i.w.	24	187	17	7	27	14	172	92	5	187	2.7	Discontinued treatment due to AE
	ALM 12 mg q.d.		376	51	14	69	18	361	96	1	376	0.3	
CARE-MS-II	IFN beta-1a 44 mcg t.i.w.	24	202	26	13	44	22	191	95	6	202	3	Discontinued treatment due to AE
	ALM 12 mg q.d.		435	58	13	85	20	428	98	2	426	0.5	

Study ID	Treatment Arms	Follow-Up (Months)	Total Number of Patients Analyzed	Any SAE Excluding MS Relapse		Any SAE Including MS Relapse		Any AE		Treatment Discontinuation Due to AEs			
				Events (n)	%	Events (n)	%	Events (n)	%	Events (n)	Total Number Analyzed	%	Outcome Definition
CombiRx	GA 20 mg q.d.	–	–	–	–	–	–	–	–	–	–	–	–
	IFN beta-1a 30 mcg q.w.												
CONFIRM	DMF 240 mg b.i.d.	22.1	359	22	6	61	17	338	94	36	359	10	Discontinued treatment due to AE
	GA 20 mg q.d.		351	24	7	60	17	304	87	27	350	8	
	PL		363	28	8	79	22	333	92	21	363	6	
Copolymer I Study	GA 20 mg q.d.	–	–	–	–	–	–	–	–	2	125	1.6	Discontinued study due to AE
	PL									0	126	0	
DECIDE	DAC 150 mg q.4.w.	22.1	919	85	9	157	17	784	85	47	919	5	Discontinued treatment due to AE
	IFN beta-1a 30 mcg q.w.		922	54	6	153	17	792	86	65	922	7	
DEFINE	DMF 240 mg b.i.d.	22.2	410	35	9	74	18	395	96	65	410	16	Discontinued treatment due to AE
	PL		408	26	6	86	21	387	95	55	408	13	
Etemadifar (2006)	IFN beta-1a 30 mcg q.w.	–	–	–	–	–	–	–	–	–	–	–	–
	IFN beta-1a 44 mcg t.i.w.												
	IFN beta-1b, 250 mcg q.o.d.												
EVIDENCE	IFN beta-1a 30 mcg q.w.	11	337[a]	NR	18	18	5	NR	NR	14	338	4.1	Discontinued study based on CONSORT flow chart
	IFN beta-1a 44 mcg t.i.w.		339[a]	NR	NR	21	6	NR	NR	16	339	4.7	
FREEDOMS	Fingolimod 0.5 mg q.d.	24	429[b] 425[a] 425[c]	39	9	43	10	401	94	32	425	7.5	Discontinued treatment due to AE
	PL		418	55	13	56	13	387	93	32	418	7.7	
FREEDOMS II	Fingolimod 0.5 mg q.d.	24	358[a,c]	53	15	NR	NR	350	98	66	358	18	Discontinued treatment due to AE
	PL		355[a,c]	45	13	NR	NR	343	97	37	355	10	

Study ID	Treatment Arms	Follow-Up (Months)	Total Number of Patients Analyzed	Any SAE Excluding MS Relapse		Any SAE Including MS Relapse		Any AE		Treatment Discontinuation Due to AEs			
				Events (n)	%	Events (n)	%	Events (n)	%	Events (n)	Total Number Analyzed	%	Outcome Definition
GALA	GA 40mg t.i.w.	12	943[a,c]	42	5	NR	NR	680	72	29	943	3.1	Discontinued study due to AE
	PL		461[a,c]	21	5	NR	NR	284	62	6	461	1.3	
Gobbi (2013)	IFN beta-1b 250 mcg q.o.d.	12	9[a,c]	0	0	NR	NR	7	78	–	–	–	–
	NAT 300 mg q.4.w.		10[a,c]	1	10	NR	NR	8	80				
IFNB MS study	IFN beta-1b 250 mcg q.o.d.	24	–	–	–	–	–	–	–	10	124	8.1	Discontinued treatment due to AE
	PL									1	123	0.8	
INCOMIN	IFN beta-1a 30 mcg q.w.	24	–	–	–	–	–	–	–	1	92	1.1	Discontinued treatment due to AE
	IFN beta-1b 250 mcg q.o.d.									5	96	5.2	
MSCRG	IFN beta-1a 30 mcg q.w.	–	–	–	–	–	–	–	–	–	–	–	–
	PL												
PRISMS	IFN beta-1a 22 mcg t.i.w.	24	–	–	–	–	–	–	–	6	189	3.2	Discontinued treatment due to AE
	IFN beta-1a 44 mcg t.i.w.									9	184	4.9	
	PL									2	187	1.1	
REGARD	GA 20 mg q.d.	22.2	375[a,c]	27	7	NR	NR	320	85	–	–	–	–
	IFN beta-1a 44 mcg t.i.w.		381[a,c]	29	8	NR	NR	346	91				
SELECT	DAC 150mg q.4.w.	12	208[b,c]	NR	NR	32	15	151	73	6	208	2.9	Discontinued treatment due to AE
	PL		204[b,c]	NR	NR	53	26	161	79	2	204	1.0	
TEMSO	TER 14 mg q.d.	24.9	358[a,c]	57	16	NR	NR	325	91	39	358	10.9	Discontinued treatment due to AE
	PL		360[a,b]	46	13	NR	NR	315	88	29	363	8.1	
TENERE	IFN beta-1a 44 mcg t.i.w.	14-15	101[a,c]	7	7	NR	NR	97	96	22	104	21.2	Discontinued study based on

Study ID	Treatment Arms	Follow-Up (Months)	Total Number of Patients Analyzed	Any SAE Excluding MS Relapse		Any SAE Including MS Relapse		Any AE		Treatment Discontinuation Due to AEs			
				Events (n)	%	Events (n)	%	Events (n)	%	Events (n)	Total Number Analyzed	%	Outcome Definition
	TER 14 mg q.d.		110[a,c]	6	6	NR	NR	102	93	12	111	10.8	CONSORT flow chart
TOWER	TER 14 mg q.d.	18-19	371[a,c]	44	12	NR	NR	320	86	58	371	16	Discontinued treatment due to AE
	PL		385[a,c]	47	12	NR	NR	320	83	24	385	6	
TRANS-FORMS	IFN beta-1a 30 mcg q.w.	12	431[a,c]	25	6	NR	NR	395	92	16	431	3.7	Discontinued treatment due to AE
	Fingolimod, 0.5 mg q.d.		429[a,c]	30	7	NR	NR	369	86	24	429	5.6	

AE = adverse event; ALM = alemtuzumab; b.i.d. = twice daily; DAC = daclizumab; DMF = dimethyl fumarate; GA = glatiramer acetate; ITC = indirect treatment comparison; IFN = interferon; MS = multiple sclerosis; n = number of patients with event; NAT = natalizumab; NR = not reported; PEG = pegylated; PL = placebo; q.2.w. = once every two weeks; q.4.w. = once every four weeks; q.d. = once daily; q.w. = once weekly; SAE = serious adverse event; TER = teriflunomide; t.i.w. = three times a week.

[a] Number analyzed only for any SAE, including MS relapse category.

[b] Number analyzed only for any SAE, excluding MS relapse category.

[c] Number analyzed only for any AE category.

Source: Manufacturer-submitted ITC.[50]

Any SAE at 24 Months

Six studies were included in the network that looked at any SAE at 24 months (Figure 5). The results were obtained for any SAE at 24 months while excluding MS relapses. No statistically significant differences in the odds of an SAE at 24 months were observed when comparing DAC beta 150 mg every four weeks to any other treatment in the network in the overall population. Any SAE at 24 months results from the RE model NMA are provided in Table 22.

A sensitivity analysis was performed using a FE model and the DIC was lower in the RE model (DIC FE was 26.16; DIC RE was 25.96). The base-case analysis used any SAE at 24 months, excluding MS relapse; however, when performing a sensitivity analysis (to observe the impact of including MS relapse as an AE) it was evident that there were differences in the glatiramer 20 mg once daily, dimethyl fumarate (DMF) 240 mg twice daily, DAC 150 mg every four weeks, and natalizumab 300 mg every four weeks groups relative to placebo. A reduction in the odds ratio was noted for all four comparisons relative to placebo. However, these did not reach statistical significance. Sensitivity analyses using a range of prior distributions showed that the estimated odds ratios were similar or identical to the base-case analysis results.

All comparisons in the network were based on a single study each; therefore, there was a substantial amount of uncertainty associated with the effect estimates. Inconsistency was not assessed as there was only one closed loop in the network and this was due to one three-armed study.

Treatment Discontinuation Due to Any Cause

Sixteen studies were included in the network for treatment discontinuation due to any cause regardless of the definition (14 studies reported the proportion of patients who discontinued study treatment due to any cause; two studies reported the proportion of patients who discontinued the study due to any cause). No statistically significant differences in the odds of discontinuing treatment due to any cause were observed when comparing DAC beta 150 mg every four weeks to any other treatment in the network in the overall population. Treatment discontinuation due to any cause results from the RE model NMA are provided in Table 22.

A sensitivity analysis was performed using a FE model and the DIC was lower in the RE model (DIC FE was 74.00; DIC RE was 70.55). In addition, another sensitivity analysis was performed, which removed the two studies that differed with regard to the discontinuation of treatment due to any cause definition. The exclusion of the BRAVO study (one of the studies with the alternate definition) increased the uncertainty and also changed some of the effect estimates (especially with regard to IFN beta-1a 30 mcg once weekly, whereby the odds ratio increased, and DAC beta 150 mg once every four weeks, whereby the odds ratio also increased; both were against placebo and both were not statistically significant) (data not shown); however, neither the base-case and sensitivity analysis estimates of effects were statistically significant.

Node splitting was used to test for the presence of inconsistency, which was subsequently observed with regard to comparisons with IFN beta-1a 30 mcg once weekly, IFN beta-1b 250 mcg every other day, glatiramer acetate 20 mg once daily, or placebo.

TABLE 22: HARMS RESULTS OF THE NETWORK META-ANALYSIS FROM THE MANUFACTURER-SUBMITTED ITC

Treatment	Outcomes[a]	
	Any SAE at 24 Months OR (95% CrI)	**Treatment Discontinuation – Any Cause OR (95% CrI)**
DAC 150 mg q.4.w. relative to:		
IFN beta-1a 30 mcg q.w.	1.644 (0.485, 5.578)	0.864 (0.361, 2.051)
IFN beta-1a 44 mcg t.i.w.	–	0.596 (0.165, 2.464)
Peg-IFN beta-1a 125 mcg q.2.w.	–	–
IFN beta-1b 250 mcg q.o.d.	–	1.192 (0.374, 4.021)
IFN beta-1a 22 mcg t.i.w.	–	0.538 (0.128, 2.550)
GA 20 mg q.d.	1.030 (0.127, 8.525)	0.975 (0.300, 3.425)
GA 40 mg t.i.w.	–	–
TER 14 mg q.d.	–	0.815 (0.205, 3.786)
DMF 240 mg b.i.d.	0.989 (0.143, 7.141)	0.866 (0.255, 3.370)
Fingolimod 0.5 mg q.d.	1.562 (0.185, 13.304)	0.982 (0.289, 3.928)
NAT 300 mg q.4.w.	0.837 (0.102, 7.196)	0.976 (0.243, 4.577)
ALM 12 mg q.d.	–	2.852 (0.642, 13.570)
Measures of model fit		
Total residual deviance (mean) RE	13.14	37.13
Total residual deviance (mean) FE	14.08	45.92
DIC RE	25.96	70.55
DIC FE	26.16	74.00

ALM = alemtuzumab; b.i.d. = twice daily; CrI = credible interval; DAC = daclizumab; DIC = deviance information criterion; DMF = dimethyl fumarate; FE = fixed effect; GA = glatiramer acetate; ITC = indirect treatment comparison; IFN = interferon; NAT = natalizumab; OR = odds ratio; peg = pegylated; q.2.w. = once every two weeks; q.4.w. = once every four weeks; q.d. = once daily; q.o.d. = every other day; q.w. = once weekly; RE = random effects; SAE = serious adverse event; TER = teriflunomide; t.i.w. = three times a week.

[a] RE model.

Source: Manufacturer-submitted ITC.[50]

A1.2.3 Critical Appraisal of Manufacturer-Submitted ITC

The manufacturer's rationale for conducting the ITC (i.e., absence of head-to-head studies) and the objectives of the ITC (to indirectly compare the efficacy and safety of DAC beta 150 mg once every four weeks to other DMTs in patients with RRMS) were clearly reported. A comprehensive systematic review was performed with a two-stage dual-selection process, whereby articles were first selected based on titles and abstracts and then full-text articles were retrieved and ascertained for their inclusion criteria. In addition, data extraction was performed and quality checked by two independent reviewers. Risk of bias was assessed using the Cochrane Collaboration risk of bias tool and detailed results of these assessments were provided. The manufacturer provided both inclusion and exclusion criteria that were used for screening and reported lists of both included and excluded references with accompanying reasons. In addition, the manufacturer provided an a priori list of a subgroup and sensitivity analyses they wanted to perform in order to ascertain the robustness of their base-case analysis for each outcome of interest. The manufacturer also provided figures of all networks, including those for each sensitivity analysis.

While the authors did provide all of the information pertaining to how they assessed the risk of bias using the Cochrane Collaboration risk of bias tool, it was evident that there was a lack of reporting in the majority of studies regarding at least one of the domains. With only seven of the 30 included studies

reporting a low risk of bias, the high risk of bias associated with insufficient blinding (in patients, caregivers, and/or assessors) in 12 of the studies remains problematic in that it could have potentially affected the original trial results. Hence, there is the potential that either the high risk of bias in the blinding domain or the lack of reporting for the other domains could have subsequently affected the results of the NMA and lead to an increased uncertainty surrounding the NMA conclusions.

The ITC methodology was robust and NMA results were confirmed by the performance of indirect meta-analysis using the Bucher method and direct head-to-head meta-analysis for treatments that could be directly compared. The results were similar to those resulting from the NMA in comparisons that could be assessed via the Bucher method and direct meta-analysis; therefore, it appeared that one can have confidence in the actual NMA results. Inconsistency was assessed using node-splitting methodology when there were closed loops included in any networks, with results consistent between both the direct and indirect methods for the outcomes assessed. In addition, the manufacturer included all relevant DMT comparators for patients with RRMS, thereby performing their due diligence in this respect. Convergence was assessed using the Brooks-Gelman-Rubin method and the manufacturer stated that convergence was achieved even though no graphs were provided. A prior subgroup and sensitivity analyses were planned and performed when possible. The manufacturer did notice differences when performing sensitivity analysis between the FE and RE models (with tighter credible intervals observed with the FE model results); however, in the case of ARR, the results were similar enough that they decided to stay with the RE model (even though the FE model had a lower DIC). For the other outcomes of interest, differences in the models were also noted; however, the manufacturer determined that this was most likely due to the small number of studies informing the comparisons and therefore decided to remain conservative and use the RE model results.

That being said, the main limitations associated with the manufacturer's ITC involve the differences in baseline patient characteristics between the included studies, the differences in certain inclusion criteria for the included studies, and the fact that the ITC was limited by the inconsistent or absent reporting of key data in the included studies. With regard to effect modifiers such as the duration of disease of the included patients, differences were noted not only in the definition of disease duration (some studies reported this as time since first MS symptoms [n = 12], others reported this as time since MS diagnosis [n = 8], and other studies did not report or the manufacturer was unsure of the definition [n = 10]) but also in the duration itself, with mean disease durations ranging between one year and 10.4 years (standard deviation ranging from 1.3 years to eight years). This wide range and difference in definitions (or lack of reporting) indicate considerable heterogeneity in this characteristic, thereby decreasing confidence in the NMA results. While EDSS scores (ranging between one and three [standard deviation ranging between 0.7 and 1.4]), mean age (ranging between 30 and 40 years, [standard deviation] ranging between 1.2 and 10.6 years), and proportion of each sex (proportion of females ranging between 65% and 75%) were similar between studies, study sizes ranged between 19 and 1,841, with trial group patient numbers ranging between nine and 992 (therefore, there was the potential for the smaller studies to disproportionally affect the results). The previous relapses in the year before entering the study (another potential effect modifier) was either reported as such or was reported as the number of relapses in the past two years, for which the manufacturer estimated that the number of relapses in the previous year was half of the number over the previous two years. This potentially introduces errors in such values, as one cannot assume that half of these relapses did in fact occur during the first previous year. In addition, some studies did not report these values. With regard to previous treatment (another potential effect modifier), some studies included only treatment-naive patients, some had mixed populations, and others did not report on this. This indicated that the NMA included a range of patients (including patients who may be harder to treat, as evidenced by previous treatment failure) and

that combining all these patients in the same network may not be appropriate. All of these reasons together undermine the ability one has to generalize the results to all patients with RRMS. In addition, the aforementioned issues add to the uncertainty surrounding the actual NMA effect estimates; hence one must use caution in the interpretation of the results.

Another important issue that potentially decreases confidence in the results of the NMA and how it pertains to this particular submission is that the NMA results were performed in the overall population. For the purposes of this submission, it would have more beneficial to ascertain results with regard to the indication (e.g., in patients who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of multiple sclerosis [MS]). While they endeavoured to perform a priori subgroup analysis in non-responders and previously treated patients, limited data precluded most of these being performed, or the treatments were looked at relevant to placebo, which was not helpful to this review.

With regard to the NMAs done for the harms outcomes, there were not a lot of studies informing the network for the SAEs at 24 months (n = 6) and the network only included the SAE definition that excluded MS relapses. That being said, the SAE definition excluding MS relapses is probably the more accurate of the two as those that included MS relapses simply included those patients for whom treatment no longer worked. Inconsistency could not be ascertained due to the lack of direct evidence and the substantial amount of uncertainty associated with the effect estimates was most likely due to the fact that all comparisons in the network were only informed by one study each. All of these issues together decrease the confidence one has in the effect estimates and does not allow for solid conclusions to be made regarding the SAEs at 24 months.

While more studies were included in the NMA for treatment discontinuations due to any cause, there were issues with the manufacturer including both definitions (14 studies reported the proportion of patients who discontinued study treatment due to any cause; two studies reported the proportion of patients who discontinued the study due to any cause). A sensitivity analysis was performed removing the two studies and increased uncertainty was noted with the effect estimates. While these results of the both the sensitivity analysis and the base-case analysis were not statistically significant, this increased uncertainty decreases confidence in the overall results of this harm outcome.

A1.3 Review of ITC by Tramacere et al.

Study Eligibility, Selection Process, and Study Assessment

Tamacere et al. conducted an ITC with aim of comparing the benefit and acceptability of IFN beta-1b, IFN beta-1a (Avonex, Rebif), glatiramer acetate, mitoxantrone, peg-IFN beta-1a, dimethyl fumarate, fingolimod, natalizumab, teriflunomide, alemtuzumab, ocrelizumab, laquinimod, DAC, azathioprine, and immunoglobulins (irrespective of dose) for the treatment of patients with RRMS. In addition, they sought to ascertain the ranking of these treatments according to their benefit and acceptability; however, for the purposes of this review, these rankings will not be appraised or presented. A full list of the primary and secondary outcomes along with the eligibility criteria is listed in Table 17. The authors performed a systematic search and included all RCTs with durations of more than six months that examined at least one of the aforementioned treatments (regardless of dose) in patients with RRMS. Studies with multiple treatment arms were included if the intervention groups could be included in a pairwise comparison that would have met the inclusion criteria if examined alone. Exclusion criteria included combination treatments, trials that only compared different doses of the same drug (i.e., no other active treatment or placebo group), non-pharmacological treatments, and comparisons of over-the-counter drugs. The authors performed a systematic review to ascertain all relevant published

citations. In addition, the authors conducted a search of the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Groups Trial Register which included, but was not limited to, the following databases: Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL, LILACS, clinicaltrials.gov, and the World Health Organization International Clinical Trial Registry Portal. In addition, they attempted to contact principal authors when warranted, and searched FDA reports.

Based on the inclusion and exclusion criteria, first and second level selection was performed independently by two reviewers, with any discrepancies resolved using a third reviewer.

Data extraction was performed in parallel by two independent reviewers with any discrepancies reconciled using a third reviewer. Baseline patient characteristics, study design, and key efficacy outcomes were extracted.

In addition to the ITC, pairwise meta-analysis was performed using an RE model for each primary outcome comparison that was informed by at least two studies.

Methodological quality of the included studies was assessed based on the Cochrane Collaboration criteria which focused on allocation concealment, random sequence generation, blinding of patients/investigators/assessors, incomplete outcome data, and selective outcome reporting. Risk classifications of the aforementioned criteria included “low,” “high,” or “unclear” risk of bias. In addition, the authors assessed the potential roles of the study funders. Grading of the evidence and reasons for obtaining set grading was provided. Missing data were assumed to indicate that the patient had an unfavourable outcome and was reported as such. Transitivity was assumed to be upheld if pairwise comparisons did not differ with regard to the effect modifier distributions and was subsequently assessed by comparing potential effect modifiers across these different pairwise comparisons. Reporting bias was assessed using funnel plots. Clinical heterogeneity within the treatment comparisons was assessed by examining the differences in disease duration, baseline EDSS scores, and age across trials. The study details and patient characteristics of the included trials are presented in Table 23.

TABLE 23: OVERVIEW OF STUDIES INCLUDED IN THE INDIRECT TREATMENT COMPARISON BY TRAMACEREET ET AL.

Trial, Year	Trial Duration (Months)	Treatment	Sample Size	Age in Years, Mean (SD)	Duration of Disease in Years, Mean (SD)	EDSS Baseline Score, Mean (SD)	Number of Relapses 1 Year Prior to Baseline, Mean (SD)
Achiron (1998)	24	Immunoglobulins 0.4 g/kg body weight[f]	20	19 to 60[a]	4 (NR)	3.0 (NR)	NR
		PL	20				
ADVANCE	12	Peg-IFN beta-1a 125 mcg q.2.w.[b]	512	36.9 (9.8)	4.0 (5.09)	2.47 (1.26)	1.6 (0.67)
		Peg-IFN beta-1a 125 mcg q.4.w.	500	36.4 (9.9)	3.4 (4.36)	2.48 (1.24)	1.5 (0.62)
		PL	500	36.3 (9.7)	3.5 (4.63)	2.44 (1.18)	1.6 (0.67)
AFFIRM	24	NAT 300 mg q.4.w.	627	18 to 50[a]	5 (0 to 34)[a]	2.3 (NR)	NR
		PL	315				
ALLEGRO	24	Laquinimod 0.6 mg q.d.	550	18 to 55[a]	9 (NR)	2.6 (NR)	NR
		PL	556				
BECOME	24	GA 20 mg q.d.	39	36 (NR)	1.2 (0.2 to 34)[a]	2[a] (NR)	NR
		IFN beta-1b 250 mcg q.o.d.	36	36 (NR)	0.9 (0.1 to 24)[a]	2[a] (NR)	NR
BEYOND	24	GA 20 mg q.d.	448	35.2 (NR)	5.1 (NR)	2.28 (NR)	1.6 (NR)
		IFN beta-1b 250 mcg q.o.d.	897	35.8 (NR)	5.3 (NR)	2.35 (NR)	1.6 (NR)
		IFN beta-1b 500 mcg q.o.d[b]	899	NR[c]	NR[c]	NR[c]	NR[d]
Bornstein (1987)	24	GA 20 mg q.d.	25	30 (NR)	4.9 (NR)	2.9 (NR)	NR
		PL	25	31 (NR)	4.6 (NR)	3.2 (NR)	NR
BRAVO	24	IFN beta-1a 30 mcg q.w.	447	38.5[a] (NR)	5.3[a] (NR)	2.5[a] (NR)	1.0[c] (NR)
		Laquinimod 0.6 mg q.d.	434	NR[c]	NR[c]	NR[c]	NR[d]
		PL	450	37.5[a] (NR)	4.7[c] (NR)	2.5[a] (NR)	1.0[c] (NR)
CAMMS223	36	ALM24 mg q.d.[d]	110	18 to 50[a]	NR	1.9 (NR)	NR
		ALM12 mg q.d.[d]	113				
		IFN beta-1a 44 mcg t.i.w.	111				
CARE-MS I	24	ALM 12 mg q.d.[e]	386	18 to 50[a]	2 (NR)	2.0 (NR)	NR
		IFN beta-1a 44 mcg t.i.w.	195				
CARE-MS-II	24	ALM 24 mg q.d.[d]	170	18 to 55[a]	5 (NR)	2.7 (NR)	NR
		ALM 12 mg q.d.[d]	436				
		IFN beta-1a 44 mcg t.i.w.	231				
CombiRx	36	GA 20 mg q.d.	259	39 (9.5)	1 (2.9)	1.9 (1.2)	1.6 (0.7)
		IFN beta-1a 30 mcg q.w.	250	37.6 (10.2)	1.4 (4)	2 (1.2)	1.7 (0.9)

Trial, Year	Trial Duration (Months)	Treatment	Sample Size	Age in Years, Mean (SD)	Duration of Disease in Years, Mean (SD)	EDSS Baseline Score, Mean (SD)	Number of Relapses 1 Year Prior to Baseline, Mean (SD)
Comi (2001)	9	GA 20 mg q.d.	119	18 to 50[a]	8 (NR)	2.4 (NR)	NR
		PL	120				
CONFIRM	24	DMF 240 mg t.i.d.	345	18 to 55[a]	5 (NR)	2.6 (NR)	NR
		DMF 240 mg b.i.d.	362				
		GA 20 mg q.d.	350				
		PL	363				
DEFINE	24	DMF 240 mg t.i.d.	416	18 to 55[a]	6 (NR)	2.4 (NR)	NR
		DMF 240 mg b.i.d.	411				
		PL	410				
Etemadifar (2007)	12	Azathioprine 3mg/kg q.d.	47	13 to 50[a]	NR	1.5 (NR)	NR
		IFN beta-1b 250 mcg q.o.d.	47				
		IFN beta-1a 30 mcg q.w.	19				
		IFN beta-1a44 mcg t.i.w.	13				
EVIDENCE	12	IFN beta-1a 30 mcg q.w.	338	37.4	6.7 (NR)	2.3 (NR)	NR
		IFN beta-1a 44 mcg t.i.w.	339	38.3	6.5 (NR)	2.3 (NR)	
Fazekas (1997)	24	Immunoglobulins 0.15 to 0.2 g/kg q.m.t.	75	15 to 64[a]	7 (NR)	3.3 (NR)	NR
		PL	75				
Fazekas (2008)	12	Immunoglobulins 0.2 g/kg q.m.t.	45	18 to 55[a]	3 (NR)	2.0 (NR)	NR
		Immunoglobulins 0.4 g/kg q.m.t.	42				
		PL	41				
FREEDOMS	24	Fingolimod 1.25 mg q.d.	429	18 to 55[a]	8 (NR)	2.4 (NR)	NR
		Fingolimod 0.5 mg q.d.	425				
		PL	418				
FREEDOMS II	24	Fingolimod 1.25 mg q.d.	370	18 to 55[a]	11 (NR)	2.4 (NR)	NR
		Fingolimod 0.5 mg q.d.	358				
		PL	355				
GALA	12	GA 40 mg t.i.w.[b]	943	18 to 55[a]	8 (NR)	2.8 (NR)	NR
		PL	461				
Goodkin (1991)[b]	24	Azathioprine 3.0 mg/kg q.d.	30	18 to 65[a]	6 (NR)	3.5 (NR)	NR
		PL	29				

Trial, Year	Trial Duration (Months)	Treatment	Sample Size	Age in Years, Mean (SD)	Duration of Disease in Years, Mean (SD)	EDSS Baseline Score, Mean (SD)	Number of Relapses 1 Year Prior to Baseline, Mean (SD)
IFNB MS	60	IFN beta-1b 250 mcg q.o.d.	124	35.2	4.7 (NR)	3 (NR)	NR
		IFN beta-1b 50 mcg q.o.d.	125	NR[c]	NR[c]	NR[c]	
		PL	123	36	3.9 (NR)	2.8 (NR)	
INCOMIN	24	IFN beta-1a 30 mcg q.w.	92	18 to 50[a]	6 (NR)	2.0 (NR)	NR
		IFN beta-1b 250 mcg q.o.d.	96				
Johnson (1995)	24	GA 20 mg q.d.	125	18 to 45[a]	7 (NR)	2.6 (NR)	NR
		PL	126				
Koch-Henriksen (2006)	24	IFN beta-1b 250 mcg q.o.d.	158	18 to 55[a]	8 (NR)	2.9 (NR)	NR
		IFN beta-1a 22 mcg q.w.	143				
Lewanska (2002)	12	Immunoglobulins 0.2 g/kg q.m.t.	17	18 to 55[a]	9 (NR)	3.0 (NR)	NR
		Immunoglobulins 0.4 g/kg q.m.t.	16				
		PL	18				
MAIN	24	Azathioprine 36 mg/kg q.d.	77	18 to 55[a]	6 (NR)	1.9 (NR)	NR
		IFN beta-1a 30 mcg q.w.	26				
		IFN beta-1a 22 mcg t.i.w.	35				
		IFN beta-1a 44 mcg t.i.w.	7				
		IFN beta-1b 250 mcg q.o.d.	5				
Millefiorini (1997)	24	Mitoxantrone 8mg/m^2 q.m.t.	27	18 to 45[a]	5 (NR)	3.6 (NR)	NR
		PL	24				
MSCRG	24	IFN beta-1a 30 mcg q.w.	158	36.7	6.6 (NR)	2.4 (0.8)	NR
		PL	143	36.9	6.4 (NR)	2.3 (0.8)	
OWIMS	12	IFN beta-1a 22 mcg t.i.w.	95	18 to 50[a]	7 (NR)	2.6 (NR)	NR
		IFN beta-1a 44 mcg t.i.w.	98				
		PL	100				
PRISMS	24	IFN beta-1a 22 mcg t.i.w.	189	34.8[c]	5.4[c]	2.5 (1.2)	NR
		IFN beta-1a 44 mcg t.i.w.	184	35.6[c]	6.4[a]	2.5 (1.3)	
		PL	187	34.6[c]	4.3[c]	2.4 (1.2)	
REGARD	24	GA 20 mg q.d.	378	36.8 (9.5)	–	2.33 (1.31)	NR
		IFN beta-1a 44 mcg t.i.w.	386	36.7 (9.8)	3.7	2.35 (1.28)	1[c]
SELECT	12	DAC 300 mg q.4.w.[b]	209	18 to 55[a]	3 (NR)	2.7 (NR)	NR

Trial, Year	Trial Duration (Months)	Treatment	Sample Size	Age in Years, Mean (SD)	Duration of Disease in Years, Mean (SD)	EDSS Baseline Score, Mean (SD)	Number of Relapses 1 Year Prior to Baseline, Mean (SD)
		DAC 150 mg q.4.w.	208				
		PL	204				
TEMSO	24	TER 14 mg q.d.	359	18 to 55[a]	9 (NR)	2.7 (NR)	NR
		TER 7 mg q.d.[b]	366				
		PL	363				
TENERE	12	TER14 mg q.d.	111	≥ 18	7 (NR)	2.1 (NR)	NR
		TER 7 mg q.d.[b]	109				
		IFN beta-1a 44 mcg t.i.w.	104				
TOWER	12	TER 14 mg q.d.	372	18 to 55[a]	8 (NR)	2.7 (NR)	NR
		TER 7 mg q.d.[b]	408				
		PL	389				
TRASFORMS	12	IFN beta-1a 30 mcg q.w.	435	18 to 55[a]	7 (NR)	2.2 (NR)	NR
		Fingolimod 1.25 mg q.d.[b]	426				
		Fingolimod 0.5 mg q.d.	431				

ALM = alemtuzumab; b.i.d. = twice daily; DAC = daclizumab; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFN = interferon; IV = intravenously; NAT = natalizumab; NR = not reported; peg = pegylated; PL = placebo; q.d. = once daily; q.2.w. = once every two weeks; q.4.w. = once every four weeks; q.d. = once daily; q.m.t. = monthly; q.o.d. = every other day; q.w. = once weekly; SD = standard deviation; TER = teriflunomide; t.i.d. = three times a day; t.i.w. = three times a week.

[a] Median and/or range.

[b] Not approved or indicated by Health Canada.

[c] Only reported as a total across all groups.

[d] ALM 24 mg q.d. IV on five consecutive days during first month and on three consecutive days at months 12 and 24.

[e] ALM 12 mg q.d. IV on five consecutive days at month 0 and three consecutive days at month 12.

[f] Immunoglobulins 0.4 g per kg body weight IV daily for five consecutive days, followed by additional booster doses of immunoglobulins 0.4 g per kg body weight IV daily every two months for 24 months.

Source: Tramacere et al.[16]

ITC Methods

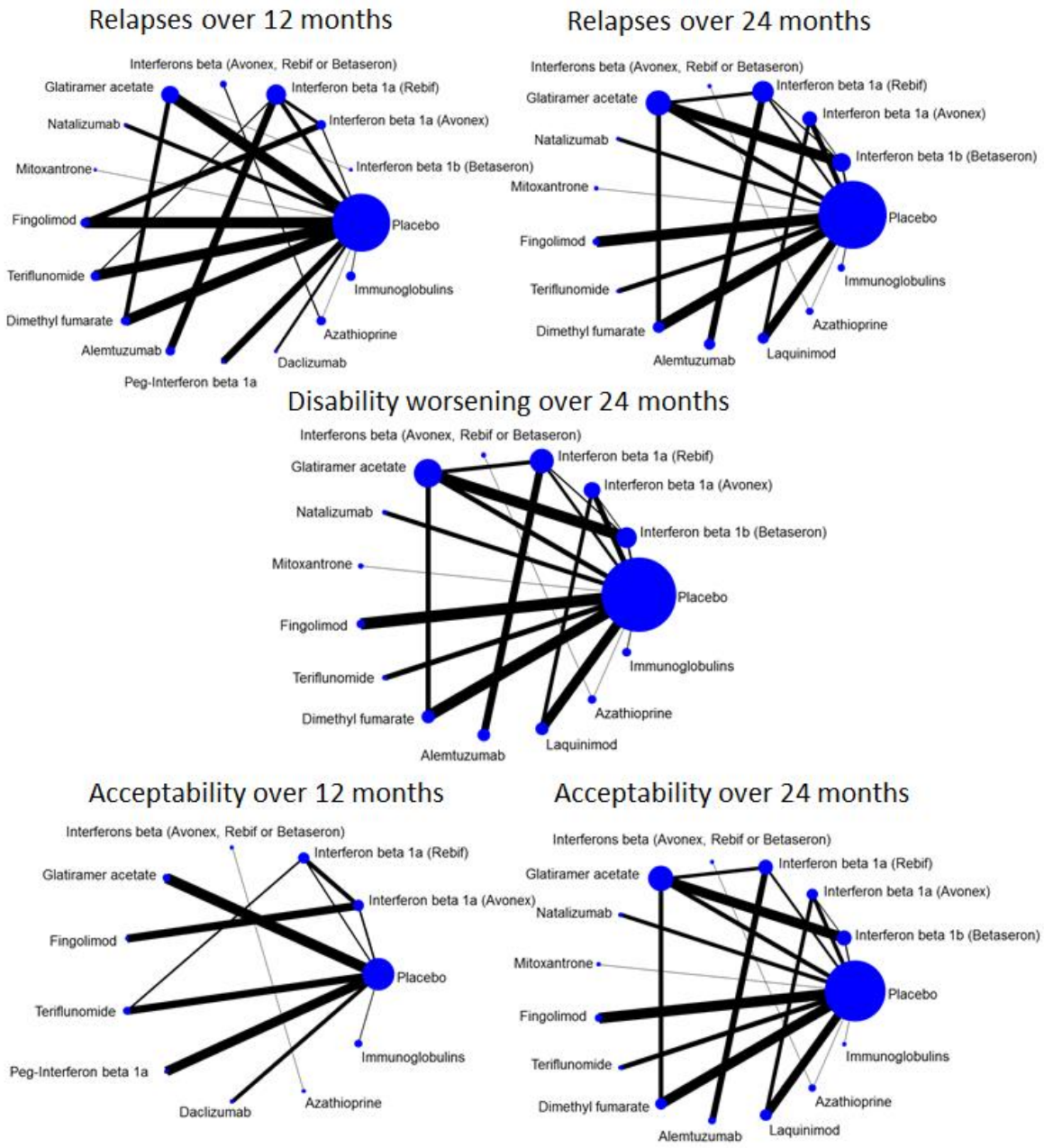
The NMA was performed using the "mvmeta" command (along with other self-programmed routines) in Stata 13. An RE frequentist model was used, with the authors assuming equal heterogeneity across comparisons. In addition, correlations induced by multi-group trials were accounted for. Statistical heterogeneity was assessed based on the magnitude of heterogeneity variance parameter (T^2) and this was estimated from previous NMA models. Local inconsistency was assessed using a loop-specific method, whereby each closed loop in the network was evaluated separately as the difference between direct and indirect estimates (termed the inconsistency factor). Inferences regarding the presence of inconsistency in each loop were ascertained by examining the magnitude of these factors and their corresponding 95% CIs (the results of which were presented in a forest plot). Global inconsistency of the entire network was ascertained using the "design-by-treatment" model, whereby a Chi^2 test was performed in Stata. This method accounts for inconsistency when studies with different designs give different results or there are differences between the direct and indirect evidence. The authors also evaluated the inconsistency using I^2, as this specifically measures the variability percentage not attributable to random error or heterogeneity.

A priori subgroup analyses were performed to assess the benefit at 12, 24, and 36 months for the following potential effect modifiers: diagnostic criteria (for those diagnosed with Poser or McDonald), previous immunomodulator or immunosuppressant treatment, relapse definition (24 or 48 hours), pre-trial relapse rates and the years over which this was calculated (number of relapses; one or greater than one relapse in the year before randomization, one or greater than one relapse in the two years before randomization, two or greater than two relapses in the two or three years before randomization). The authors also performed a priori sensitivity analyses that evaluated the following: including only low risk of bias trials, excluding trials that did not report or insufficiently reported dropout rates, excluding trials with small sample size (e.g., less than 50 patients).

Evidence Networks

Evidence networks were presented for each outcome at each time point in Figure 7.

FIGURE 7: NETWORKS OF TREATMENT COMPARISONS USED TO ASSESS BENEFIT AND ACCEPTABILITY



Reproduced with permission from Tramacere et al., "Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: A network meta-analysis." Cochrane Database system review 2015;9:CD011381.

Results

Study and Patient Characteristics

Of the 39 included studies (n = 25,113) that were published between 1987 and 2014, 15 studies (40%) were active-comparator trials and 24 studies (60%) were placebo-controlled. For the assessment of overall risk of bias, the authors noted that three (8%), 16 (41%), and 20 (51%) studies were deemed to be of low risk of bias, moderate risk of bias, and high risk of bias, respectively. Allocation methods were

reported in 34 (87%) studies, while the authors noted that the other five trials (13%) were lacking in the information necessary to assess this. According to the authors, adequate allocation concealment was evident in 21 (54%) studies, one study used an unconcealed procedure (Bornstein 1987), and the other 17 (44%) studies did not provide adequate information on allocation concealment. In addition, both investigators and patients were blinded in 12 (31%) studies, no blinding was reported in 15 (38%) studies, and sufficient information on blinding was not reported in 12 (31%) other studies. A low risk of detection bias was evident in 19 (49%) studies, high risk was evident in seven studies (18%), and sufficient information on detection bias was not provided in 13 (33%) studies, according to the authors. The criteria for low risk of incomplete outcome data was determined to be met in 20 (51%) studies, 14 studies (36%) were at high risk, and the remaining five studies (13%) did not provide sufficient information for this assessment. Patients lost to follow-up in the 39 included studies ranged between 0% and 43%, with a median of 11.9% and a mean of 13.5%. Only three trials did not report primary benefit outcomes (CONFIRM, DEFINE, and TEMSO).

A high risk of bias was noted in 33 (85%) studies with regard to either the role of the sponsor or in the management or assessment of the data (27 studies), or incomplete reporting of data on outcomes or discontinuations (27 studies).

The authors noted that AEs were appropriately and actively monitored in 28 (72%) trials, with the other eight trials (21%) not providing sufficient information on how they monitored such events. A high risk of bias was noted in the three studies (Bornstein 1987, EVIDENCE, and Goodkin 1991) that spontaneously reported AEs. Fifteen studies (38%) provided a definition of SAEs, 15 trials (38%) reported SAEs but did not provide sufficient information regarding their definition, and nine studies (23%) did not report any SAEs.

Trial durations ranged between nine and 36 months and total study sample sizes ranged between 40 and 2,244, with sample sizes per arm ranging between five and 943 patients. The mean age of the included patients ranged between fewer than 18 years to 39 years of age (standard deviation of 9.5 to 10.2 years [when reported; however, most did not report standard deviation]), while ages were more often reported as ranges (one study reported its range between 19 years and 60 years, one study reported its range between 13 years and 50 years, one study reported its range between 15 years and 64 years, six studies reported ranges between 18 years and 50 years, and 15 studies reported ranges between 18 years and 55 years). Mean disease duration in years ranged between 0.9 years to 11 years (standard deviation ranging between 2.9 years and 5.09 years when reported; however, most studies did not report). Mean EDSS baseline scores ranged between 1.5 and 3.6 (standard deviation ranging between 0.8 and 1.31 when reported; however, most studies did not report). Most studies did not report on the number of relapses occurring in the year before randomization; however, in those that did (n = 3) the number of relapses ranged between 1.5 and 1.7 (standard deviation ranging between 0.7 and 0.9). Two other studies reported the number of relapses in the year before randomization as a total across all groups.

Efficacy — Relapses at 12 Months

Since this review focused upon the efficacy and safety of DAC beta, only those results that were available with regard to this specific drug will be included; therefore, only the risk of relapses over 12 months (in terms of efficacy) was presented.

No statistically significant differences were observed in the risk of relapse over 12 months when comparing DAC beta to IFN beta-1a (Avonex, Rebif), IFN beta-1b (Betaseron), peg-IFN beta-1a (Plegridy),

azathioprine, the interferons beta (as a complete group), or teriflunomide. When other DMTs were compared for the risk of relapse over 12 months relative to DAC beta (dimethyl fumarate, fingolimod, glatiramer acetate, immunoglobulins, mitoxantrone, natalizumab, or alemtuzumab), only alemtuzumab had a statistically significant risk reduction (risk ratio of 0.50 [95% confidence interval, 0.5 to 0.72]). Detailed efficacy and acceptability results are presented in Table 24. No direct pairwise meta-analysis was available to ascertain whether there were inconsistencies between the direct pairwise results or for the indirect evidence of risk of relapse over 12 months as there was only one study that informed the comparison of DAC beta (SELECT).

No data were available to compare DAC beta with other drugs on disability progression at 12 months.

While the authors did not find any evidence of differences of variables across treatment comparisons (and did not alter treatment efficacy), or that any of the potential effect modifiers were a source of heterogeneity or inconsistency, they did note that not only were there few studies informing each comparison but results were uncertain with regard to both the subgroup and sensitivity analyses. It is for these reasons that the authors were unable to form any firm conclusions regarding the existence or lack of heterogeneity and the transitivity. For this reason they downgraded the quality of the evidence for inconsistency in most of the comparisons.

Acceptability – Discontinuations due to AEs over 12 Months
No statistically significant differences were observed with regard to discontinuations due to AEs over 12 months for DAC beta relative to IFN beta 1-a (Avonex, Rebif), peg-IFN beta-1a (Plegridy), azathioprine, the IFNs beta (as a complete group), or teriflunomide. No statistically significant differences were observed when other DMTs were compared for the risk of discontinuations due to AEs relative to DAC beta (fingolimod, glatiramer acetate, immunoglobulins, mitoxantrone, or natalizumab).

No direct pairwise meta-analysis was available to ascertain whether there were inconsistencies between the direct pairwise results and the indirect evidence for discontinuations due to AEs over 12 months, as there was only one study that informed the comparison of DAC beta (SELECT).

Harms — SAEs
Since DAC beta 150 mg every four weeks was only examined in one study (which compared another dose of DAC beta and placebo), it was not included in any formal pairwise analysis for SAEs.

However, it is important to note that, in the included trials, the authors observed that SAEs were poorly reported, there were a very low number of events, or the results were heterogeneous.

TABLE 24: RESULTS OF THE NETWORK META-ANALYSIS BY TRAMACERE ET AL.

Treatment	Outcomes Over 12 Months[a]	
	Relapse RR (95% CI)	Discontinuations due to AEs RR (95% CI)
DAC beta relative to:		
Avonex (IFN beta-1a)	0.85 (0.63 to 1.16)	0.90 (0.17 to 4.73)
Azathioprine	0.90 (0.56 to 1.46)	3.43 (0 to NA)
Betaseron (IFN beta-1b)	0.81 (0.43 to 1.52)	–
IFNs beta	0.76 (0.42 to 1.36)	3.43 (0 to NA)
Plegridy (peg-IFN beta-1a)	0.89 (0.63 to 1.26)	1.40 (0.28 to 7.06)

Treatment	Outcomes Over 12 Months[a]	
	Relapse RR (95% CI)	**Discontinuations due to AEs RR (95% CI)**
Rebif (IFN beta-1a)	0.90 (0.68 to 1.21)	0.81 (0.17 to 3.97)
Teriflunomide	0.94 (0.70 to 1.27)	1.75 (0.38 to 7.95)
Other comparisons:		
Alemtuzumab vs. DAC beta	**0.50 (0.5 to 0.72)**	–
Dimethyl fumarate vs. DAC beta	0.98 (0.73 to 1.34)	–
Fingolimod vs. DAC beta	0.79 (0.59 to 1.07)	2.11 (0.37 to 11.93)
Glatiramer acetate vs. DAC beta	1.01 (0.75 to 1.35)	0.55 (0.11 to 2.90)
Immunoglobulins vs. DAC beta	0.99 (0.69 to 1.40)	0.52 (0.04 to 7.17)
Mitoxantrone vs. DAC beta	0.50 (0.25 to 1.01)	–
Natalizumab vs. DAC beta	0.70 (0.49 to 1.02)	–

AE = adverse event; CI = confidence interval; DAC = daclizumab; IFN = interferon; NA = not available; peg = pegylated; RR = risk ratio.
[a] Values below 1 positively favour drug listed first.
Note: Statistically significant results are bolded.
Source: Tramacere et al.[16]

A1.3.1 Critical Appraisal of ITC B

The authors provided clear objectives and rationale for performing their ITC. Their eligibility criteria, information sources, search strategy, dual-study selection process, dual-data extraction, and dual-study quality assessment were clearly outlined and appropriate for a comprehensive systematic review. In particular, they assessed the risk of bias associated with allocation concealment, blinding, incomplete outcome data, selective reporting, potential bias associated with sponsorship, methods of AE monitoring, and SAE definitions and reporting. High-level descriptions of the baseline characteristics in the included studies were provided along with reasons pertaining to why certain evidence was downgraded. A list of excluded studies was also provided along with reasons for exclusion. DECIDE was not included because it was ongoing at the time the NMA was conducted.

Methods for performing the NMA were provided, along with detailed network diagrams for each of the pre-specified outcome measures of interest. Data analyses were based on frequentist RE NMAs (for indirect and mixed comparisons) and pairwise meta-analysis (for direct comparisons), and subgroups and sensitivity analyses were also performed as specified a priori. While the methodology was appropriate, the authors did not perform regression analysis to assess model fit, particularly when the wide CIs for the discontinuations due to AEs were obtained. These wide CIs decrease the confidence in the precision of the effect estimates and increase the uncertainty of the results for this outcome.

The main limitation with this ITC was the fact that the baseline study designs and patient characteristics were heterogeneous across studies. For instance, trial durations ranged between nine and 36 months, with a median duration of 24 months. In addition, sample sizes ranged from five to 943 patients. These differences in study designs could affect the results of the NMA, thereby reducing the confidence in the results. The authors did perform different subgroup analyses for the assessment of potential effect modifiers (diagnostic criteria, previous treatments, definition of relapse, and pre-trial relapse rate) which did not differ from the base-case analyses; however, they only presented their results for these according to the three best drugs based on moderate– to high-quality evidence (alemtuzumab, natalizumab, and fingolimod). Therefore, one cannot fully assess whether the results were similar or discordant for those pertaining to DAC. In addition, the authors acknowledged that there were few

studies informing these comparisons and, due to the limitations associated with study reporting, differences between the subgroups could not be completely excluded. With regard to the baseline patient characteristics, there were many that were observed to be heterogeneous. For instance, the mean disease duration ranged between 0.9 and 11 years. This range has the potential to reduce the generalizability to the overall population with RRMS as studies that included patients with longer disease duration may have included patients whose disease is more resistant to treatment. Furthermore, most studies did not report on the number of relapses occurring in the year before randomization; therefore, uncertainty in this parameter (which could help to indicate disease severity) remains.

The authors sought to assess both transitivity and heterogeneity; however, there were numerous problems with the assumptions underlying these analyses. The authors noted that there were few studies that informed each of the NMA comparisons and, as previously mentioned, there was uncertainty regarding both the subgroup and sensitivity analyses. While they did state that they did not find any evidence of differences of variables across treatment comparisons (treatment efficacy was not altered) or that any of the potential effect modifiers were a source of heterogeneity or inconsistency, the authors were unable to determine the existence or lack of heterogeneity or transitivity. With regard to inconsistency, the authors noted some evidence of local inconsistency (two loops for relapse over 24 months and three loops for disability worsening over 24 months; none were noted for relapses over 12 months or acceptability over 12 and 24 months) but no evidence in global inconsistency. However, evidence quality for inconsistency was downgraded as there were few studies informing the comparisons and few closed loops. In addition, evidence was frequently downgraded by the authors based on GRADE criteria from high quality to moderate or low quality for most comparisons. Only three of the 39 studies were judged to be at low risk of bias for outcome data being complete, outcome assessor blinding, and allocation concealment. It was also noted that reporting bias could not be excluded as supported by their contour-enhanced funnel plot for relapses over 12 and 24months.

The authors noted that, with MS being a chronic life-long disease (once diagnosed), the long-term safety and efficacy of the MS treatments were lacking because the trials were too short in duration. In addition, there were significant limitations noted in individual trials with respect to reporting of SAEs. The authors noted that SAE data were often sparsely or poorly reported, and were heterogeneous; therefore, the confidence surrounding the interpretation of these results was decreased.

A1.4 Discussion

Two ITCs were summarized and critically appraised in this review: the manufacturer-submitted ITC[50] and the Tramacere et al. ITC[16] that was identified in a supplemental literature search. While both ITCs included many of the same studies, their conclusions were different with regard to the efficacy of DAC beta in terms of the relative risk reduction in relapses over 12 months (reported as ARR in the manufacturer-submitted ITC). The manufacturer-submitted ITC observed statistically significant reductions in the risk of relapse in favour of DAC beta 150 mg once every four weeks in the overall population, relative to IFN beta-1a 30 mcg once weekly, IFN beta-1a 44 mcg three times a week, IFN beta-1b 250 mcg every other day, glatiramer acetate 20 mg once daily, glatiramer acetate 40 mg three times a week, and teriflunomide 14 mg once daily. In contrast, Tramacere et al. did not observe any statistically significant differences in the risk of relapse over 12 months when comparing DAC to IFN beta-1a (Avonex, Rebif), IFN beta-1b (Betaseron), peg-IFN beta-1a (Plegridy), azathioprine, the IFNs beta (as a complete group), or teriflunomide. There were differences in the number of included studies (n = 30 and n = 39 for the manufacturer-submitted and Tramacere et al. ITCs, respectively), which could have been a factor for some of the differences. DECIDE — one of the pivotal studies included in the CADTH

Common Drug Review (CDR) review of DAC — was ongoing at the time of the Tramacere et al. ITC and therefore was not included in their analysis. Bias in favour of DAC beta may have been introduced in the manufacturer-submitted ITC as they funded their analysis and all results were conducted to observe whether DAC beta held up to the other DMTs (while that of Tramacere et al. was more objective in the sense that they were observing how well all treatments compared with each other). In addition, the included studies in both ITCs were heterogeneous in terms of study and patient characteristics. In the manufacturer-submitted ITC, the authors had difficulty assessing the actual disease duration of the patients and hence combined all patients for analyses, regardless of the differing definitions (years since diagnosis, years since first MS symptoms, and those studies that did not report). In addition, both ITCs noted that there was a lack of reporting of the differing domains of the Cochrane risk of bias tool, with both authors stating a lack of reporting in at least one domain in most studies and a lack of appropriate blinding among a lot of studies (hence reducing the confidence in the results of that individual trial). Another potential issue was that the overall population was used to obtain the effect estimates in all of the networks. In addition, Tramacere et al. included a broader range of comparators, while the manufacturer-submitted ITC only included the DMTs. Finally, in the manufacturer-submitted ITC, all trials that reported on ARR were combined into the network regardless of the differences between follow-up times (e.g., some studies reported ARR at 12 months, while other studies reported ARR at 24 months or different time points). All of these aforementioned issues have the potential to affect the results of both NMAs. Of note: while the ITCs were different with regard to most risk of relapse estimates, both reported a statistically significant reduction in the risk of relapse in favour of alemtuzumab relative to DAC beta.

With regard to confirmed disability at three or six months, no significant risk reductions were observed between DAC beta relative to other DMTs in the manufacturer-submitted ITC. There were substantial uncertainties associated with both networks for these outcomes; however, the authors ascertained that this was most likely due to the small number of studies informing the networks. Tramacere et al. did not look at confirmed disability at three or six months; rather they looked at disability worsening at 24 and 36 months. There were no results pertaining to DAC beta in this respect.

The manufacturer performed a NMA for any SAE at 24 months (while excluding MS relapse as an SAE) in their ITC. Relative to other DMTs, no statistically significant differences in the risks of SAEs were observed for DAC beta. The fact that some of the CIs surrounding the effect estimates were quite large indicated a lot of imprecision and uncertainty, something the authors attributed to the NMA comparisons being affected by single studies. The FE model confirmed these results even though it produced tighter CIs. No formal pairwise comparison was performed for DAC beta with regard to SAEs in the Tramacere et al. ITC as there was only one study identified that examined DAC beta (SELECT), and it was compared against placebo. The authors did note that SAEs were poorly reported, there were low numbers of events, and the SAE results were heterogeneous in their included studies.

Both ITCs reported on discontinuations; however, the manufacturer's ITC focused on treatment discontinuations due to any cause (including the proportion of patients who discontinued study treatment due to any cause or who discontinued the study due to any cause), while the Tramacere et al. ITC focused on discontinuations due to AEs. No statistically significant differences in the risks of treatment discontinuations due to any cause were evident when comparing DAC beta to other DMTs. In addition, the CIs surrounding the effect estimate were wide, indicating imprecision and uncertainty. The FE model confirmed these results even though it produced tighter confidence intervals. Results for discontinuations due to AEs in the Tramacere et al. ITC were similar to the aforementioned results from

the other ITC, with no statistically significant differences in the risk of discontinuations observed between DAC and the other drugs assessed.

One important aspect to note is that both of the ITCs performed their analysis in the overall population of patients with RRMS, which does not necessarily help for the purposes of this review. Subgroup analyses that would have included the population of interest were either performed in small (one– or two-study) networks or were not performed at all (due to the lack of studies). This precludes one's ability to assess the results in the indicated population of interest (in patients who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of MS).

A1.5 Conclusion

Two ITCs were summarized and critically appraised in this review; the manufacturer-submitted ITC[50] and the Tramacere et al. ITC[16] that was identified in a supplemental literature search. In the manufacturer's ITC, DAC beta 150 mg once every four weeks was observed to reduce the risk of relapse relative to the older DMTS, including IFN beta-1a 30 mcg once weekly, IFN beta-1a 44 mcg three times a week, IFN beta-1b 250 mcg every other day, glatiramer acetate 20 mg once daily, glatiramer acetate 40 mg three times a week, and teriflunomide 14 mg once daily. In contrast, Tramacere et al. did not observe any statistically significant differences in the risk of relapse over 12 months when comparing DAC to IFN beta-1a (Avonex, Rebif), IFN beta-1b (Betaseron), peg-IFN beta-1a (Plegridy), azathioprine, the IFNs beta (as a complete group), or teriflunomide. While many of the same studies were included in both ITCs (the manufacturer included 30 studies, while Tramacere et al. included 39 studies), there were differences between the ITCs. For instance, Tramacere et al. included a broader range of comparators while the manufacturer-submitted ITC only included the DMTs. Also, all trials that reported on ARR were combined into the network regardless of the differences between follow-up times in the manufacturer's ITC (e.g., some studies reported ARR at 12 months, while other studies reported ARR at 24 months or different time points). In addition to the aforementioned differences, there remains considerable uncertainty and lack of confidence in the results due to the clinical heterogeneity of the patients, differences in certain definitions, and lack of reporting in the included studies (in both ITCs). It should also be noted that the results from both ITCs were observed in the overall population, which included both treatment-naive and treatment-experienced patients, not only in the patient population of interest (patients who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of MS). All of these aforementioned issues have the potential to affect the results of both NMAs, which reduces one's confidence in the NMA results for all of the outcomes examined. Of note: while the ITCs were different with regard to most of the risk of relapse estimates, both reported a statistically significant reduction in the risk of relapse in favour of alemtuzumab relative to DAC beta.

In the manufacturer-submitted ITC, no statistically significance differences in reducing the risk of confirmed disability at three or six months were observed in DAC beta relative to any of the DMTs.

With regard to the NMA for any SAE at 24 months (while excluding MS relapse as an SAE), no statistically significant differences in the risks of SAEs were observed for DAC beta relative to any of the DMTs in the manufacturer-submitted ITC. No formal pairwise comparison was performed for DAC beta with regard to SAEs in the Tramacere et al. ITC, as there was only one study identified that examined DAC beta (SELECT) and it was compared against placebo. No statistically significant differences in the risks of treatment discontinuations due to any cause were evidence when comparing DAC beta to other DMTs in the manufacturer-submitted ITC. In addition, the confidence intervals surrounding the effect estimate

were wide, indicating imprecision and uncertainty. Results for discontinuations due to AEs in the Tramacere et al. ITC were similar to the aforementioned results from the other ITC, with no statistically significant differences in the risk of discontinuations observed between DAC and the other drugs assessed. Even though these two harms results were not statistically significant, uncertainty remains regarding these results (presumably due to the heterogeneity of the studies and patient characteristics) and they should be interpreted with caution.

While the systematic reviews and NMA methodologies appeared to have been conducted in a rigorous manner in both ITCs, there were numerous issues with heterogeneity between the baseline patient characteristics and study characteristics, as well as limitations with respect to the design and conduct of included studies, and relatively sparse networks that reduce confidence in and increase uncertainty with regard to the NMA results. In addition, neither ITC examined the comparative efficacy and safety of DAC versus other drugs in the population specified in the Health Canada indication for DAC, making it difficult to generalize these results to applicable patients with RRMS. With regard to all of the aforementioned issues associated with the included trials, it is uncertain whether or not transitivity was upheld in either ITC; therefore, caution should be heeded when interpreting the results for all of the outcomes. Overall, there is insufficient evidence to determine if there is a meaningful clinical difference between DAC and other DMTs for the treatment of RRMS.

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