Common Drug Review
Clinical Review Report

June 2015

Drug	alemtuzumab (Lemtrada, intravenous)
Indication	For the management of adult patients with relapsing-remitting multiple sclerosis (RRMS), with active disease defined by clinical and imaging features, who have had an inadequate response to interferon beta or other disease-modifying therapies.
Listing request	[redacted]
Manufacturer	Genzyme Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

9HPT	9-Hole Peg Test
Advocare	The Consumer Advocare Network
ARR	annualized relapse rate
B-CLL	B-cell chronic lymphocytic leukemia
CDR	CADTH Common Drug Review
CI	confidence interval
CMSWG	Canadian Multiple Sclerosis Working Group
DMT	disease-modifying therapy
EDSS	Kurtzke Expanded Disability Status Scale
EQ-5D	EuroQol 5-Dimensions Questionnaire
FA	full analysis
FAMS	Functional Assessment of Multiple Sclerosis
FDA	Food and Drug Administration
FS	functional system
Gd	gadolinium
IAR	infusion-associated reaction
ITP	idiopathic thrombocytopenic purpura
IV	intravenous
MCID	minimal clinically important difference
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MS Society	Multiple Sclerosis Society of Canada
MTC	mixed treatment comparison
PASAT3	Paced Auditory Serial Addition Test (3-Second Version)
PML	progressive multifocal leukoencephalopathy
RRMS	relapsing-remitting multiple sclerosis
SAD	sustained accumulation of disability
SD	standard deviation
SF-36	Short Form (36) Health Survey
SRD	sustained reduction in disability
T25FW	Timed 25-Foot Walk Test
VAS	visual analogue scale

EXECUTIVE SUMMARY

Introduction

Multiple sclerosis (MS) is a chronic, progressive immune-mediated disease of the central nervous system during which the white matter within the brain or spinal cord becomes inflamed and destroyed in a process called demyelination. MS involves a complex interplay of genetic and environmental factors that result in the abnormal activation and proliferation of T-cells and other immune cells. Relapsing-remitting multiple sclerosis (RRMS) 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 period between relapses. The goal of therapy is to decrease the number and severity of relapses, limit disability progression, and maintain patient quality of life. Therapies available for the management of RRMS in Canada include interferon beta, glatiramer acetate, fingolimod, natalizumab, dimethyl fumarate, teriflunomide, and now alemtuzumab.

Alemtuzumab is a recombinant, humanized, monoclonal antibody directed against CD52 and may exert its effect through the depletion of autoreactive T and B lymphocytes and subsequent rebalancing of the immune system. According to the Health Canada–approved product monograph, alemtuzumab is administered at a recommended dose of 12 mg/day over two treatment cycles: an initial treatment cycle over five consecutive days, and a second treatment cycle given 12 months after the initial treatment over three consecutive days. Alemtuzumab is available as a concentrated solution for infusion as 1.2 mL (10 mg/mL) single-use vials. The indication under review is listed below.

Indication under review
For the management of adult patients with relapsing-remitting multiple sclerosis (RRMS), with active disease defined by clinical and imaging features, who have had an inadequate response to interferon beta or other disease-modifying therapies.

The objective of this systematic review is to examine the beneficial and harmful effects of intravenous alemtuzumab in the treatment of RRMS in patients who have had an inadequate response to interferon beta or other disease-modifying therapies.

Results and Interpretation

Included Studies

One two-year, randomized, rater-blind, active-controlled study met the inclusion criteria for this systematic review. CARE-MS II (N = 810) evaluated the efficacy and safety of intravenous alemtuzumab 12 mg compared with subcutaneous interferon beta-1a 44 mcg in patients 18 to 55 years of age who meet the 2005 McDonald criteria for active RRMS with a disease duration of 10 years or less who had previously experienced a relapse while on at least six months of interferon beta or glatiramer acetate therapy. Patients were originally randomized to an alemtuzumab 24 mg group as well, but a protocol amendment discontinued randomization into this group and subsequent efficacy analyses were considered exploratory and are not presented in this review. The majority of study participants were female, and the mean age was 35 years. Baseline median Kurtzke Expanded Disability Status Scale (EDSS) score was 2.5, with scores ranging from 0.0 to 6.5, and the mean number of relapses in the past year was 2.7. The majority of patients (71.7%) had taken only one prior MS medication. The co-primary efficacy outcomes in CARE-MS II were annualized relapse rate (ARR) and time to six-month sustained accumulation of disability. Patients who completed the CARE-MS II study were eligible for entry into a rater-blind extension study (CAMMS03409) for up to four years of efficacy and safety assessments.

The limitations of the available evidence include the open-label design of CARE-MS II and the differences in study withdrawals between the alemtuzumab 12 mg and interferon beta-1a groups, which may have biased the results of the between-treatment comparisons. As alemtuzumab is being reviewed for patients who have had an inadequate response to interferon beta or other disease-modifying therapies, interferon beta-1a may not be the most appropriate comparator. There is a lack of trials directly comparing alemtuzumab with other disease-modifying therapies (DMTs) and, in particular, those generally recommended by Health Canada for patients who have had an inadequate response to other DMTs (e.g., natalizumab or fingolimod).

Efficacy

Key outcomes identified in this CADTH Common Drug Review (CDR) were: relapse rate, disability, health-related quality of life, and fatigue.

The ARR through two years was statistically significantly lower in the alemtuzumab group (0.26 [95% confidence interval (CI), 0.21 to 0.33]) compared with the interferon beta-1a group (0.52 [95% CI, 0.41 to 0.66]); rate ratio 0.51 (95% CI, 0.39 to 0.65). The proportion of patients with six-month sustained accumulation of disability (SAD) over two years, based on Kaplan–Meier estimates, was statistically significantly lower for the alemtuzumab group (12.7%) compared with interferon beta-1a (21.1%), and time to six-month SAD was statistically significantly less for interferon beta-1a, hazard ratio 0.58 (95% CI, 0.38 to 0.87). Sensitivity analyses were conducted to assess the influence of alternative MS treatments, unblinded EDSS raters, patient dropout prior to receiving treatment, and other factors that could potentially affect the co-primary outcomes. The results of the sensitivity analyses were similar to the estimated treatment effects in the primary relapse rate and time to six-month SAD analyses.

Other disability measures included the change from baseline in EDSS and Multiple Sclerosis Functional Composite (MSFC). The change from baseline in EDSS score at year 2 was statistically significantly different between treatment groups, with the alemtuzumab group showing a mean improvement from baseline and the interferon beta-1a group showing a mean decline from baseline (mean difference: 0.41 [95% CI, –0.61 to –0.22]). Statistical testing was not performed on the change from baseline in MSFC scores at year 2 due to the rank order of the hierarchical chain of testing.

Health-related quality of life measures that were used in CARE-MS II include the Functional Assessment of Multiple Sclerosis (FAMS), Short Form (36) Health Survey (SF-36), and EuroQol 5-Dimensions Questionnaire (EQ-5D). There was a greater improvement from baseline in overall FAMS scores (mean difference 5.34 [95% CI, 1.31 to 9.38]), in the physical component summary score of the SF-36 (mean difference 1.90 [95% CI, 0.57 to 3.23]), and in the EQ-5D visual analogue scale score (mean difference 5.27 [95% CI, 2.40 to 8.13]) in the alemtuzumab group compared with the interferon beta-1a group. Fatigue was measured in the thinking and fatigue domain of the FAMS, and the improvement from baseline in this domain score was found to be greater in the alemtuzumab group compared with the interferon beta-1a group (mean difference 1.43 [95% CI, 0.21 to 2.65]). As these were tertiary end points, results need to be interpreted with caution.

The CARE-MS II study is limited by its design, in which patients were aware of their assigned treatment, which may have influenced patient-reported outcomes and EDSS scores, despite blinded rater assessments. There was a greater proportion of patients who withdrew from the study prior to receiving treatment in the interferon beta-1a group than in the alemtuzumab group, which may result in loss of randomization and unbalanced distribution of baseline characteristics, as these patients were not included in the main efficacy analyses. Thus, the magnitude of the between-treatment differences may be overestimated.

In the CAMMS03409 extension, two additional years of efficacy data were available for patients enrolled in the CARE-MS II study, where patients originally enrolled in the alemtuzumab 12 mg group were re-treated upon relapse and all patients originally enrolled in the interferon beta-1a group were given two annual cycles of alemtuzumab. Results from year 3 and year 4 in patients in the alemtuzumab 12 mg group in CARE-MS II found that ARRs were similar to those in year 1 and year 2. Relapse rates declined in patients in the interferon beta-1a group in CARE-MS II. Similar results were seen in disability status. Re-treatment rates of CARE-MS II patients originally randomized to the alemtuzumab 12 mg group were generally low, with 24% of patients receiving one additional course of treatment, and 7% of patients receiving two additional courses of treatment.

In a single-group cohort study by Tuohy et al. (N = 87) conducted to evaluate long-term clinical benefits (including the proportion of patients requiring re-treatment) and safety with alemtuzumab, with a mean follow-up time frame of seven years, 36% of patients received three courses of treatment, 8% of patients received four courses of treatment, and one patient received five courses of treatment. The mean ARR after alemtuzumab was 0.16 (standard deviation 0.26) compared with 1.78 (standard deviation 0.82), which was assessed retrospectively for the two pre-treatment years. Limitations of this study include: small sample size, no comparator group, enrolled both treatment-naive and treatment-experienced patients, used non–Health Canada approved doses of alemtuzumab at the beginning of the study, and enrolled patients with more severe disease than those in CARE-MS II, limiting the generalizability of these findings.

As alemtuzumab is being reviewed for use in RRMS patients who have had an inadequate response to interferon beta or other DMTs, interferon beta-1a may not be the most appropriate comparator. The CARE-MS II trial is relevant to the question of the potential benefit of switching therapy, but does not compare alemtuzumab with other treatments recommended for use in patients who have failed interferon or glatiramer.

The manufacturer provided a mixed treatment comparison (MTC) with a subgroup analysis in previously treated patients to compare alemtuzumab with other DMTs. [redacted]

Harms

Two deaths were reported in the alemtuzumab 12 mg group: one due to aspiration pneumonia and another due to a traffic accident.

The proportion of patients reporting adverse events was slightly higher in the alemtuzumab 12 mg group compared with the interferon beta-1a group (98.4% versus 94.6%, respectively). The most commonly reported adverse events with alemtuzumab included headache, rash, nasopharyngitis, nausea, pyrexia, urinary tract infection, and fatigue. A total of 19.5% of patients in the alemtuzumab 12 mg group and 21.8% of patients in the interferon beta-1a group experienced a serious adverse event. More patients in the interferon beta-1a group discontinued study treatment due to an adverse event compared with the alemtuzumab 12 mg group (8.9% versus 3.2%, respectively).

Four patients in the alemtuzumab 12 mg group had reports of immune thrombocytopenic purpura (ITP). A greater proportion of patients experienced a thyroid adverse event in the alemtuzumab 12 mg group compared with the interferon beta-1a group (15.9% versus 5.0%, respectively). Two patients in the alemtuzumab 12 mg group experienced a serious thyroid adverse event. A greater proportion of patients

experienced an infection with alemtuzumab 12 mg than with interferon beta-1a (76.8% versus 66.3%, respectively). The majority (90.3%) of patients in the alemtuzumab 12 mg group experienced an infusion-associated reaction. No cases of progressive multifocal leukoencephalopathy (PML) were reported.

In CAMMS03409, two additional years of safety data were available for patients enrolled in the CARE-MS II study. There were no new safety concerns that emerged in patients who were treated with alemtuzumab 12 mg in the original studies. The incidence of infections was lower in the third and fourth year of treatment when compared with the first two years of treatment in the original studies. Infusion-associated reactions decreased in the third year but increased again in the fourth year. The incidence of autoimmune disorders, however, increased in the third year but declined in the fourth year. Thyroid disorders continued to be the most frequently reported autoimmune adverse event in the extension study, and there were six cases of ITP in the fourth year among patients who were treated with alemtuzumab 12 mg in CARE-MS II. Similar safety results were seen in the cohort study conducted by Tuohy et al. in which thyroid events were the most frequently reported autoimmune disease, and three patients experienced ITP during the entire study. In addition, 11 patients experienced varicella zoster virus reactivation in the observational study.

Other Considerations

In December 2013, the Food and Drug Administration (FDA) declined approval for alemtuzumab (Lemtrada) in RRMS, citing that the manufacturer had not submitted evidence from adequate and well-controlled studies that demonstrate that the benefits outweigh the serious adverse effects.[1] In November 2014, the FDA approved alemtuzumab for the treatment of patients with RRMS after reviewing a resubmission by Genzyme US that included additional long-term data from existing studies. The European Medicines Agency (EMA) granted marketing authorization for alemtuzumab (Lemtrada) in RRMS in September 2013. In December 2013, Health Canada restricted its marketing authorization for alemtuzumab to patients with RRMS who have had an inadequate response to interferon beta or other DMTs, due to inconsistencies in efficacy results in the two studies performed in treatment-naive patients (CAMMS223 and CARE-MS I) and the limitations of the rater-blind study designs. Although Health Canada reviewers had concerns with the study design of CARE-MS II, they concluded that there is a potential clinical efficacy benefit in using alemtuzumab in RRMS patients who have had an inadequate response to other DMTs.

Conclusions

One two-year, randomized, rater-blind, active-controlled study (CARE-MS II) evaluating the efficacy and safety of alemtuzumab 12 mg compared with interferon beta-1a in patients with active RRMS who had previously experienced a relapse while on at least six months of interferon beta or glatiramer acetate therapy was included in the systematic review. The results of CARE-MS II suggest that alemtuzumab is superior to interferon beta-1a in reducing the ARR and the risk of six-month SAD over two years of treatment in treatment-experienced patients. These findings need to be interpreted with caution due to the limitations of the rater-blind design and the differences in study withdrawals between treatment groups.

A manufacturer-provided mixed treatment comparison in treatment-experienced patients [redacted]

[redacted]

The most common harms associated with alemtuzumab included headache, rash, and nasopharyngitis. Safety concerns associated with alemtuzumab include immune thrombocytopenic purpura, thyroid disorders, infection, and infusion-associated reactions. There were no reports of PML. Two additional years of data from the CAMMS03409 extension study found no new safety concerns in patients treated with alemtuzumab 12 mg in CARE-MS II. Similar safety results were seen in a single-group cohort study that looked at long-term efficacy and safety of alemtuzumab with a median seven-year follow-up, where thyroid events were the most frequently reported autoimmune disease. However, both studies are limited by study design and lack of a comparator group, which leads to considerable uncertainty as to the findings of these studies.

TABLE 1: SUMMARY OF RESULTS

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Annualized relapse rate		
ARR — years 0 to 2 (95% CI)	0.26 (0.21, 0.33)	0.52 (0.41, 0.66)
Rate ratio (95% CI)	0.51 (0.39, 0.65)	
P value	< 0.0001	
Sustained accumulation of disability (6 months)		
Kaplan–Meier estimate, % (95% CI)	12.71 (9.89, 16.27)	21.13 (15.95, 27.68)
Hazard ratio (95% CI)	0.58 (0.38, 0.87)	
P value	0.0084	
EDSS scores		
N	413	174
Change from baseline (95% CI)	–0.17 (–0.29, –0.05)	0.24 (0.07, 0.41)
Difference (95% CI)	–0.41 (–0.61, –0.22)	
P value	< 0.0001	
MSFC scores		
N	402	171
Change from baseline (95% CI)	0.08 (0.04, 0.12)	–0.04 (-0.10, 0.02)
Difference (95% CI)	0.12 (0.05, 0.19)	
FAMS scores		
Change from baseline (95% CI)	[redacted]	
Difference	[redacted]	
SF-36 mental component summary		
Change from baseline (95% CI)	[redacted]	
Difference	[redacted]	
SF-36 physical component summary		
Change from baseline (95% CI)	[redacted]	
Difference	[redacted]	
EQ-5D Utility SCORE		
Change from baseline (95% CI)	[redacted]	
Difference	[redacted]	
EQ-5D VAS score		
Change from baseline (95% CI)	[redacted]	
Difference	[redacted]	
Harms, n (%)		
N (safety set)	435	202

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Death	2 (0.5)	0
AEs	428 (98.4)	191 (94.6)
SAEs	85 (19.5)	44 (21.8)
WDAEs	1 (0.2)	6 (3.0)
Notable harms, n (%)		
N (safety set)	435	202
ITP/autoimmune thrombocytopenia	4 (0.9)	0
Thyroid AEs	69 (15.9)	10 (5.0)
Infections	334 (76.8)	134 (66.3)
Infusion-associated reactions	393 (90.3)	NA

AEs = adverse events; ARR = annualized relapse rate; CI = confidence interval; EDSS = Kurtzke Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions Questionnaire; FAMS = Functional Assessment of Multiple Sclerosis; ITP = idiopathic thrombocytopenic purpura; MSFC = Multiple Sclerosis Functional Composite; NA = not applicable; SAEs = serious adverse events; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale; WDAEs = withdrawals due to adverse event.
Source: Clinical Study Report,[2] Coles et al. (2012).[3]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Multiple sclerosis (MS) is a chronic, progressive, immune-mediated disease of the central nervous system (CNS) during which the white matter within the brain or spinal cord becomes inflamed and destroyed in a process called demyelination.[4] MS affects up to three times as many women as men and typically has an age of onset between 20 to 50 years.[5] 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.[6]

The etiology of MS is unknown, but appears to involve a complex interplay of genetic and environmental factors that result in the abnormal activation and proliferation of T-cells and other immune cells, and subsequent inflammatory damage to CNS tissue.[7] The majority of people (85%) who later develop MS experience an initial episode of neurological disturbance known as clinically isolated syndrome (CIS), which may manifest by various motor or sensory deficits.[8] After an initial disease phase, a patient may experience a series of relapses and remissions.

According to the McDonald criteria (2010), MS can be diagnosed on the basis of evidence of at least two relapses, achieved through a detailed medical history and neurological examination.[9] Diagnosis is confirmed by objective clinical evidence of at least two lesions that are disseminated in space and time as demonstrated clinically or by magnetic resonance imaging (MRI).[9]

MS is classified into four clinical subtypes: relapsing-remitting multiple sclerosis (RRMS); primary-progressive multiple sclerosis (PPMS), secondary-progressive multiple sclerosis (SPMS), and progressive-relapsing multiple sclerosis (PRMS). 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.[5] The relapsing forms of MS are associated with better prognosis than progressive forms of disease.

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 quality of life through the use of disease-modifying therapies (DMTs; Table 2).[10] According to the Canadian Multiple Sclerosis Working Group (CMSWG, 2013), the currently recommended first-line agents for RRMS are interferon beta or glatiramer acetate, with the choice of agent being guided by the adverse effect profile, dosing schedule, reimbursement, and patient preference.[10] The clinical expert consulted for this review also considered dimethyl fumarate and teriflunomide as first-line agents, both of which were approved by Health Canada for the treatment of RRMS in 2013.

Treatment should be guided by the level of disease activity and progression at a given point in time, and is highly individualized. The CMSWG provides criteria to assess the level of concern (low, medium, high) on whether to modify a treatment regimen based on the number and severity of relapses in the first year of treatment, disability progression as determined by worsening of the Kurtzke Expanded Disability Status Scale (EDSS) score, and number of new contrast-enhancing or T2-weighted lesions per year as determined by MRI. A suboptimal response that warrants a change in therapy may be indicated by a combination of varying levels of concern in these three areas of relapses, progression, and MRI findings.

A lateral switch between first-line agents may be indicated for patients who have had an adequate treatment response but poor tolerability to a medication. Second-line therapies, including fingolimod and natalizumab, may be indicated for patients with a suboptimal response to a first-line agent. Natalizumab has been associated with the development of progressive multifocal leukoencephalopathy (PML), while there are concerns of cardiovascular adverse events with fingolimod.[11,12] The clinical expert consulted for this review noted that he would use fingolimod prior to natalizumab due to safety risks. Alemtuzumab was not approved in Canada at the time of the CMSWG guideline update, but the clinical expert said that it would also be considered after fingolimod due to potential serious autoimmune adverse events.

Although no clinical criteria have been established to identify patients who should discontinue treatment, the CMSWG suggests that it may be necessary to consider stopping treatment in patients with significant disease progression (EDSS > 6) who have not experienced a relapse in the preceding two years.[10]

1.3 Drug

Alemtuzumab (Lemtrada) is a recombinant, humanized, monoclonal antibody directed against CD52, a protein expressed at high levels on T and B lymphocytes. Although the function of alemtuzumab is not fully known, it may exert its effect through the depletion of autoreactive T and B lymphocytes and subsequent rebalancing of the immune system.[7] For RRMS, alemtuzumab is administered by intravenous (IV) infusion at a recommended dose of 12 mg/day over two treatment cycles. The initial treatment cycle is administered over five consecutive days (60 mg total dose). The second treatment cycle is given 12 months after the initial treatment and is administered over three consecutive days (36 mg total dose). Alemtuzumab is available as a concentrated solution for infusion as 1.2 mL (10 mg/mL) single-use vials. A Notice of Compliance (NOC) for alemtuzumab for the management of RRMS was granted by Health Canada on December 12, 2013.[13]

In 2005, alemtuzumab (MabCampath) was approved in Canada for the treatment of B-cell chronic lymphocytic leukemia (B-CLL).[14] For B-CLL, alemtuzumab is administered by IV infusion at a recommended initial dose of 3 mg/day with dose escalation to 10 mg/day, followed by a maintenance dose of 30 mg/day three times per week on alternate days for up to 12 weeks.

Indication under review
For the management of adult patients with relapsing-remitting multiple sclerosis (RRMS), with active disease defined by clinical and imaging features, who have had an inadequate response to interferon beta or other disease-modifying therapies.
Listing criteria requested by sponsor
[redacted]

TABLE 2: KEY CHARACTERISTICS OF DISEASE-MODIFYING TREATMENTS FOR MS

	Mechanism of Action	Approved Indications	Route of Administration	Recommended Dose	Contraindications (According to PM)
Alemtuzumab (Lemtrada)[13]	Binds to CD52	RRMS; patients who have had an inadequate response to interferon 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; have a history of PML.
Dimethyl fumarate (Tecfidera)[15]	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)[12]	Not known; likely reduces lymphocyte migration in the CNS	RRMS; generally recommended in MS patients who have had inadequate response to, or are unable to tolerate, one or more therapies for MS	Oral capsule	0.5 mg/day	Contraindicated in patients who: are hypersensitive to fingolimod; are at risk for an opportunistic infection; immunocompromised due to treatment or to disease); have hepatic insufficiency, active severe infections, or known active malignancies. Varicella zoster vaccination recommended.
Glatiramer acetate (Copaxone)[16]	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.
Interferon beta-1a (Avonex; Rebif)[17,18]	Not completely understood; likely the upregulation of IL-10	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 interferon, patients with liver disease, pregnant women.

	Mechanism of Action	Approved Indications	Route of Administration	Recommended Dose	Contraindications (According to PM)
Interferon beta-1b (Betaseron; Extavia)[19,20]	Not completely understood; likely mediated by binding to cell surface receptors	RRMS; SPMS; single demyelinating event accompanied by at least two clinically silent lesions typical of MS	SC injection (Betaseron, Extavia)	0.25 mg every other day	Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, pregnant women.
Natalizumab (Tysabri)[11]	Blocks interaction of alpha4beta7 integrin with the mucosal address in cell adhesion molecule-1; reduces formation or enlargement of MS lesions	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, or are at risk for PML; are hypersensitive to this drug or to any ingredient in the formulation or any component of the drug; are immunocompromised, including those immunocompromised due to immunosuppressant or antineoplastic therapies, or immunodeficiencies.
Teriflunomide (Aubagio)[21]	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; are currently treated with leflunomide; have severe hepatic impairment; are pregnant or are women of child-bearing age who are not using contraception; have immunodeficiency states such as AIDS; have serious active infection; have impaired bone marrow function or significant anemia, leucopenia, neutropenia, or thrombocytopenia.

AIDS = acquired immunodeficiency syndrome; CDMS = clinically definite multiple sclerosis; CNS = central nervous system; HIV = human immunodeficiency virus; IM = intramuscular; IV = intravenous; MS = multiple sclerosis; MRI = magnetic resonance imaging; PM = product monograph; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis; TB = tuberculosis.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of intravenous alemtuzumab for the treatment of relapsing-remitting multiple sclerosis.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other phase 3 studies were 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 interferon beta or other disease-modifying therapies
Intervention	Intravenous alemtuzumab, used as monotherapy
Comparators	• Interferon beta-1a (IM or SC) • Interferon beta-1b • Glatiramer acetate • Natalizumab • Fingolimod • Dimethyl fumarate • Teriflunomide • Placebo
Outcomes	**Key efficacy outcomes:** • Relapse rate • Disability using a validated scale (e.g., EDSS, MSFC) • HRQoL using a validated scale (e.g., SF-36) • Fatigue **Other efficacy outcomes:** • Brain lesions on MRI (gadolinium-enhancing lesions, new or enlarging T2 lesions) • Productivity (ability to attend work or school) • Medication acceptance • Relapse requiring corticosteroids • Relapse requiring hospitalization **Harms outcomes:** • AEs, SAEs, WDAEs, mortality • Notable harms/harms of special interest: autoimmune conditions (e.g., immune thrombocytopenic purpura, thyroid disorders, anti-glomerular basement membrane disease), serious infections (e.g., progressive multifocal leukoencephalopathy), infusion-associated reactions
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; EDSS = Kurtzke Expanded Disability Status Score; HRQoL = health-related quality of life; IM = intramuscular; MRI = magnetic resonance imaging; MSFC = Multiple Sclerosis Functional Composite; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SAE = serious adverse event; SC = subcutaneous; SF-36 = Short Form (36) Health Survey; WDAE = withdrawal due to adverse event.

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 through Ovid; Embase (1974–) through 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 Lemtrada (alemtuzumab) and multiple sclerosis.

This search updates the original Lemtrada CADTH Common Drug Review (CDR) search completed in January 2014. No filters were applied to limit the retrieval by study type. Conference abstracts were excluded from the search results.

The updated search was completed on January 15, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on May 20, 2015. 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 CADTH Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug regulatory approvals, advisories and warnings, drug class reviews, databases (free). 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 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 one study was 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

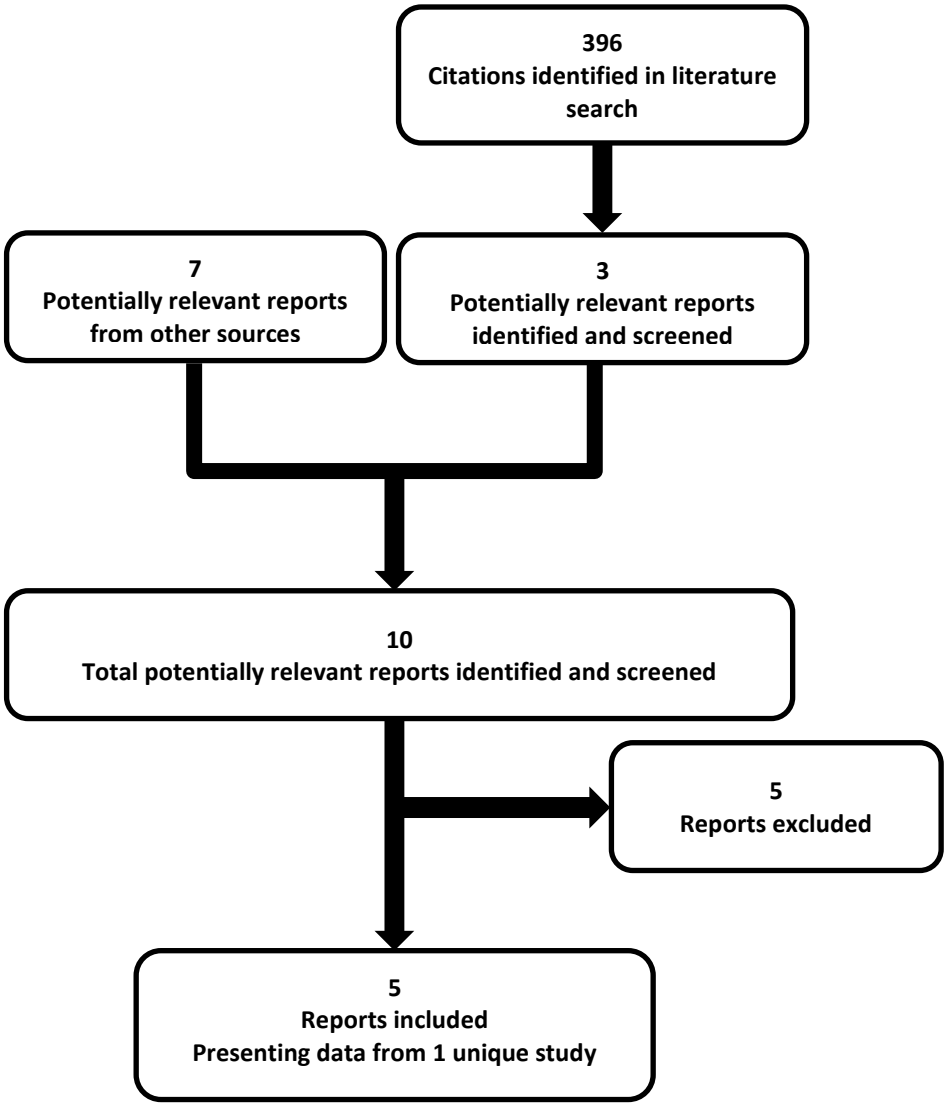

TABLE 4: DETAILS OF INCLUDED STUDIES

		CARE-MS II (CAMMS324)
DESIGNS & POPULATIONS	**Study Design**	Rater-blind, active-controlled, parallel-group RCT
	Locations	Multi-centre: 23 countries, 193 study centres (including 12 centres in Canada and 85 centres in the US)
	Randomized (N)	840
	Inclusion Criteria	Patients 18 to 55 years of age meeting the 2005 McDonald criteria for active RRMS with a disease duration of 10 years or less and at least one relapse while on ≥ 6 months of interferon beta or glatiramer acetate within the last 10 years: • EDSS score 0.0 to 5.0 at screening • ≥ 2 attacks (first episode or relapse) in the previous 2 years, with ≥ 1 attack in the previous year— with objective neurological signs confirmed by a physician, nurse practitioner, or other manufacturer-approved health care provider • MRI scan demonstrating white matter lesions attributable to MS and meeting at least one of the following criteria as determined by a neurologist or radiology: (i) ≥ 9 T2 lesions at least 3 mm in any axis; (ii) a gadolinium-enhancing lesion at least 3 mm in any axis plus ≥ 1 brain T2 lesions; (iii) a spinal cord lesion consistent with MS plus ≥ 1 brain T2 lesion
	Exclusion Criteria	• Progressive forms of MS • Previous treatment with alemtuzumab, mitoxantrone, cyclophosphamide, cladribine, rituximab, or any other immunosuppressant or cytotoxic therapy (other than steroids) • Had treatment within the past 6 months with natalizumab, methotrexate, azathioprine, or cyclosporine • Confirmed platelet, CD4+, CD8+, CD19+, or absolute neutrophil counts less than the lower limit of normal at screening • History of malignancy, except basal cell carcinoma • Latent TB unless effective anti-TB therapy has been completed, or active TB • Seropositivity for HIV, hepatitis B, or hepatitis C • Significant autoimmune disease • Presence of anti-thyroid stimulating hormone antibodies • Pregnancy
DRUGS	**Intervention**	IV alemtuzumab, 12 mg or 24 mg daily over two treatment courses: • Initial treatment cycle (cycle 1; month 0): 5 consecutive days • Second treatment cycle (cycle 2; month 12): 3 consecutive days, administered 12 months after initial treatment cycle + IV methylprednisolone, 1 g daily for 3 consecutive days at month 0 and month 12 + Acyclovir, 200 mg twice daily starting the first day of each alemtuzumab cycle and continuing for 28 days after the last day
	Comparator(s)	SC interferon beta-1a 44 mcg, 3 times per week; dose could be decreased or discontinued at the investigator's discretion (if discontinued, alternative therapy could be initiated with the manufacturer's approval) + IV methylprednisolone 1 g daily for 3 consecutive days at month 0 and month 12

		CARE-MS II (CAMMS324)
DURATION	**Phase**	
	Rater-blind, active controlled	2 years
	Rater-blind extension	4 years (see Appendix 7: Summary of Additional Studies)
OUTCOMES	**Co-Primary End Points**	• ARR • Time to 6-month SAD

	Other End Points	• Change from baseline at year 2 in:
		  • EDSS scores
		  • MSFC scores
		  • T2 hyperintense lesion volume
		• Proportion of relapse-free patients
		• Time to first relapse
		• Time to 3-month SAD
		• Time to SRD
		• FAMS
		• SF-36
		• EQ-5D
		• MRI outcomes

NOTES	**Publications**	Coles et al. (2012)[3]

ARR = annualized relapse rate; EDSS = Kurtzke Expanded Disability Status Score; EQ-5D = EuroQol 5-Dimensions Questionnaire; FAMS = Functional Assessment of Multiple Sclerosis; HIV = human immunodeficiency virus; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SAD = sustained accumulation of disability; SC = subcutaneous; SF-36 = Short Form (36) Health Survey; SRD = sustained reduction in disability; TB = tuberculosis.
Note: Two additional reports were included: European Public Assessment Report[22] and Health Canada Reviewer's Report.[23]
Source: Clinical Study Report[2] and CDR submission.[24]

3.2 Included Studies

3.2.1 Description of Studies

One two-year, randomized, rater-blind, active-controlled study met the inclusion criteria for this systematic review. CARE-MS II (N = 810) included patients with RRMS who had previously experienced a relapse on interferon beta or glatiramer acetate. Patients were originally randomized in a 2:2:1 ratio with stratification by study site to receive IV alemtuzumab 12 mg, IV alemtuzumab 24 mg, or subcutaneous (SC) interferon beta-1a. A protocol amendment discontinued randomization in the alemtuzumab 24 mg group in order to reduce the overall sample size, the duration of the enrolment period, and the overall duration of the study. Efficacy analyses performed with the alemtuzumab 24 mg group were considered exploratory and are not presented in this review.

After the two-year, active-controlled, rater-blind phase, all patients were eligible for entry into a rater-blind extension study (CAMMS03409) for up to an additional four years of efficacy and safety assessments (see Appendix 7: Summary of Additional Studies). In the extension study, patients were re-treated with IV alemtuzumab 12 mg upon documented evidence of resumed disease activity.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients aged 18 to 55 years who met the 2005 McDonald criteria for RRMS and experienced at least one relapse while on at least six months of interferon beta or glatiramer acetate were eligible for inclusion in the CARE-MS II study. These patients were to have an EDSS ≤ 5.0 at screening, disease duration of 10 years or less prior to study entry, experienced at least two relapses in the previous two years with at least one attack occurring in the previous year, and white matter lesions meeting specific criteria as determined by an MRI scan.

Patients were excluded if they had progressive forms of MS, previous treatment with immunosuppressant or cytotoxic therapy, or used natalizumab, methotrexate, azathioprine, or cyclosporine in the past six months. Due to the concerns of various autoimmune conditions with alemtuzumab, patients with low platelet counts or anti-thyroid stimulating hormone antibodies were excluded from the study.

b) Baseline Characteristics

Baseline characteristics were well balanced across treatment groups in the full analysis population and reflective of patients with RRMS (Table 5). The majority of patients were female (65.6%) and the mean age was approximately 35 years. Almost all patients had reported at least one relapse in the past year and two relapses in the past two years, as per the inclusion criteria.

All patients had received prior medications for MS within 10 years prior to enrolment, with the majority of patients having received one prior MS medication (71.7%). The majority of patients had received interferon beta therapy. The time of last treatment of disease-modifying therapy (DMT) was not specified.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS; FULL ANALYSIS SET

Characteristics	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Mean age, years (SD)	34.8 (8.4)	35.8 (8.8)
Female sex, n (%)	281 (66.0)	131 (64.9)
Mean weight, kg (SD)	76.1 (18.2)	78.5 (20.2)
Disease Characteristics		
Mean time since initial episode, years (SD)	4.5 (2.7)	4.7 (2.9)
Median time since initial episode, years (range)	3.8 (0.2, 14.4)	4.1 (0.4, 10.1)
Mean time since last relapse, years (SD)	0.40 (0.23)	0.41 (0.24)
Median time since last relapse, years (range)	0.34 (0, 1.16)	0.34 (0, 1.22)
Mean number of relapses in the past year (SD)	1.7 (0.86)	1.5 (0.75)
Number of relapses in the past year, n (%)		
0	6 (1.4)	5 (2.5)
1	211 (49.5)	107 (53.0)
2	151 (35.4)	68 (33.7)
≥ 3	58 (13.6)	22 (10.9)
Mean number of relapses in the past 2 years (SD)	2.8 (1.20)	2.6 (0.97)
Number of relapses in the past 2 years, n (%)		
0	0	0
1	15 (3.5)	7 (3.5)
2	215 (50.5)	109 (54.0)
≥ 3	196 (46.0)	86 (42.6)

Characteristics	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Mean number of relapses in the past 3 years (SD)	3.4 (1.45)	3.3 (1.26)
Number of relapses in the past 3 years, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥ 3	[redacted]	[redacted]
Mean EDSS score (SD)	[redacted]	[redacted]
Median EDSS score (range)	[redacted]	[redacted]
Prior MS medications		
Interferon beta-1a SC	146 (34.3)	73 (36.1)
Interferon beta-1a IM	120 (28.2)	46 (22.8)
Interferon beta-1b	154 (36.2)	63 (31.2)
Glatiramer acetate	146 (34.3)	69 (34.2)
Natalizumab	15 (3.5)	7 (3.5)
Immunoglobulin	11 (2.6)	1 (0.5)
Azathioprine	6 (1.4)	5 (2.5)
Number of prior MS medications, n (%)		
1	299 (70.2)	151 (74.8)
2	92 (21.6)	41 (20.3)
3	24 (5.6)	9 (4.5)
≥ 4	11 (2.6)	1 (0.5)
Mean duration of prior MS medications, months (SD)	35 (25.0)	36 (23.7)

EDSS = Kurtzke Expanded Disability Status Scale; IM = intramuscular; MS = multiple sclerosis; SC = subcutaneous; SD = standard deviation.
Source: Clinical Study Report.[2]

3.2.3 Interventions

Patients were randomized in a 2:2:1 ratio to receive IV alemtuzumab 12 mg, IV alemtuzumab 24 mg, or SC interferon beta-1a (Rebif) over the two-year study. Enrolment was closed to the alemtuzumab 24 mg group after a protocol amendment, after which randomization continued in a 2:1 ratio between the alemtuzumab 12 mg and interferon beta-1a groups.

Alemtuzumab was administered by daily intravenous infusion at 12 mg or 24 mg doses over two treatment cycles:

- Cycle 1: five consecutive days at month 0 (60 mg or 120 mg total)
- Cycle 2: three consecutive days at month 12 (36 mg or 72 mg total)

Interferon beta-1a was administered by subcutaneous injection at 44 mcg, three times per week, with the option to decrease the dose depending on patient tolerance. An initial titration was performed over a four-week period, with 20% dose for the first two weeks, 50% dose over the next two weeks, and the full dose after four weeks.

Methylprednisolone was administered intravenously to all patients at 1 g per day for three consecutive days at month 0 and month 12 for prophylaxis against infusion-associated reactions in the alemtuzumab group. Methylprednisolone was also administered to the interferon beta-1a group to avoid bias by differential use of steroid across the treatment groups.

After a protocol amendment, the alemtuzumab group was administered acyclovir 200 mg orally twice daily starting the first day of each treatment cycle and continuing for 28 days after the last day for prophylaxis against herpes simplex virus infections, based on a review of safety data.

On-study relapses could be treated with corticosteroids at the discretion of the treating neurologist. If study treatment was discontinued, alternative therapy could be initiated with the manufacturer's approval.

3.2.4 Outcomes

The co-primary efficacy end points in the CARE-MS II study were annualized relapse rate (ARR) and time to six-month sustained accumulation of disability.

The secondary and tertiary outcomes in CARE-MS II included:

- Change from baseline at year 2 in EDSS scores, Multiple Sclerosis Functional Composite (MSFC) scores, and T2 hyperintense lesion volume (secondary)
- Proportion of relapse-free patients (secondary)
- Time to first relapse (tertiary)
- Time to three-month sustained accumulation of disability (tertiary)
- Time to sustained reduction in disability (tertiary)
- Health-related quality of life outcomes: Functional Assessment of Multiple Sclerosis (FAMS), Short Form (36) Health Survey (SF-36), EuroQol 5-Dimensions Questionnaire (EQ-5D; tertiary)
- MRI outcomes (tertiary): new and enlarging T2 hyperintense lesion count, gadolinium (Gd)-enhancing lesions

The outcomes of interest identified in the protocol are described below. For a more detailed description of study outcomes, see Appendix 5: Validity of Outcome Measures.

a) Relapse

Relapse: Any new or worsening neurological symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability with an objective change on neurological examination. A relapse adjudication panel composed of six independent, blinded neurologists with expertise in MS clinical research and who were not investigators in the study was assembled to analyze relapse end points. In CARE-MS II, this outcome was reported as an ARR over the two years of the study.

b) Disability

Sustained Accumulation of Disability

An increase from baseline of ≥ 1 EDSS point, or ≥ 1.5 points if the baseline EDSS was 0, confirmed over three or six months.

Sustained Reduction in Disability

A decrease from baseline by ≥ 1 EDSS point confirmed over six months for patients with a baseline EDSS ≥ 2.0.

Kurtzke Expanded Disability Status Scale

An assessment of a patient's neurological functional impairment, based on the neurological testing of pyramidal (ability to walk), cerebellar (coordination), brainstem (including speech and swallowing), sensory (including touch and pain), bowel and bladder, visual, mental, and other functions attributed to MS.

Multiple Sclerosis Functional Composite
A three-part, standardized, quantitative MS assessment instrument that consists of measurements of three components: ambulation (timed 25-foot walk), arm coordination and dexterity (9-hole peg test), and cognitive function (paced auditory serial addition test).

c) Health-Related Quality of Life

Functional Assessment of Multiple Sclerosis
A patient-reported, MS-specific, quality of life questionnaire that consists of 58 items on seven domains (mobility, symptoms, emotional well-being, general contentment, thinking and fatigue, family/social well-being, and additional concerns).

Short Form (36) Health Survey
The 36-item short-form generic health survey measuring health-related quality of life. Two summary scores (physical health and mental health components), and eight domains (physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional, and mental health) were reported.

EuroQol 5-Dimensions Questionnaire
A standardized, generic health-related quality of life questionnaire that consists of the EQ-5D descriptive system (comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the visual analogue scale that rates a patient's perceived health on a vertical visual analogue scale.

d) MRI Outcomes

New and Enlarging T2 Lesions
Changes in the number and volume of T2 hyperintense lesions and the interval development of new lesions were analyzed.

Gadolinium-Enhancing T1 Lesions
T1 lesions were scored using signal hypointensity thresholds of 75% and 85%, with volumes corresponding to the 85% threshold used for analysis. Changes were analyzed in the number of Gd-enhancing lesions, number and volume of T1 hypointense lesions, and interval development of new lesions.

e) Harms
Safety evaluations were based on treatment-emergent adverse events, which included any event with a start date and time on or after the date and time of the first study treatment. An adverse event was considered a serious adverse event if it was fatal, life-threatening, required patient hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability/incapacity, a congenital anomaly, or an important medical event. Infusion-associated reactions were defined as any adverse event that occurred between the start and stop of any alemtuzumab infusion or within 24 hours after the end of the infusion.

3.2.5 Statistical Analysis

a) Sample Size Calculation

- Under the original protocol, assuming a 2:2:1 randomization to alemtuzumab 12 mg, alemtuzumab 24 mg, or interferon beta-1a, a sample size of 1,200 patients was planned in order to provide 80% power to detect a 45% treatment effect in time to six-month sustained accumulation of disability (SAD), assuming a treatment discontinuation rate of 10%. Based on previous trials, a two-year SAD rate of 20% or 25% (hazard rate 0.11 or 0.14) for interferon beta-1a was assumed.

- After a protocol amendment, the alemtuzumab 24 mg group was closed to further enrolment and randomization continued until approximately 382 patients were assigned to alemtuzumab 12 mg and 191 patients were assigned to interferon beta-1a. Based on 573 patients allocated 2:1 to alemtuzumab 12 mg and interferon beta-1a, the study had 80% power to detect a 50% treatment effect in time to SAD with a two-sided significance level of 0.05, assuming a two-year SAD of 20% for interferon beta-1a. The study had 95% power to detect a 40% treatment effect on relapse rate, assuming a two-year relapse rate of 68% for interferon beta-1a (hazard rate 0.57), a hazard ratio of 0.60 comparing alemtuzumab 12 mg with interferon beta-1a, and a two-sided significance level of 2.5%.

b) Statistical Tests

Sustained Accumulation of Disability

- The effect of treatment on time to SAD was assessed using a Cox proportional hazards model, with robust variance estimation and covariate adjustment for treatment group and geographic region.
- The proportion of patients with SAD was estimated using the Kaplan–Meier method.

Relapse

- Relapse rate was assessed using a proportion means (Andersen-Gill multiplicative intensity) model, with robust variance estimation and covariate adjustment for treatment group and geographic region.
- The ARR (year 1 and year 2) was estimated using a negative binomial regression model with robust variance estimation and geographic region as a covariate.
- The proportion of relapse-free patients was estimated using the Kaplan–Meier method and compared using a Cox proportional hazards regression model with robust variance estimation and covariate adjustment for geographic region.

Patient-Reported Outcomes

- Change from baseline in EDSS and MSFC scores were estimated every three months using a mixed model for repeated measures with baseline score, treatment group, geographic region, study visit, and study visit by treatment group interaction as covariates. Treatment comparisons were performed using the Wei-Lachin nonparametric test for repeated measures.
- The FAMS, SF-36, and EQ-5D scores were analyzed using a mixed model for repeated measures with baseline score, treatment group, and geographic region as covariates. Summaries will include changes from baseline and the Wilcoxon-Mann-Whitney test.

MRI Outcomes

- The per cent change from baseline in T2 hyperintense lesion volume was analyzed using a ranked analysis of covariance model with covariate adjustment for baseline lesion volume.
- The proportion of patients with Gd-enhancing or T2 hyperintense lesions at year 1 or year 2 was compared using logistic regression with covariate adjustment for baseline Gd-enhancing lesion count or baseline T2 hyperintense lesion volume, respectively.

Multiplicity

- The primary efficacy analysis was adjusted for multiple comparisons with the Hochberg method. The study was considered to have met its primary efficacy objective if the maximum of the two *P* values from the analysis of the co-primary efficacy end points was ≤ 0.05, or the minimum of these two *P* values was ≤ 0.025.
- Secondary efficacy end points were controlled for multiple comparisons by using a closed testing procedure in the following rank order: proportion of relapse-free patients at year 2; change from baseline at year 2 in EDSS scores; per cent change from baseline at year 2 in T2 hyperintense lesion

volume; change from baseline at year 2 in MSFC scores. Formal sequential testing stopped when $P > 0.05$.

Sensitivity Analyses

- Sensitivity analyses were conducted to assess factors that could potentially affect the co-primary efficacy end points (relapse rate and SAD). The primary model was reanalyzed by: (i) censoring patients at the time of alternative MS therapy; (ii) including all patients who were randomized to receive therapy; (iii) including covariates selected using a backward-elimination method; (iv) adjusting for patient dropout prior to receiving treatment using the method of inverse probability weighting.
- For relapse rate, the proportional means model was reanalyzed after moving relapses that were associated with EDSS assessments performed by unblinded raters.
- For SAD, additional pre-specified sensitivity analyses were performed to address the impact of EDSS assessments made by unblinded raters.

Missing Data

- For the co-primary efficacy end points and other time-to-event end points, patients were censored at their last visit if the respective event had not occurred.
- For continuous, repeated measures efficacy end points, missing at random was assumed and method appropriate to the assumption was used.
- For the assessment of change from baseline to a specific time point, the last post-treatment observation was used for the analysis if data were missing.
- For the assessment of binary end points, the last known status of the efficacy measure was used for the analysis if data were missing.

c) Analysis Populations

In the CARE-MS II study, the following data sets were defined:

Full Analysis

All patients who were randomized to treatment and had received any amount of study drug. Efficacy analyses were performed according to the treatment patients were randomized to receive, irrespective of the treatment they actually received.

Per Protocol

The subset of patients from the full analysis (FA) population who had no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy.

- Alemtuzumab-treated patients who received alemtuzumab at month 0 and month 12 without any major protocol deviations, or if SAD was experienced in the first 12 months, had received alemtuzumab at month 0 without any major protocol deviations.
- Interferon beta-1a-treated patients who took at least 80% of the required doses and remained on therapy for at least 12 months, or if SAD was experienced, who took at least 80% of the required doses prior to the event.

Safety

All patients who received any amount of study drug. Safety analyses were performed according to the treatment patients actually received. This population differed from the FA set because nine patients who were randomized to the alemtuzumab 24 mg group actually received alemtuzumab 12 mg.

3.3 Patient Disposition

The disposition of patients in the CARE-MS II study is presented in Table 6.

A greater proportion of patients randomized to the interferon beta-1a group discontinued the study prior to receiving treatment than in the alemtuzumab 12 mg group (12.6% versus 2.3%), with the majority of patients withdrawing consent. Similarly, a greater proportion of patients discontinued treatment in the interferon beta-1a group than in the alemtuzumab 12 mg group (11.7% versus 2.3%). In total, 95.4% of patients randomized to alemtuzumab 12 mg completed the study, compared with 75.8% of patients randomized to interferon beta-1a. The most common reason for discontinuing prior to treatment and from the study was the withdrawal of patient consent.

TABLE 6: PATIENT DISPOSITION

Criteria, N (%)	CARE-MS II		
	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Interferon Beta-1a
Screened	1046		
Randomized	840		
	436 (100)	173 (100)	231 (100)
Discontinued prior to treatment	10 (2.3)	3 (1.7)	29 (12.6)
Withdrew consent	7 (1.6)	2 (1.2)	27 (11.7)
Physician decision	2 (0.5)	1 (0.6)	0
Adverse event	1 (0.2)	0	0
Other	0	0	2 (0.8)
Treated	426 (97.7)	170 (98.3)	202 (87.4)
Discontinued study following treatment	10 (2.3)	6 (3.5)	27 (11.7)
Withdrew consent	4 (0.9)	3 (1.7)	9 (3.9)
Adverse event	1 (0.2)	0	6 (2.6)
Lack of efficacy	0	0	6 (2.6)
Physician decision	2 (0.5)	0	3 (1.3)
Lost to follow-up	1 (0.2)	2 (1.2)	1 (0.4)
Death	1 (0.2)	1 (0.6)	0
Other	1 (0.2)	0	2 (0.8)
Completed study	416 (95.4)	164 (94.8)	175 (75.8)
FA	426 (97.7)	170 (98.3)	202 (87.4)
PP	398 (91.3)	153 (88.4)	171 (74.0)
Safety[a]	435 (99.8)	161 (93.1)	202 (87.4)

FA = full analysis; PP = per protocol.
[a] Nine patients randomized to the alemtuzumab 24 mg group received alemtuzumab 12 mg.
Source: Clinical Study Report[2] p. 93, 97, 321, 322, 422, Coles et al. (2012).[3]

3.4 Exposure to Study Treatments

The exposure to alemtuzumab infusions and interferon beta-1a injections is presented in Table 7 and Table 8, respectively. The majority of patients (92.9%) in the alemtuzumab 12 mg group completed two full cycles of treatment with 100% of the planned dose. Five patients did not receive the full dose of alemtuzumab 12 mg in cycle 1 due to infusion-associated reactions, but went on to complete cycle 2. Fifteen patients were still in the study at month 12 but did not receive cycle 2 infusions.

More than 80% of patients in the interferon beta-1a group were on a study drug for greater than 18 months. The majority of patients (89.6%) were titrated up to a 44 mcg dose within four weeks. The most common reason for treatment discontinuation in the interferon beta-1a group was adverse events.

TABLE 7: EXTENT OF EXPOSURE TO ALEMTUZUMAB INFUSIONS IN THE CARE-MS II STUDY; SAFETY SET

	Alemtuzumab 12 mg (N = 435)[a]
Cycle 1 (month 0), n (%)	435 (100)
Complete	[redacted]
Partial	[redacted]
Cycle 2 (month 12), n (%)	[redacted]
Complete	[redacted]
Partial	[redacted]
Not dosed	[redacted]
Total dose received as % of total dose expected (mg/mg), n (%)[b]	
100	[redacted]
80 to < 100	[redacted]
60 to < 80	[redacted]
40 to < 60	[redacted]
20 to < 40	[redacted]
0 to < 20	[redacted]

[a] Nine patients randomized to the alemtuzumab 24 mg group received alemtuzumab 12 mg.
[b] Total dose expected was 60 mg for cycle 1 (month 0) and 36 mg for cycle 2 (month 12).
Source: Clinical Study Report.[2]

TABLE 8: EXTENT OF EXPOSURE TO INTERFERON BETA-1A IN THE CARE-MS II STUDY; SAFETY SET

	Interferon Beta-1a (N = 202)
Completed treatment, n (%)	[redacted]
Months on study drug, n (%)	
≥ 18	[redacted]
12 to < 18	[redacted]
6 to < 12	[redacted]
0 to < 6	[redacted]
Titrated to 44 mcg after 4 weeks, n (%)	
Yes	[redacted]
No	[redacted]
Total number of doses missed	
Mean (SD)	[redacted]
Median (range)	[redacted]
Total doses missed as % of total doses expected, n (%)[a]	
100	[redacted]
80 to < 100	[redacted]
60 to < 80	[redacted]
40 to < 60	[redacted]
20 to < 40	[redacted]
0 to < 20	[redacted]

SD = standard deviation.
[a] Total doses expected was derived as (total days expected on study drug x 3/7 [doses per week/days per week]).
Source: Clinical Study Report.[2]

TABLE 9: ALTERNATIVE THERAPY AFTER DISCONTINUATION OF STUDY DRUG; FULL ANALYSIS SET

Generic Name	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Patients with alternative therapy, n (%)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Clinical Study Report.[2]

3.5 Critical Appraisal

3.5.1 Internal Validity

- CARE-MS II was a rater-blind study where the patients and treating physicians were not blinded to study treatment, which may have resulted in bias, especially in the evaluation of patient-reported outcomes. Patients in the alemtuzumab group may have had higher expectations of success based on results from CAMMS223 that were released prior to enrolment in CARE-MS II. However, it would have been difficult to conduct a double-blind study due to infusion-associated reactions associated with alemtuzumab, and the clinical expert consulted for this review noted that it would also be difficult to conduct a double-dummy study in which patients would require placebo interferon injections over two years.
- Patients included in the CARE-MS II study had to have relapsed while on at least six months of treatment with interferon beta or glatiramer acetate in the past 10 years. The majority of patients enrolled had relapsed while on interferon beta treatment. Thus patients randomized to interferon beta treatment may have been less likely to adhere to treatment, which may have biased the estimates of between-treatment differences.
- CARE-MS II used blinded raters in an attempt to minimize bias in the assessment of EDSS for disability and relapse end points, and MSFC scores. In addition, a blinded relapse adjudication panel was assembled to review information on suspected on-study relapses to determine whether the event constituted a relapse. Each adjudication was performed by two panel members, with a third member added if assessments conflicted.
- There were differential dropout rates between treatment groups prior to receiving treatment, with more patients dropping out in the interferon beta-1a group (12.6%) than the alemtuzumab 12 mg group (2.3%). As these patients were not considered in the primary efficacy analysis, this adds uncertainty to the results presented using the FA set due to potential differences in baseline characteristics between treatment groups and the lost benefit of randomization. Sensitivity analyses were performed to explore the impact of patients who discontinued prior to receiving treatment using a regression model to identify if dropouts were associated with a specific covariate ($P < 0.20$). The problem with this approach is that confounding factors cannot be judged by statistical significance and may not be completely identified. Additional sensitivity analyses submitted by the manufacturer that assumed all patients assigned to the interferon beta-1a group who withdrew prior to treatment did not experience SAD or did not relapse (most conservative assumption) showed similar rate ratios to the primary analyses.
- More patients dropped out in the interferon beta-1a group (11.7%) than the alemtuzumab 12 mg group (2.3%) after study treatment, with the most common reason being withdrawal of patient consent. Given the differential dropout, use of last observation carried forward (LOCF) to analyze

change from baseline for many outcomes (e.g., EDSS and quality of life scales) may have biased between-treatment comparisons. The direction of the bias, however, is uncertain.
- 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. Thus, results for tertiary outcomes should be interpreted with caution.

3.5.2 External Validity

- The CARE-MS II study assessed the effects of two treatment cycles (two years of treatment) for alemtuzumab; there is a lack of comparative evidence beyond two years.
- The CARE-MS II study compared alemtuzumab to interferon beta-1a, which is often the initial DMT used when a patient is diagnosed with RRMS. As alemtuzumab is being reviewed for use in RRMS patients who have had an inadequate response to interferon beta or other DMTs, interferon beta-1a may not be the most appropriate comparator. The CARE-MS II trial is relevant to the question of switching therapy, but does not compare alemtuzumab with other treatments recommended for use in patients who have failed interferon or glatiramer. As noted by the manufacturer, neither natalizumab nor fingolimod, drugs currently recommended for patients who have failed interferon or glatiramer, were commercially available at the time CARE-MS II was initiated.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See Appendix 4: Detailed Outcome Data for detailed efficacy data.

In the CARE-MS II study, the alemtuzumab 24 mg group was closed to enrolment after a protocol amendment and efficacy analyses performed with the alemtuzumab 24 mg group were considered exploratory. As the approved Health Canada dose is 12 mg/day, efficacy and safety results for the alemtuzumab 24 mg group are not presented in this review.

3.6.1 Relapse

The adjusted ARR through two years was statistically significantly lower in the alemtuzumab group (0.26 [95% confidence interval (CI), 0.21 to 0.33]) compared with the interferon beta-1a group (0.52 [95% CI, 0.41 to 0.66]); rate ratio 0.51 (95% CI, 0.39 to 0.65) (Table 12). Results using the per protocol set were comparable to the result of the full analysis set (Table 16).

The ARR was also analyzed separately for year 1 and year 2 and was statistically significantly lower in the alemtuzumab group compared with the interferon beta-1a group for both years. The rate ratio of ARR of alemtuzumab compared with interferon beta-1a was 0.46 (95% CI, 0.34 to 0.61) for year 1 and 0.59 (95% CI, 0.42 to 0.82) for year 2.

Sensitivity analyses were conducted to assess the influence of alternative MS treatments, unblinded EDSS raters, dropouts prior to treatment, and other factors that could potentially affect the primary relapse analysis (Table 16). The rate ratios of the sensitivity analyses were similar to the estimated rate ratio from the primary relapse rate analysis.

3.6.2 Disability

The proportion of patients with six-month SAD over two years, based on Kaplan–Meier estimates, was statistically significantly lower for the alemtuzumab group (12.7%) compared with interferon beta-1a (21.1%), and time to six-month SAD was statistically significantly less for interferon beta-1a, hazard ratio 0.58 [95% CI, 0.38 to 0.87]; Table 13. Results using the per protocol set were comparable to the result of

the full analysis set (Table 16). Sensitivity analyses were conducted to assess the influence of alternative MS treatments, unblinded EDSS raters, dropouts prior to treatment, and other factors that could potentially affect the primary six-month SAD analysis (Table 16). The hazard ratios were similar to the estimated hazard ratio from the primary time to six-month SAD analysis. There was no statistically significant difference between treatment groups in the time to three-month SAD.

Alemtuzumab-treated patients were reported to be more likely to achieve six-month sustained reduction in disability compared with interferon beta-1a (hazard ratio 2.57 [95% CI, 1.57 to 4.20]; Table 14). However, this outcome was one of many tertiary outcomes tested.

The change from baseline in EDSS score at year 2 was –0.17 (95% CI, –0.29 to –0.05) in the alemtuzumab group and 0.24 (95% CI, 0.07 to 0.41) in the interferon beta-1a group; mean difference –0.41 (95% CI, –0.61 to –0.22) (Table 15).

The change from baseline in MSFC scores at year 2 was 0.08 (95% CI, 0.04 to 0.12) in the alemtuzumab group and –0.04 (95% CI, –0.10 to 0.02) in the interferon beta-1a group (Table 15).

3.6.3 Health-Related Quality of Life

[redacted]

3.6.4 Fatigue

[redacted]

3.6.5 MRI Outcomes

T2 hyperintense lesion volume decreased from baseline after treatment with alemtuzumab and interferon beta-1a, but there was no statistically significant difference in the per cent change from baseline between groups (Table 20). The proportion of patients with new or enlarging T2 hyperintense lesions over two years was 46.2% in the alemtuzumab group and 67.9% in the interferon beta-1a group (Table 20). The proportion of patients with Gd-enhancing lesions over two years was 18.5% in the alemtuzumab group and 34.2% in the interferon beta-1a group (Table 20).

3.6.6 Productivity

Productivity was not measured in the CARE-MS II study.

3.6.7 Medication Acceptance

Medication acceptance was not measured in the CARE-MS II study.

3.6.8 Relapse Requiring Corticosteroids or Hospitalization

The ARR of relapses treated with IV corticosteroids [redacted]; (Table 21).

A sensitivity analysis [redacted] (Table 21).

TABLE 10: KEY EFFICACY OUTCOMES; FULL ANALYSIS SET

	Alemtuzumab 12 mg (N = 426)	Interferon beta-1a (N = 202)
Annualized Relapse Rate		
ARR — years 0 to 2 (95% CI)	0.26 (0.21 to 0.33)	0.52 (0.41 to 0.66)
Rate ratio (95% CI)	0.51 (0.39 to 0.65)	
P value	< 0.0001	
Sustained Accumulation of Disability (6 Months)		
Kaplan–Meier estimate, % (95% CI)	12.71 (9.89 to 16.27)	21.13 (15.95 to 27.68)
Hazard ratio (95% CI)	0.58 (0.38 to 0.87)	
P value	0.0084	
EDSS Scores		
N	413	174
Change from baseline (95% CI)	–0.17 (–0.29 to –0.05)	0.24 (0.07 to 0.41)
Difference (95% CI)	–0.41 (–0.61 to –0.22)	
P value	< 0.0001	
MSFC Scores		
N	402	171
Change from baseline (95% CI)	0.08 (0.04 to 0.12)	–0.04 (–0.10 to 0.02)
Difference (95% CI)	0.12 (0.05 to 0.19)	
FAMS Scores		
Change from baseline (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
SF-36 Mental Component Summary		
Change from baseline (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
SF-36 Physical Component Summary		
Change from baseline (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
EQ-5D Utility Score		
Change from baseline (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
EQ-5D VAS Score		
Change from baseline (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
MRI — T2 Hyperintense Lesion Volume		
Mean % change from baseline (SD)	–1.12 (24.40)	2.41 (26.48)
P value	0.1371	

	Alemtuzumab 12 mg (N = 426)	Interferon beta-1a (N = 202)
MRI — New or Enlarging T2 Hyperintense Lesions		
n/N (%)	186/403 (46.2)	127/187 (67.9)
OR (95% CI)	0.38 (0.26 to 0.55)	
MRI — Gd-enhancing Lesions		
n/N (%)	74/399 (18.5)	64/187 (34.2)
OR (95% CI)	0.41 (0.27 to 0.62)	
Relapse Requiring Corticosteroids		
ARR (95% CI)	[redacted]	[redacted]
Rate ratio	[redacted]	
Relapse Requiring Hospitalization		
ARR (95% CI)	[redacted]	[redacted]
Rate ratio	[redacted]	

ARR = annualized relapse rate; CI = confidence interval; EDSS = Kurtzke Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions Questionnaire; FAMS = Functional Assessment of Multiple Sclerosis; Gd = gadolinium; MRI = magnetic resonance imaging; MSFC = Multiple Sclerosis Functional Composite; OR = odds ratio; SD = standard deviation; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.
Source: Clinical Study Report,[2] Coles et al. (2012).[3]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Table 11 for detailed harms data.

3.7.1 Adverse Events

A total of 98.4% of patients in the alemtuzumab 12 mg group experienced an adverse event compared with 94.6% of patients in the interferon beta-1a group. The most commonly reported adverse events with alemtuzumab included: headache (52.9% versus 17.8% interferon beta-1a), rash (44.4% versus 5.4% interferon beta-1a), MS relapse (32.9% versus 49.0% interferon beta-1a), nasopharyngitis (29.4% versus 23.8% interferon beta-1a), [redacted], pyrexia (21.8% versus 8.9% interferon beta-1a), urinary tract infection (21.4% versus 11.4% interferon beta-1a), and fatigue (18.6% versus 12.9% interferon beta-1a).

3.7.2 Serious Adverse Events

A total of 19.5% of patients in the alemtuzumab 12 mg group experienced a serious adverse event compared with 21.8% of patients in the interferon beta-1a group. Serious adverse events reported in more than two patients in the alemtuzumab group included MS relapse (33 patients, 7.6%), gastroenteritis (three patients), and ITP/autoimmune thrombocytopenia (three patients).

3.7.3 Withdrawals Due to Adverse Events

A total of 3.2% of patients in the alemtuzumab 12 mg group discontinued study treatment due to an adverse event compared with 8.9% of patients in the interferon beta-1a group. The most common adverse events that led to discontinuation of treatment in the alemtuzumab 12 mg group were infusion-associated reactions (five patients). One patient (0.2%) in the alemtuzumab 12 mg group discontinued participation in the study due to an adverse event (non-cardiac chest pain), compared with six patients (3.0%) in the interferon beta-1a group (MS relapse [two patients], migraine, muscle spasms, acute myeloid leukemia, and eye pain).

3.7.4 Mortality

Two deaths were reported in the alemtuzumab 12 mg group. One patient died after being hit by a car while she was walking, and another patient died of aspiration pneumonia. There were no deaths in the interferon beta-1a treatment group.

3.7.5 Notable Harms

a) Immune Thrombocytopenic Purpura

Four patients in the alemtuzumab 12 mg group met the adverse event criteria for immune thrombocytopenic purpura (ITP) (coded to a preferred term of idiopathic thrombocytopenic purpura or autoimmune thrombocytopenia).

b) Thyroid Adverse Events

A greater proportion of patients experienced a thyroid adverse event in the alemtuzumab 12 mg group compared with the interferon beta-1a group (15.9% versus 5.0%). Two patients in the alemtuzumab 12 mg group experienced a serious thyroid adverse event. One patient experienced Grade 2 hyperthyroidism after the second cycle of treatment and another patient experienced Grade 3 hypothyroidism after the first cycle of treatment.

c) Autoimmune Hemolytic Anemia

One patient in the alemtuzumab 12 mg group experienced Grade 2 autoimmune hemolytic anemia after the second cycle of treatment.

d) Infusion-Associated Reactions

The majority of patients (90.3%) in the alemtuzumab 12 mg group experienced at least one adverse event associated with alemtuzumab 12 mg/day infusions. Twelve patients (2.8%) in the alemtuzumab 12 mg group reported serious infusion-associated reactions that included pyrexia, urticaria, nausea, and chest pain.

e) Infections

A greater proportion of patients experienced an infection with alemtuzumab 12 mg than with interferon beta-1a (76.8% versus 66.3%). A greater proportion of patients experienced a serious infection with alemtuzumab 12 mg than with interferon beta-1a (3.7% versus 1.5%).

There were no reports of progressive multifocal leukoencephalopathy.

TABLE 11: HARMS; SAFETY SET

	Alemtuzumab 12 mg (N = 435)	Interferon Beta-1a (N = 202)
AEs		
Subjects with > 0 AEs, N (%)	428 (98.4)	191 (94.6)
Most common AEs (≥ 10%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Dizziness	48 (11.0)	11 (5.4)
Fatigue	81 (18.6)	26 (12.9)
Headache	230 (52.9)	36 (17.8)
[redacted]	[redacted]	[redacted]

	Alemtuzumab 12 mg (N = 435)	Interferon Beta-1a (N = 202)
MS relapse	143 (32.9)	99 (49.0)
Nasopharyngitis	128 (29.4)	48 (23.8)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Paresthesia	50 (11.5)	20 (9.9)
Pruritus	66 (15.2)	5 (2.5)
Pyrexia	95 (21.8)	18 (8.9)
Rash	193 (44.4)	11 (5.4)
Sinusitis	58 (13.3)	20 (9.9)
URTI	71 (16.3)	25 (12.4)
UTI	93 (21.4)	23 (11.4)
Urticaria	75 (17.2)	2 (1.0)
SAEs		
Subjects with > 0 SAEs, N (%)	85 (19.5)	44 (21.8)
Most common SAEs		
[redacted]	[redacted]	[redacted]
Appendicitis	2 (0.5)	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
ITP/autoimmune thrombocytopenia	3 (0.7)	0
MS relapse	33 (7.6)	25 (12.4)
Pneumonia	4 (0.9)	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
WDAEs		
AEs leading to treatment withdrawal, N (%)	[redacted]	[redacted]
Most common reasons		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
AEs leading to study discontinuation, N (%)	1 (0.2)	6 (3.0)
Most common reasons		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Deaths		
Number of deaths, N (%)	2 (0.5)	0
Reasons		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	Alemtuzumab 12 mg (N = 435)	Interferon Beta-1a (N = 202)
Notable harms		
ITP/autoimmune thrombocytopenia	4 (0.9)	0
Thyroid AEs	69 (15.9)	10 (5.0)
Thyroid SAEs	2 (0.5)	0
[redacted]	[redacted]	[redacted]
Infusion-associated reactions[a]	393 (90.3)	NA
Serious infusion-associated reactions[a]	12 (2.8)	NA
Infections	334 (76.8)	134 (66.3)
Serious infections	16 (3.7)	3 (1.5)

AE = adverse event; ITP = idiopathic thrombocytopenic purpura; MS = multiple sclerosis; NA = not applicable; SAE = serious adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.
[a] Infusion-associated reactions were defined as any adverse events that occurred during or within 24 hours following an alemtuzumab infusion, regardless of relationship to treatment.
Source: Clinical Study Report[2], Coles et al. (2012).[3]

4. DISCUSSION

4.1 Summary of Available Evidence

One two-year, randomized, rater-blind, active-controlled study met the inclusion criteria for this systematic review. CARE-MS II (N = 810) evaluated the efficacy and safety of alemtuzumab 12 mg and 24 mg compared with interferon beta-1a in patients with active RRMS who had previously experienced a relapse while on at least six months of interferon beta or glatiramer acetate therapy.

CARE-MS II initially randomized patients to an alemtuzumab 24 mg group, but discontinued randomization into this group after a protocol amendment. As the efficacy results performed with this group were considered exploratory and the Health Canada–approved dose is 12 mg, only results from the alemtuzumab 12 mg group are presented in this review.

The limitations of the available evidence include the open-label design of CARE-MS II and the differences in study withdrawals between the alemtuzumab 12 mg and interferon beta-1a groups, which may have biased the results of the between-treatment comparisons. There are no head-to-head trials of alemtuzumab and other DMTs recommended for patients who have had an inadequate response to other therapies for MS (e.g., natalizumab or fingolimod).

4.2 Interpretation of Results

4.2.1 Efficacy

CARE-MS II employed an open-label design with rater blinding, which may be subject to various biases. As there were differential withdrawal rates between the alemtuzumab and interferon beta-1a groups prior to receiving treatment, it appears that patients' knowledge of which treatment group they were randomized to may have influenced this imbalance. Patients assigned to the interferon beta-1a group were more likely to withdraw consent than those in the alemtuzumab group, which may be due to the enrolment of patients who had previously relapsed while on interferon beta therapies who would not be willing to receive the same treatment again. The differential withdrawal rates prior to treatment in CARE-MS II is of concern, as the primary efficacy analyses were performed using a modified intention-to-treat population consisting of patients who were randomized and received a study drug. However, the manufacturer performed sensitivity analyses accounting for pre-treatment withdrawals and found that relapse rate and time to six-month SAD were similar to the primary analyses.

As alemtuzumab is being reviewed for use in RRMS patients who have had an inadequate response to interferon beta or other DMTs, interferon beta-1a may not be the most appropriate comparator. The CARE-MS trial is relevant to the question of switching therapy, but does not compare alemtuzumab with other treatments recommended for use in patients who have failed interferon or glatiramer. The manufacturer submitted a mixed treatment comparison (MTC) comparing alemtuzumab with other DMTs and included a subgroup analysis in previously treated patients (see Appendix 8: Summary of Indirect Comparison). [redacted]

[redacted] Additional head-to-head trials are needed to determine the comparative effectiveness of alemtuzumab against other MS drugs.

Both primary end points, ARR and time to six-month sustained accumulation of disability, were met in CARE-MS II, although unequal study withdrawal across treatment groups may have biased estimates of effect. In addition, the open-label design may have resulted in bias, especially for patient-reported outcomes. Patients may have under- or over-reported symptoms depending on which treatment group they were assigned to, resulting in potential misreporting of relapses and health-related quality of life outcomes. It may be worth noting that the change from baseline in T2 hyperintense lesion volume, a relatively objective outcome, was not statistically significantly different between alemtuzumab and interferon beta-1a groups. The manufacturer asserted that the effect of high-dose, high-frequency interferon beta-1a on MRI outcomes precluded the ability to determine an effect with alemtuzumab on T2 lesion volume. The clinical expert consulted for this review agreed that this is a common effect seen with interferon beta-1a. Other MRI outcomes in CARE-MS II, including the proportion of patients with new or enlarging T2 hyperintense lesions and the proportion of patients with Gd-enhancing lesions, saw statistically significant improvements with alemtuzumab 12 mg compared with interferon beta-1a, with these improvements maintained into year 3 (see Appendix 7: Summary of Additional Studies). However, these were tertiary outcomes and were not part of the hierarchical statistical analysis plan that attempted to adjust for multiple comparisons. Findings from systematic reviews and randomized controlled trials (RCTs) report correlations between conventional MRI outcomes and clinical outcomes (relapse rate and disability progression), but correlations are variable across studies (see Appendix 5: Validity of Outcome Measures). The clinical expert consulted for this review noted that MRI outcomes are a valid surrogate outcome.

Patients who completed CARE-MS II were enrolled in the CAMMS03409 extension study, where patients originally enrolled in the alemtuzumab 12 mg group were re-treated upon relapse and all patients originally enrolled into the interferon beta-1a group were given two annual cycles of alemtuzumab (see Appendix 7: Summary of Additional Studies). Two years of extension data are available for patients originally enrolled in CARE-MS II, giving a total of four years of data. Results from year 3 and year 4 in patients in the alemtuzumab 12 mg group in CARE-MS II found that ARRs were similar to those in year 1 and year 2. Relapse rates declined in patients in the interferon beta-1a group in CARE-MS II. Similar results were seen in disability status.

Re-treatment rates of CARE-MS II patients originally randomized to the alemtuzumab 12 mg group were generally low, with 24% of patients receiving one additional course of treatment during the two years of follow-up, and 7% of patients receiving two additional courses of treatment.

In a single-group cohort study by Tuohy et al. (N = 87) with a mean follow-up time frame of seven years, 36% of patients received three courses of treatment, 8% of patients received four courses of treatment, and one patient received five courses of treatment (see Appendix 7: Summary of Additional Studies).[25] However, the study by Tuohy et al. had no comparator group, enrolled both treatment-naive and treatment-experienced patients, used non–Health Canada approved doses of alemtuzumab at the beginning of the study, and enrolled patients with more severe disease than those in CARE-MS II, limiting the generalizability of these findings.

4.2.2 Harms

The most common adverse events associated with alemtuzumab included headache, rash, and nasopharyngitis. Serious adverse events included gastroenteritis and immune thrombocytopenic purpura (ITP). Cases of ITP were initially reported in CAMMS223, which resulted in the temporary suspension of alemtuzumab dosing in that study and the development of a formal safety monitoring plan.[26] In CARE-MS II, there were four people who met the adverse event criteria for ITP in the alemtuzumab group. Other autoimmune disorders associated with alemtuzumab from CAMMS223 were thyroid disorders. In CARE-MS II, thyroid adverse events occurred in 15.9% of patients who received alemtuzumab compared with 5.0% of patients who received interferon beta-1a. Two patients experienced a serious thyroid adverse event in the alemtuzumab group. Infections and serious infections occurred more frequently with alemtuzumab than interferon beta-1a, which was consistent with what was observed in CAMMS223 and CAMMS323/CARE-MS I (see Appendix 6: Summary of Efficacy and Harms From Excluded Studies).

Patient group input suggested that the dosing regimen of alemtuzumab would be beneficial as infusions would need to be administered only infrequently (for five consecutive days in the initial cycle and for three consecutive days 12 months later). Although this dosing schedule would allow for a longer period between treatment administration, patients should be monitored frequently for signs and symptoms suggestive of autoimmune conditions and other safety concerns associated with alemtuzumab. According to the Health Canada product monograph, patients who received alemtuzumab should have complete blood counts and urinalysis performed at monthly intervals, and laboratory tests should be conducted for at least 48 months following the last treatment course in order to monitor for early signs of autoimmune disease.[13] The clinical expert consulted for this review indicated that adherence to monthly monitoring visits may be an issue, particularly if patients are feeling well.

Nearly all patients (90.3%) in the alemtuzumab group reported an infusion-associated reaction (IAR), with 2.3% reporting a serious IAR. IARs were the most common reason for treatment withdrawal in the alemtuzumab group. The proportion of patients withdrawing from treatment due to an adverse event was higher in the interferon beta-1a group than the alemtuzumab group. However, the majority of patients who withdrew from treatment remained in the study, with only one patient in the alemtuzumab group and six patients in the interferon beta-1a group withdrawing from the study due to an adverse event. Two deaths were reported in the alemtuzumab group, but none was considered by the investigators to be related to alemtuzumab treatment.

In the CAMMS03409 extension, there were two additional years of safety data for CARE-MS II patients (see Appendix 7: Summary of Additional Studie). There were no new safety concerns that emerged in patients who were treated with alemtuzumab 12 mg in the original studies. The incidence of infections was lower in the third and fourth year of treatment when compared with the first two years of treatment in the original studies. IARs decreased in the third year but increased again in the fourth year. The incidence of autoimmune disorders, however, increased in the third year, but declined in the fourth year. Thyroid disorders continued to be the most frequently reported autoimmune disease in the extension study, and there were six cases of ITP in the fourth year among patients who were treated with alemtuzumab 12 mg in CARE-MS II. Similar safety results were seen in the cohort study conducted by Tuohy et al., in which thyroid events were the most frequently reported autoimmune disease, and three patients experienced ITP during the entire study.[25] In addition, 11 patients (12.6%) experienced varicella zoster virus reactivation in the observational study.[25] The clinical expert consulted for this review noted that there is currently no method to ascertain which patients would be at increased risk of developing autoimmune diseases with alemtuzumab treatment, and that alemtuzumab would be

prescribed by a neurologist to a population with more severe disease after weighing the potential safety risks.

Progressive multifocal leukoencephalopathy (PML) is a rare and often fatal opportunistic infection caused by reactivation of the JC virus and is characterized by progressive damage of the white matter of the brain. The risk of PML increases in severely immunocompromised hosts, and has been associated with other MS therapies such as natalizumab.[11] PML has been reported in patients with B-CLL who were treated with alemtuzumab.[27-29] However, the alemtuzumab doses used for B-CLL are much higher than that for RRMS, and B-CLL patients may have an increased risk of developing PML due to immunosuppression from other treatments. CDR did not identify any reports of PML in patients with MS treated with alemtuzumab.

4.3 Other Considerations

In December 2013, the Food and Drug Administration (FDA) declined approval for alemtuzumab (Lemtrada) in RRMS, citing that the manufacturer had not submitted evidence from adequate and well-controlled studies that demonstrate that the benefits outweigh the serious adverse effects.[1] In November 2014, the FDA approved alemtuzumab for the treatment of patients with RRMS after reviewing a resubmission by Genzyme US that included additional long-term data from existing studies. The European Medicines Agency (EMA) granted marketing authorization for alemtuzumab (Lemtrada) in RRMS in September 2013. In December 2013, Health Canada restricted its marketing authorization for alemtuzumab to patients with RRMS who have had an inadequate response to interferon beta or other DMTs due to inconsistencies in efficacy results in the two studies performed in treatment-naive patients (CAMMS223 and CARE-MS I) and the limitations of the rater-blind study designs. Although the Health Canada reviewers had concerns with the study design of CARE-MS II, they concluded that there is a potential clinical efficacy benefit in using alemtuzumab in RRMS patients who have had an inadequate response to other DMTs.

5. CONCLUSIONS

One two-year, randomized, rater-blind, active-controlled study (CARE-MS II) evaluating the efficacy and safety of alemtuzumab 12 mg compared with interferon beta-1a in patients with active RRMS who had previously experienced a relapse while on at least six months of interferon beta or glatiramer acetate therapy was included in the systematic review. The results of CARE-MS II suggest that alemtuzumab is superior to interferon beta-1a in reducing the ARR and the risk of six-month SAD over two years of treatment in treatment-experienced patients. These findings need to be interpreted with caution due to the limitations of the rater-blind design and the differences in study withdrawals between treatment groups.

A manufacturer-provided mixed treatment comparison in treatment-experienced patients [redacted]

The most common harms associated with alemtuzumab included headache, rash, and nasopharyngitis. Safety concerns associated with alemtuzumab include immune thrombocytopenic purpura, thyroid disorders, infection, and IARs. There were no reports of PML. Two additional years of data from the CAMMS03409 extension study found no new safety concerns in patients treated with alemtuzumab 12 mg in CARE-MS II. Similar safety results were seen in a single-group cohort study that looked at long-term efficacy and safety of alemtuzumab with a median seven-year follow-up, where thyroid events were the most frequently reported autoimmune disease. However, both studies are limited by study design and lack of a comparator group, which leads to considerable uncertainty as to the findings of these studies.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Multiple Sclerosis Society of Canada (MS Society) is a national voluntary organization that supports research and services related to multiple sclerosis (MS) for patients with MS and their families. Its membership of 20,500 is governed by a 14-member, elected National Board of Directors. Conflict of interest declarations include the receipt of educational grants in 2013 from Bayer, Biogen Idec, EMD Serono, Novartis, Pfizer, Genzyme, Allergan, and Teva Neuroscience, representing less than 2% of MS Society's overall revenue. All contributions are subject to strict policies that prevent any control or influence by the donor on the MS Society's decision-making. No conflicts of interest were declared in preparation of this submission.

The Consumer Advocare Network (Advocare) is a not-for-profit organization that provides education and support to patient groups to promote engagement in health care policy and decision-making. It also provides input to health policy-makers and health care providers. Advocare has received unrestricted educational grants from Canada's Research-Based Pharmaceutical Companies, Merck Canada, Pfizer Canada, Sanofi, Janssen-Ortho, Amgen Canada, Lilly Canada, Hoffman-LaRoche, Wyatt Health Management, and the University of Alberta. It declared no conflict of interest in the preparation of this submission.

2. Condition and Current Therapy-Related Information

Patient input information from the MS Society was collected through an online survey targeted at MS patients and their caregivers, for the purposes of gathering data for this submission. The survey respondents (N = 579) included patients (90%) and caregivers (10%). Information from Advocare was collected through individual interviews with patients, caregivers, and nurses supporting MS patients (N = 12), and an online survey (link of the survey was sent to the MS Society also; 63 responses were received). Five per cent of respondents in the Advocare patient group were caregivers. In both submissions, most of the patients had relapsing-remitting multiple sclerosis (RRMS), 66% in the MS Society submission and 82% in the Advocare submission, respectively.

MS is an unpredictable, disabling disease of the central nervous system and is characterized by a wide variety of symptoms: fatigue, MS-related pain, difficulty in walking, memory or attention problems, bladder problems, numbness or weakness in one or more body parts, tingling, heat intolerance and sensitivity, and electric shock sensations. Respondents reported that RRMS had a significant impact not only on the patients' physical activity, but also on their quality of life, mental health, work or career, and their family members/caregivers.

Currently, 10 drugs have been approved in Canada in reducing the frequency and severity of MS relapses and some may slow the accumulation of disability over time. In the MS Society survey, more than half (54%) of respondents were using a disease-modifying therapy (DMT). Copaxone, Rebif, Tecfidera, Gilenya, Avonex, Tysabri, Aubagio, and Betaseron were commonly prescribed. Among respondents, 44.1% indicated that their DMT was effective in managing the disease, 43.3% were not sure if it was effective, and 12.6% indicated that it was not effective. Commonly reported side effects included injection site reactions, headache, flu-like symptoms, flushing, gastrointestinal symptoms, back pain, skin rashes or hives, infections, and abnormal blood or liver tests. In the Advocare survey, Copaxone, Aubagio, Tecfidera, Gilenya and Tysabri were currently used by respondents. Patients

reported differently with respect to the effectiveness of DMTs in treating MS symptoms. Severity of the side effects of interferon beta and Copaxone were rated as "much" or "very much" in majority of patients, while side effects of Tecfidera, Gilenya, Tysabri, and Aubagio were rated as "little" or "none".

Accessing the currently available DMTs is a notable challenge for 42.5% of respondents in the MS Society survey. The following factors were reported as hurdles to drug access: high cost, difficulty in drug administration, access to public or private insurance, difficulty in taking time off work for drug administration, and limited transportation to treatment centre.

Caregivers are an important part of the patients' ability to maintain their quality of life and independence in the community. Providing assistance to MS patients impacted the caregivers' own daily routines. Caregivers indicated that the disease and the treatment had negative impact on the patients' daily lives, work, and family and social life.

3. Related Information About the Drug Being Reviewed

Ten respondents in the MS Society survey had experience with alemtuzumab and identified minimal challenges related to drug access. In the Advocare patient group, 15% of respondents reported previous or current use of alemtuzumab. Patients who received alemtuzumab reported fewer hospital visits, fewer relapses, the ability to remain in the workforce, better mobility, pain relief, and improved psychological impact from the disease and treatment. Alemtuzumab is administrated annually with a "drug free" period between doses. This was cited as a benefit, because the patients would not experience side effects as frequently (daily, weekly, or monthly administration) as those treated with other DMTs. One respondent from the MS Society commented that, "*The ability for a short-term treatment versus a daily or weekly treatment allows a person with MS to operate without having the illness contribute to a general feeling of poor health.*" The common side effects reported in the MS Society survey were IARs, fatigue, bruising, and tingling sensations. About two-thirds of patients in the Advocare patient group rated side effects during the infusion as "much" or "some" but none after the infusion. One-third reported no side effects during infusions. All patients indicated that they were aware of the potential long-term risks and would like to receive continuous alemtuzumab therapy. One patient from Advocare said, "*I know all of the possible side effects and I can deal with them; I know how to treat thyroid disease but not MS.*"

The majority of survey respondents in the two patient groups had no experience with alemtuzumab. Patient expectations for a new DMT were improved symptom relief, improved daily functioning, reduced or eliminated relapses, lower and/or limited side effects, affordability, and better convenience (e.g., no refrigeration and no need to take regular injections or medications).

4. Additional Information

The potential choice of more MS drugs that have greater efficacy and easier mode of administration is desirable, and respondents indicated that having options that match a person's disease and life situation are important considerations.

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 15, 2015
Alerts:	Weekly search updates until May 20, 2015.
Study Types:	No search filters were applied
Limits:	Date limit: January 2014-present (update of previous Lemtrada submission search) No language limits 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
fs	Floating subheading
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
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
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
.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	
Line#	**Strategy**
1	(alemtuzumab* or Lemtrada* or Campath* or MabCampath* or LDP-03 or LDP03).ti,ab,rn,nm,sh,hw,ot.
2	(216503-57-0 or 126775-97-1 or 478159-77-2 or 727728-72-5).rn,nm.
3	1 or 2
4	exp Multiple sclerosis/
5	(multiple sclerosis or disseminated sclerosis or insular sclerosis or ms or rrms or neurolog* or relapse rate* or relapse remit* or relapseremit*).ti,ab,sh,hw,ot.
6	4 or 5
7	3 and 6
8	7 use pmez
9	*Alemtuzumab/
10	(alemtuzumab* or Lemtrada* or Campath* or MabCampath* or LDP-03 or LDP03).ti,ab.
11	9 or 10
12	Multiple sclerosis/
13	(multiple sclerosis or disseminated sclerosis or insular sclerosis or ms or rrms or neurolog*or relapse rate* or relapse-remit*).ti,ab.
14	12 or 13
15	11 and 14
16	15 use oemezd
17	16 not conference abstract.pt.
18	8 or 17
19	remove duplicates from 18
20	limit 19 to yr="2014 -Current"

Other Databases	
PubMed	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 15, 2015
Keywords:	Drug name, Indication
Limits:	No language limits used; Date limit: January 2014 to present (update of previous Lemtrada submission search)

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/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
Clinical study report: CAMMS223[26]	Patient population
Clinical study report: CAMMS323[30]	
Coles et al. (2008)[31]	
Cohen et al. (2012)[32]	
Clinical protocol: CAMMS03409[33]	Study design

APPENDIX 4: DETAILED OUTCOME DATA

Relapse

TABLE 12: RELAPSE; FULL ANALYSIS SET

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Patients with a relapse through 2 years	147 (35)	104 (53)
Total number of relapses	236	201
ARR — years 0 to 2 (95% CI)[a]	0.26 (0.21 to 0.33)	0.52 (0.41 to 0.66)
Rate ratio (95% CI)	0.51 (0.39 to 0.65)	
Risk reduction, %	49.4	
P value	< 0.0001	
ARR — year 1 (95% CI)[a]	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	
Risk reduction, %	[redacted]	
P value	[redacted]	
ARR — year 2 (95% CI)[a]	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	
Risk reduction, %	[redacted]	
P value	[redacted]	
Mean relapses per patient (SD)	[redacted]	[redacted]
Median relapses per patient (range)	[redacted]	[redacted]
Relapses per patient, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]
Proportion of relapse-free patients through 2 years, % (95% CI)[b]	[redacted]	[redacted]
Hazard ratio (95% CI)[c]	[redacted]	
Risk reduction, %	[redacted]	
P value[c]	[redacted]	

ARR = annualized relapse rate; CI = confidence interval; SD = standard deviation.
[a] Estimated through negative binomial regression with robust variance estimation and covariate adjustment for geographic region.
[b] Derived from Kaplan–Meier estimates.
[c] Hazard ratio and *P* value are from proportional hazards regression with robust variance estimation and covariate adjustment for geographic region.
Source: Clinical Study Report[2], Coles et al. (2012).[3]

Disability

TABLE 13: TIME TO SUSTAINED ACCUMULATION OF DISABILITY; FULL ANALYSIS SET

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Sustained for 6 months — co-primary end point		
Patients with SAD, n (%)	54 (12.6)	40 (19.8)
Percentage of patients (95% CI)[a]	12.71 (9.89 to 16.27)	21.13 (15.95 to 27.68)
Hazard ratio (95% CI)[b]	0.58 (0.38 to 0.87)	
P value[b]	0.0084	

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Sustained for 3 months — tertiary end point		
Patients with SAD, n (%)	[redacted]	[redacted]
Percentage of patients (95% CI) [a]	[redacted]	[redacted]
Hazard ratio (95% CI) [b]	[redacted]	
P value [b]	[redacted]	

CI = confidence interval; SAD = sustained accumulation of disability.
[a] Derived from Kaplan–Meier estimates.
[b] Hazard ratio and *P* value are from proportional hazards regression with robust variance estimation and covariate adjustment for geographic region.
Source: Clinical Study Report,[2] Coles et al. (2012).[3]

TABLE 14: TIME TO SIX-MONTH SUSTAINED REDUCTION IN DISABILITY — TERTIARY END POINT; FULL ANALYSIS SET

	Alemtuzumab 12 mg (N = 321)[a]	Interferon Beta-1a (N = 153)[a]
Patients with SRD, n (%)	92 (28.8)	18 (12.9)
Percentage of patients (95% CI)[b]	28.82 (24.18 to 34.13)	12.93 (8.34 to 19.77)
Hazard ratio (95% CI) [c]	2.57 (1.57 to 4.20)	
P value [c]	0.0002	

CI = confidence interval; SRD = sustained reduction in disability.
[a] Patients with a baseline EDSS ≥ 2.0.
[b] Derived from Kaplan–Meier estimates.
[c] Hazard ratio and *P* value are from proportional hazards regression with robust variance estimation and covariate adjustment for geographic region.
Source: Clinical Study Report[2] p. 133, 1338, Coles et al. (2012).[3]

TABLE 15: CHANGE FROM BASELINE AT YEAR 2 IN EDSS AND MSFC SCORES — SECONDARY END POINTS; FULL ANALYSIS SET

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
EDSS		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Mean change from baseline (95% CI)	–0.17 (–0.29 to –0.05)	0.24 (0.07 to 0.41)
Difference (95% CI)	–0.41 (–0.61 to –0.22)	
P value	< 0.0001	
MSFC		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Mean change from baseline (95% CI)	0.08 (0.04 to 0.12)	–0.04 (–0.10 to 0.02)
Difference (95% CI)	0.12 (0.05 to 0.19)	
P value	[a]	

CI = confidence interval; EDSS = Kurtzke Expanded Disability Status Scale; MSFC = Multiple Sclerosis Functional Composite; SD = standard deviation.
[a] *P* value not provided as outcome falls below a non-statistically significant parameter in the hierarchical chain of testing.
Note: Mixed model for repeated measures analysis; changes from baseline and group differences estimated using an unstructured covariance model with a time by treatment interaction and covariate adjustment for geographic region and baseline score.
Source: Clinical Study Report,[2] Coles et al. (2012).[3]

Sensitivity Analyses for Co-Primary End Points

TABLE 16: SENSITIVITY ANALYSES FOR RELAPSE RATE AND SAD — CO-PRIMARY END POINTS; FULL ANALYSIS SET

Sensitivity Analysis	Relapse Rate		SAD	
	Rate ratio (95% CI)	*P* Value	Rate Ratio (95% CI)	*P* Value
Primary analysis (FA set)	0.51 (0.39 to 0.65)	< 0.0001	0.58 (0.38 to 0.87)	0.0084
PP set	[redacted]	[redacted]	[redacted]	[redacted]
Randomized set	0.50 (0.39 to 0.65)	< 0.0001	0.58 (0.38 to 0.87)	0.0085
Censoring patients at the time of alternative MS therapy	0.48 (0.38 to 0.62)	< 0.0001	0.56 (0.37 to 0.85)	0.0059
Including covariates selected using a backward-elimination method	0.50 (0.39 to 0.64)	< 0.0001	0.58 (0.38 to 0.87)	0.0083
Adjusting for patient dropout prior to receiving treatment using the method of inverse probability weighting	0.52 (0.41 to 0.68)	< 0.0001	0.57 (0.38 to 0.84)	0.0048
Removal of relapses with EDSS performed by unblinded raters	0.51 (0.40 to 0.66)	< 0.0001	0.58 (0.38 to 0.87)	0.0084

CI = confidence interval; EDSS = Kurtzke Expanded Disability Status Scale; FA = full analysis; MS = multiple sclerosis; PP = per protocol; SAD = sustained accumulation of disability.
Source: Clinical Study Report[2] p. 1111, 1148, Coles et al. (2012).[3]

Health-Related Quality of Life

TABLE 17: FUNCTIONAL ASSESSMENT OF MULTIPLE SCLEROSIS; FULL ANALYSIS SET

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Overall FAMS score		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
P value	[redacted]	
Mobility		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]
Mean difference	[redacted]	
P value	[redacted]	
Symptoms		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]
Mean difference	[redacted]	
P value	[redacted]	
Emotional well-being		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
P value	[redacted]	
General contentment		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
P value	[redacted]	
Thinking and fatigue		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
P value	[redacted]	
Family/social well-being		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Difference	[redacted]	
P value	[redacted]	

CI = confidence interval; FAMS = Functional Assessment of Multiple Sclerosis.
Note: Mixed model for repeated measures analysis adjusted for geographic region and baseline FAMS score.
Source: Clinical Study Report.[2]

TABLE 18: SHORT FORM (36) HEALTH SURVEY; FULL ANALYSIS SET

	Alemtuzumab 12 mg (N = 426)	Interferon beta-1a (N = 202)
Mental component summary		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
P value	[redacted]	
Physical component summary		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
P value	[redacted]	

CI = confidence interval.
Note: Mixed model for repeated measures analysis adjusted for geographic region and baseline score.
Source: Clinical Study Report.[2]

TABLE 19: EUROQOL 5-DIMENSIONS QUESTIONNAIRE; FULL ANALYSIS SET

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
EQ-5D utility score		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
P value	[redacted]	
EQ-5D VAS score		
Change from baseline at year 2 (95% CI)	[redacted]	[redacted]
Difference	[redacted]	
P value	[redacted]	

EQ-5D = EuroQol 5-Dimensions Questionnaire; CI = confidence interval; VAS = visual analogue scale.
Note: Mixed model for repeated measures analysis adjusted for geographic region and baseline score.
Source: Clinical Study Report.[2]

Magnetic Resonance Imaging Outcomes

TABLE 20: MAGNETIC RESONANCE IMAGING OUTCOMES; FULL ANALYSIS SET

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Per cent change from baseline at year 2 in T2 hyperintense lesion volume — secondary end point		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
P value[a]	[redacted]	
Patients with new or enlarging T2 hyperintense lesions over 2 years (composite of months 12 and 24) — tertiary end point		
N	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
OR (95% CI)[c]	[redacted]	

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
P value [c]		
Patients with Gd-enhancing lesions over 2 years (composite of months 12 and 24) — tertiary end point		
N		
n (%)		
OR (95% CI)[d]		
P value[d]		

CI = confidence interval; Gd = gadolinium; MRI = magnetic resonance imaging; OR = odds ratio; SD = standard deviation.
[a] *P* value from ranked analysis of covariance (ANCOVA) models with covariate adjustment for geographic region and baseline T2 lesion volume; no significant difference between treatment groups, hierarchical chain broken.
[b] MRI activity defined as the occurrence of ≥ 1 new or enlarging T2 lesions and/or ≥ 1 new Gd-enhancing lesions post-baseline.
[c] Odds ratios and *P* values are from logistic regressions with covariate adjustment for baseline T2 lesion volume.
[d] Odds ratios and *P* values are from logistic regressions with covariate adjustment for baseline lesion count.
Source: Clinical Study Report,[2] Coles et al. (2012).[3]

Relapse Requiring Corticosteroids or Hospitalization

TABLE 21: RELAPSE REQUIRING CORTICOSTEROIDS OR HOSPITALIZATIONS; FULL ANALYSIS SET

	Alemtuzumab 12 mg (N = 426)	Interferon Beta-1a (N = 202)
Relapse requiring corticosteroids (tertiary end point)		
Patients requiring corticosteroids due to relapse, n (%)[a]		
Number of relapses requiring corticosteroids/total number of relapses (%)[a]		
ARR (95% CI)[b]		
Rate ratio[c]		
P value[c]		
Relapse requiring hospitalization (sensitivity analysis)		
Patients requiring hospitalization due to relapse, n (%)		
Number of relapses requiring hospitalization/total number of relapses (%)		
ARR (95% CI)[b]		
Rate ratio[c]		
P value[c]		

ARR = annualized relapse rate; CI = confidence interval.
[a] All suspected relapses treated with steroids were included, analysis not restricted to relapse adjudication panel-confirmed relapses.
[b] ARR estimated through negative binomial regression with robust variance estimation and covariate adjustment for geographic region.
[c] Rate ratio and *P* value are from proportional means regression with robust variance estimation and covariate adjustment for geographic region.
Source: Clinical Study Report.[2]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

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

- Kurtzke Expanded Disability Status Scale (EDSS)
- EuroQol 5-Dimensions Questionnaire (EQ-5D)
- Functional Assessment of Multiple Sclerosis (FAMS)
- Multiple Sclerosis Functional Composite (MSFC)
- Short Form (36) Health Survey (SF-36)
- Magnetic Resonance Imaging (MRI) outcomes

Findings

Kurtzke Expanded Disability Status Scale

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.[34] 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 22). 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 2 to 3 points, and 6 to7 points, indicating that patients do not stay equally long at each step of the scale. There are many criticisms of EDSS, including the fact that it has only modest intra-rater reliability, low reproducibility, poor assessment of upper limb and cognitive function, and it lacks linearity.[35-38] 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 ability to walk, and that it requires a subjective evaluation of disability using a parametric scale.

According to the clinical expert consulted for this review, a sustained change of 1.0 in EDSS is clinically relevant.

TABLE 22: SCORING OF EDSS

	Normal Neurological Exam (All Grade 0 in Functional Systems [FS]; 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 FSs (two FSs 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 FSs (three/four FSs 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 FSs grade 2; or two FSs grade 3; or five FSs 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 [FS]; 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 assistances; 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 FSx 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 FSs 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.

EuroQol 5-Dimensions Questionnaire

The EQ-5D is a generic quality of life (QoL) instrument that may be applied to a wide range of health conditions and treatments.[39,40] 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.[39,40] 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:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system.

3. 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 less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health", respectively. Reported clinically important differences (CIDs) for this scale, although not specific for MS patients, have ranged from 0.033 to 0.074.[41] The CIDs were derived from patients with a variety of chronic and acute conditions, including rheumatoid arthritis, osteoarthritis, irritable bowel syndrome, and acute myocardial infarction.[42,43]

Validity

No studies specifically validating EQ-5D in patients with MS were identified. As with any generic health-related QoL 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 4 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 overestimated utility scores compared with a disease-specific measure.[44]

Functional Assessment of Multiple Sclerosis

FAMS is a 59-item health-related QoL scale specific for people diagnosed with MS. It was originally developed and validated in 1996.[45] The first version was formed using a 28-item general cancer QoL scale (Functional Assessment of Cancer Therapy-General, FACT-G) as its core, with the addition of 60 questions specific to MS symptoms generated through an interview process with MS patients, MS health care providers and from the literature, forming an 88-item FAMS, Version 1.[45]

Validation

Validation of FAMS, Version 1 was assessed on a survey cohort of 377 MS patients who received a battery of self-report questionnaires by mail, and a clinical cohort of 56 MS patients who completed a first battery of questionnaires at a clinic, and a second approximately seven days later, at home. The clinical cohort was also assessed with the EDSS and the Scripps Neurological Rating Scale (NRS) questionnaire by the neurologist in clinic. Mean standard deviation EDSS score for the clinical sample was 4.6 (2.2) (range 0 to 8). Patients were diagnosed with relapsing-remitting multiple sclerosis (RRMS) or progressive disease.[45]

Factor analysis revealed six sub-scales in the original 88-item questionnaire.[45] Misfitting items were eliminated via Rasch analysis, resulting in the retention of 44-items, loading onto 6 sub-scales: mobility (seven items), symptoms (seven items), emotional well-being (depression) (seven items), general contentment (seven items), thinking/fatigue (nine items), and family/social well-being (seven items). In its current version (Version 2), the FAMS comprises these 44 items plus an additional 15 items (not scored) that were originally rejected, and then reintroduced into the scale for one of two reasons: to ensure the entire FACT-G was retained within FAMS or based on clinical interest of the neurologist. FACT-G was retained in whole, as it was thought to be useful for comparisons of quality of life across two important chronic illnesses: cancer and MS. The 59-item FAMS has 44 scored items that are measured on a 5-point Likert scale, ranging from 0 (not at all) to 4 (very much). Raw scores of negatively worded items are converted to ensure high scores reflect good quality of life for each sub-scale. Those

scores are then summed to give sub-scale and total FAMS scores. Total scores range from 0 to 176, with higher scores indicating better quality of life.

All six FAMS sub-scales (44 items total) demonstrated very good internal consistency (alpha = 0.82 ± 0.96) and test–retest reliability (r range = 0.85 ± 0.91). Concurrent and construct validity of FAMS was established through concurrent administration of valid measurement tools used in other settings: RAND SF-36, the Multiscale Depression Inventory (MDI), the Hospital Anxiety and Depression Scale (HADS), and a 10-item short form of the Marlowe-Crowne Social Desirability Scale (MCSDS).[45]

Predictable patterns of correlations among FAMS sub-scales and the domains measured in the other questionnaires demonstrated convergent validity. For example, correlations between the FAMS sub-scales measuring the physical aspects of quality of life (i.e., mobility) were highly associated with other QoL questionnaires assessing the physical aspects of quality of life, such as the physical component summary of the SF-36 (r = 0.78 in the survey sample and 0.62 in the clinic sample); and was not associated with other questionnaires assessing non-physical aspects of quality of life, such as the mental component summary of the SF-36 (r = 0.24 in the survey sample and 0.07 in the clinic sample). As expected, correlations with the FAMS sub-scales and a measure of social desirability (M-CSDS) were low (range –0.03 to 0.17), demonstrating divergent validity.

FAMS differentiated between known groups of patients who differ on clinically meaningful aspects of MS: RRMS versus progressive MS, stable for > 18 months versus worsening within the past 18 months, and need for daytime bed rest versus not requiring daytime bed rest (assessed by ECOG PSR), demonstrating criterion related validity. Significant differences between the known groups were found for all FAMS sub-scales, with the exception of the symptom sub-scale. As expected, patients with remitting-relapsing MS, patients with stable disease, and patients who did not require daytime bed rest, had a better quality of life than their comparator groups. An MCID has not been published for FAMS.

Despite being one of the most widely used quality of life scales for patients with MS,[46] it has been criticized for being heavily weighted toward the assessment of the psychosocial consequences of MS, and virtually omitting assessment of visual function, bladder and bowel function, and sexual function, symptoms that have been found in more than 40% of MS patients during field testing.[47] In addition, the demonstrated psychometric properties of FAMS among patients with moderate to severe MS could not be replicated among a cohort of patients with early stage MS or clinically isolated syndrome (CIS).[46] High ceiling effects (exceeding the recommended maximum of 15%) were found on most sub-scales of FAMS among early disease patients (EDSS 0 to 1.5) but not among more severe patients (EDSS > 2). Coupled with a persistent lack of responsiveness to improvement and poor construct validity, this suggests that FAMS is not a valid measure of the quality of life among patients with less severe MS. The authors concluded that modification to FAMS would be required prior to its use as a clinical trial end point in patients with early stage MS or CIS.[46] The MCID has not been established for FAMS.

Multiple Sclerosis Functional Composite

MSFC is a measure of disability developed in 1994 by a task force convened by the US National Multiple Sclerosis Society.[48,49] MSFC assesses different clinical dimensions: arm (9-Hole Peg Test [9HPT] = time to insert and remove nine pegs), leg (Timed 25-Foot Walk Test [T25FW] = time to walk 25 feet), and cognition (Paced Auditory Serial Addition Test [3-Second Version; PASAT3] = 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 standard deviations 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 reference population from the test result and then dividing by the standard deviation of the reference population. For T25FW and 9HPT, a higher test result means the patient worsened from baseline. For PASAT3, 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.[48] Psychometric properties and MCID in MS patients are provided below:

Test–Retest Reliability
Intra-class coefficients of 0.87 to 0.96 have been reported.[49]

Construct Validity
MSFC scores were lower in more disabled patients (–0.4 in primary-progressive multiple sclerosis [PPMS], –0.3 in secondary-progressive multiple sclerosis [SPMS] versus +0.42 in RRMS).[49]

Convergent Validity (Correlation With EDSS)
A study by Ozakbas et al. (N = 38) found a significant correlation between EDSS and MSFC.[35] In looking at individual components, EDSS had the lowest correlation (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 consistent with the observation of poor assessment of upper limb function by EDSS.[35]

MCID
A 20% change in scores on T25FW and 9HPT, and a 0.5 standard deviation change on PASAT3 are considered clinically meaningful; a clinically meaningful value for overall MSFC score has not been determined.[49]

Short Form (36) Health Survey
SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life. SF-36 consists of eight dimensions: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions (GH), and role limitations due to physical and emotional problems. SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS). The PCS and MCS and eight dimensions are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status.[50] Minimal clinically meaningful improvements on the SF-36 have not been established in patients with MS. They have been established in pathologies other than MS, such as systemic lupus erythematosus, rheumatoid arthritis, and osteoarthritis, and are represented by improvements of 5 to 10 points in SF-36 domain scores and 2.5 to 5 points in the PCS and MCS summary scores.[50] It is not clear, however, if MCIDs can transfer across pathologies.[51]

Psychometric properties in MS patients are provided below:

Reliability
Internal consistency reliability was measured in one Dutch study (N = 187).[52] Cronbach's alpha ranged from 0.71 (bodily pain) to 0.93 (physical functioning). In another study (N = 149), Cronbach's alpha ranged from 0.77 to 0.94.[53]

Test–retest correlation coefficients varied from 0.46 to 0.87 in the Dutch study.[52] Coefficients were the lowest for the dimensions of role–physical functioning (r = 0.48), social functioning (r = 0.50), and role–emotional functioning (r = 0.46). The physical functioning (r = 0.87) and vitality (r = 0.71) dimensions obtained the highest scores.[52]

Construct Validity

SF-36 showed good construct validity for PCS and three dimensions: social functioning, physical functioning, role–physical functioning as it could differentiate between different levels of disease severity.[53]

Convergent Validity

(correlation to EDSS): The relation between EDSS and SF-36 scales was examined using regression analyses in one study by Janssens et al. (2003).[54] Unadjusted analyses showed that EDSS was significantly related to all SF-36 physical and mental health scales. After adjustment for anxiety and depression, EDSS was significantly related only to the SF-36 physical functioning, role–physical functioning and bodily pain scales but not SF-36 mental health scales and the general health scale.[54] Another study[55] determined that low scores on the SF-36 mental health scale were correlated with increased (worsened) EDSS scores at one year (r = –0.29, *P* = 0.006). The results were not altered by adjusting for disease activity at baseline.[55]

Magnetic Resonance Imaging Outcomes

MRI techniques play an important role in diagnosis of multiple sclerosis; 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 remained controversial.[56-58]

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-enhancing lesions. These are conventional MRI outcomes that are widely used to monitor treatment effects in clinical trials of MS. Their roles as 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 23. 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 23: SUMMARY OF CORRELATIONS BETWEEN MAGNETIC RESONANCE IMAGING OUTCOMES AND CLINICAL OUTCOMES

	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
Sormani 2013[59]	31 RCTs of all available disease-modifying drugs for RRMS, published from 2008–2012	Number of MRI lesions (new or enlarging T2 lesions; or Gd-enhancing lesions) Annual relapse rate: 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. Coefficient of determination (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[60]	3 RCTs enrolling RRMS patients: • cladribine vs. placebo • fingolimod vs. placebo • fingolimod vs. interferon Follow-up: 12 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 annualized relapse rate 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 groups. 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 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 agents.

	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
Sormani 2010[61]	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[62]	Patients in natural-course studies or were treated with placebo or observed in the pre-treatment phase of controlled clinical trials 77% of patients had RRMS; 23% had secondary progressive MS Follow-up: 6 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.

DIS = disability; EDSS = Kurtzke Expanded Disability Status Scale; Gd = gadolinium; MRI = magnetic resonance imaging; MS = multiple sclerosis; OR = odds ratio; PTE = proportion of treatment effect; R^2 = coefficient of determination; RCT = randomized controlled trial; REL = relapse; RR = relative risk; RRMS = relapsing-remitting multiple sclerosis; vs. = versus.

Conclusion

A summary of the characteristics of five instruments employed in the CARE-MS II study was provided: two measuring disability (with EDSS and MFSC) and three measuring health-related quality of life (including EQ-5D, SF-36, and FAMS). 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 have not been determined in MS patients specifically.
- SF-36 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.
- FAMS was found to be a valid and reliable measure of quality of life among patients with RRMS; however, its validity among patients with less severe MS could not be demonstrated.

There is no MCID information for EDSS, EQ-5D, FAMS, or SF-36 specific to MS. A 20% change in scores on T25FW and 9HPT, and a 0.5 standard deviation change on PASAT3 are considered clinically meaningful in MSFC; however, an MCID for overall MSFC score has not been determined.

Findings from the studies investigating the correlations of MRI outcomes and clinical outcomes suggested that conventional MRI scans may be a tool of 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 EFFICACY AND HARMS FROM EXCLUDED STUDIES

Objective

This supplemental issue will review the additional efficacy and harms data from studies of alemtuzumab 12 mg in patients with relapsing-remitting multiple sclerosis (RRMS) not included in the main review.

Findings

Two clinical studies[31,32] provided additional efficacy and harms data on the use of alemtuzumab in patients with RRMS. Both studies were sponsored by Genzyme and Bayer Schering Pharma.

The design and methodology of the phase 2 (CAMMS223)[26] and phase 3 studies (CAMMS323)[30] were similar and are described in Table 24. Both studies were randomized, open-label, rater-blind trials conducted at sites in Australia, North America, South America, and Europe during 2002-2004[31] and 2007-2009.[32] Both compared alemtuzumab with subcutaneous interferon beta-1a in treatment-naive patients with RRMS. CAMMS223 included alemtuzumab 12 mg and 24 mg groups. Based on the approved dose by Health Canada, only 12 mg dose results are presented in this supplemental issue.

TABLE 24: STUDY DESIGN AND METHODOLOGY

Study	Population	N	Treatment	Duration	Design	Primary Outcomes
CAMMS223 Phase 2	Treatment-naive patients with RRMS	334	Randomized 1:1:1 to 3 cycles[a] of: • SC INFB-1a 44 mcg 3x/week (n = 111) • IV alemtuzumab 12 mg (n = 113) • IV alemtuzumab 24 mg[a] (n = 110)	3 years	Randomized, open-label, rater-blind, active-controlled	Co-primary end points: 1. Time to sustained accumulation of disability[b] 2. Rate of relapse[c]
CAMMS323 Phase 3	Treatment-naive patients with RRMS	581	Randomized 1:2 to 2 cycles of: • SC INFB-1a 44 mcg 3x/week (n = 195) • IV alemtuzumab 12 mg (n = 386)	2 years	Randomized, open-label, rater-blind, active-controlled	Co-primary end points: 1. Time to sustained accumulation of disability[b] 2. Rate of relapse[c]

INFB-1a = interferon beta-1a; IV = intravenous; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous.
[a] Cycles at months 1, 12, and 24, with month 24 cycle requiring confirmation of adequate CD4 counts.
[b] Defined as an increase from baseline of ≥ 1 EDSS point (or ≥ 1.5 points if baseline EDSS score was 0) confirmed over six months.
[c] Defined as new or worsening neurological symptoms attributable to multiple sclerosis, lasting ≥ 48 hours, without pyrexia, after 30 days of clinical stability, with an objective change on neurological examination assessed by a masked rater.
Source: Clinical Study Reports for CAMMS223[26] and CAMMS323.[30]

Adult (> 18 years) patients with early (i.e., ≤ 3 and ≤ 5 years since diagnosis, for CAMMS323 and CAMMS223, respectively) and active RRMS (≥ 2 clinical relapses within the past two years, with the additional criteria of at least one clinical relapse within the past year for CAMMS323), with low (≤ 3) EDSS scores were enrolled.

Exposure and Disposition

Exposure

Randomization in CAMMS223 began in December 2002 and was completed in July 2004. The last patient's final study visit in this three-year study was in September 2007. In September 2005, while the study was ongoing, alemtuzumab was discontinued for the remainder of the study, due to three cases of idiopathic thrombocytopenic purpura (ITP), including one death. Patients randomized to alemtuzumab continued to be followed for efficacy and safety outcomes, but did not receive any further alemtuzumab treatment during the study, and patients on interferon beta-1a continued to receive treatment as per protocol. At the time of suspension, all patients randomized to alemtuzumab 12 mg except two (2%) had received two cycles of treatment (month 0 and month 12), and 24 of 99 eligible patients (24%) had received cycle 3 (month 24)(Table 2). Four (3.7%) alemtuzumab-treated patients and four (3.7%) interferon beta-1a-treated patients received alternative multiple sclerosis (MS) medications during the three-year study, mainly due to discontinuing study drug and beginning another treatment. Follow-up of patients after the three-year study is reported in Appendix 7: Summary of Additional Studies.

In the interferon beta-1a group, 61% of patients were exposed to treatment for at least 30 months.

Disposition

In CAMMS223, a greater percentage of interferon beta-1a-treated patients discontinued the study early (36.9%) compared with alemtuzumab 12 mg-treated patients (14.2%). The principal reason for discontinuation was refusal to receive further treatment (7.1%) for alemtuzumab 12 mg-treated patients, and sustained accumulation of disability (lack of efficacy, 14.4%) and adverse events (11.7%) for interferon beta-1a-treated patients. In total, 81.4% of patients randomized to alemtuzumab 12 mg completed the study, compared with 59.5% of patients randomized to interferon beta-1a.

In CAMMS323, a greater percentage of interferon beta-1a-treated patients discontinued from the study (7.2%) compared with alemtuzumab 12 mg-treated patients (2.3%). The principal reason for discontinuation was withdrawal by patient in both treatment groups (1.0% for alemtuzumab 12 mg-treated patients 2.6% for interferon beta-1a-treated patients). Overall, 95% of alemtuzumab 12 mg and 88.7% of interferon beta-1a-treated patients completed the two-year study.

TABLE 25: EXPOSURE AND DISPOSITION

	CAMMS223[a] Treatment-Naive to 3 Years		CAMMS323 Treatment-Naive to 2 Years	
	ALZ 12 mg (N = 113)	INFB-1a (N = 111)	ALZ 12 mg (N = 386)	INFB-1a (N = 195)
Screened	NR		733	
Randomized	113	111	386	195
Discontinued prior to treatment	5 (4.4)	4 (3.6)	10 (2.5)	8 (4.1)
• Protocol violation	3 (2.6)		-	-
• Adverse event	-		1 (0.2)	-
• Withdrew consent	-	1 (0.9)	8 (2.0)	7 (3.5)
• Other	2 (1.7)	3 (2.7)	1 (0.2)	1 (0.5)
Treated	108 (95.6)	107 (96.4)	376 (97.4)	187 (95.9)
Discontinued before end of study	16 (14.2)	41 (36.9)	9 (2.3)	14 (7.2)
Patient refused further treatment	8 (7.1)	4 (3.6)	-	-
Withdrawal by patient	-	-	4 (1.0)	5 (2.6)
Adverse event	3 (2.7)	13 (11.7)	-	5 (2.6)

	CAMMS223[a] Treatment-Naive to 3 Years		CAMMS323 Treatment-Naive to 2 Years	
	ALZ 12 mg (N = 113)	INFB-1a (N = 111)	ALZ 12 mg (N = 386)	INFB-1a (N = 195)
Lack of efficacy	2 (1.8)	16 (14.4)	-	2 (1.0)
MD decision	-	3 (2.7)	2 (0.5)	1 (0.5)
Pregnancy	-	-	-	1 (0.5)
Death	1 (0.9)[b]	-	1 (0.3)[c]	-
Loss to follow-up	2 (1.8)	-	1 (0.3)	-
Protocol violation	-	2 (1.8)	-	-
Other	-	3 (2.7)	1 (0.3)	1 (0.5)
Completed study	92 (81.4)	66 (59.5)	367 (95)	173 (88.7)
Exposure to study drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

ALZ = alemtuzumab; INFB-1a = interferon beta-1a; ITP = idiopathic thrombocytopenic purpura; MD = medical doctor; NR = not rated.

[a] Alemtuzumab was discontinued temporarily in September 2005 based on three cases of ITP and one death; the administration of alemtuzumab 12 mg was reinitiated in 2008, via Amendment 8; however, the 24 mg alemtuzumab group was discontinued and all patients were reinitiated at the 12 mg dose.

[b] Cardiovascular disease.

[c] Motor vehicle accident.

Source: Clinical Study Reports, CAMMS223[26] and CAMMS323.[30]

Efficacy

Annualized Relapse Rate

In CAMMS223, the estimated adjusted annualized relapse rate (ARR) through three years was statistically significantly lower in the alemtuzumab group (0.12 [95% confidence interval (CI), 0.091 to 0.171]) compared with the interferon beta-1a group (0.37 [95% CI, 0.30 to 0.45]); rate ratio 0.33 (95% CI, 0.20 to 0.55).

The ARR was also analyzed separately for years 1, 2, and 3, and was statistically significantly lower in the alemtuzumab 12 mg group compared with the interferon beta-1a group for all years. The rate ratio of ARR of alemtuzumab compared with interferon beta-1a was 0.36 (0.19, 0.69) for year 1, 0.30 (0.17, 0.55) for year 2, and 0.33 (0.20, 0.55) for year 3.

In CAMMS323, the estimated adjusted ARR through two years was statistically significantly lower in the alemtuzumab group (0.18 [0.13, 0.23]) compared with the interferon beta-1a group (0.39 [0.29, 0.53]); rate ratio 0.45 (0.32, 0.63).

The ARR was also analyzed separately for year 1 and year 2 and was statistically significantly lower in the alemtuzumab group compared with the interferon beta-1a group for year 1 (53.1% reduction, $P < 0.0001$) and year 2 (57.4% reduction, $P = 0.0002$).

Sustained Accumulation of Disability

Time to six-month sustained accumulation of disability (SAD) was statistically significantly less for interferon beta-1a, hazard ratio 0.24 (95% CI, 0.11 to 0.55) compared with alemtuzumab 12 mg in CAMMS223; the Kaplan–Meier-estimated percentage of patients experiencing SAD over three years was 8% in the 12 mg group and 27% in the interferon beta-1a group.

In CAMMS323, there was no statistically significant difference between the treatment groups in the rate of SAD (*P* = 0.2173). The Kaplan–Meier-estimated percentage of patients experiencing SAD over two years was 8.0% in the alemtuzumab group and 11.1% in the interferon beta-1a group.

TABLE 26: KEY EFFICACY OUTCOMES; FULL ANALYSIS SET

	CAMMS223 Treatment-Naive to 3 Years		CAMMS323 Treatment-Naive to 2 Years	
	ALZ 12 mg (N = 112)	INFB-1a (N = 111)	ALZ 12 mg (N = 376)	INFB-1a (N = 187)
Annualized Relapse Rate				
ARR — year 1 (95% CI)	[redacted]		NR	NR
Rate ratio (95% CI)				
P value				
ARR — year 2 (95% CI)	[redacted]		NR	NR
Rate ratio (95% CI)				
P value				
ARR — year 3 (95% CI)	[redacted]		NA	NA
Rate ratio (95% CI)				
P value				
ARR — years 0 to 2[a] or 3[b] (95% CI)	[redacted]		0.18 (0.13 to 0.23)	0.39 (0.29 to 0.53)
Rate ratio (95% CI)			0.45 (0.32 to 0.63)	
P value			< 0.0001	
Sustained accumulation of disability (6 months)				
Kaplan–Meier estimate, % (95% CI)	[redacted]		8.00 (5.66 to 11.24)	11.12 (7.32 to 16.71)
Hazard ratio (95% CI)			0.70 (0.40 to 1.23)	
P value			0.2173	

ALZ = alemtuzumab; ARR = annualized response rate; CI = confidence interval; INFB-1a = interferon beta-1a; NR = not rated.
[a] CAMMS323.
[b] CAMMS223.
Note: The full analysis set was comprised of all patients who were randomized and received at least one dose of study drug.
Source: Clinical Study Reports, CAMMS223[26] and CAMMS323.[30]

Harms

Safety results for CAMMS223 through three years of follow-up reflect safety with two cycles of alemtuzumab 12 mg in 102 patients (90.2%) and three cycles of alemtuzumab 12 mg in 24 patients (21%), and at least 30 months of exposure to interferon beta-1a in 67 (63%) patients in that treatment group.

Adverse Events

All patients (100%) in the alemtuzumab 12 mg group and interferon beta-1a groups experienced ≥ 1 adverse event in CAMMS223, and 96% and 92% of alemtuzumab 12 mg and interferon beta-1a patients in CAMMS323, respectively, experienced ≥ 1 adverse event.

In both studies, the most commonly reported adverse events with alemtuzumab 12 mg included rash (46.3%, 72.2%), headache (50.5%, 62.0%), and pyrexia (37.0%, 40.7%).

Serious Adverse Events

The incidence of serious adverse events was similar between the two treatment groups in CAMMS223. A total of 22.2% patients in the alemtuzumab 12 mg group experienced a serious adverse event compared with 23.4% of patients in the interferon beta-1a group in CAMMS223. In CAMMS323, 18.4% of alemtuzumab 12 mg-treated patients and 14.4% of interferon beta-1a-treated patients experienced ≥ 1 serious adverse event during the study. The only serious adverse event reported in more than 1% of patients in the alemtuzumab group was MS relapse in CAMMS223 (five patients, 4.6%) and in CAMMS323 (19 patients, 5.1%).

Withdrawals Due to Adverse Events

In the CAMMS223 study, 3.7% of patients in the alemtuzumab 12 mg group discontinued study treatment due to an adverse event compared with 12.1% of patients in the interferon beta-1a group. In CAMMS323, 1.3% of alemtuzumab 12 mg-treated patients versus 5.9% ofinterferon beta-1a-treated patients discontinued study treatment due to an adverse event. There were no adverse events that occurred in >1% of alemtuzumab-treated patients that led to discontinuation of treatment, in either study.

No patients in the alemtuzumab 12 mg group and five patients (2.7%) in the interferon beta-1a group, in CAMMS323, discontinued participation in the study due to an adverse event.

Mortality

One death was reported in the alemtuzumab 12 mg treatment group in both studies. In CAMMS223, the patient died of cardiovascular disease, and in CAMMS323, the patient died due to a motor vehicle accident. There were no deaths in the interferon beta-1a treatment group in either study.

Notable Harms

Thyroid adverse events: Thyroid adverse events were reported by 25.0% of patients treated with alemtuzumab 12 mg and 2 (1.9%) of patients treated with interferon beta-1a in CAMMS223. The most common thyroid adverse events in CAMMS223 were hyperthyroidism (8.3%) and Basedow's disease (8.3%). Only one thyroid adverse event (autoimmune thyroiditis) in the alemtuzumab 12 mg group was reported as serious. The incidence of thyroid disorders increased each year from year 1 to year 3, peaking at 14% for the alemtuzumab 12 mg group in year 3.

In CAMMS323, 18.1% of patients treated with alemtuzumab 12 mg reported a thyroid adverse event, versus 6.4% of patients treated with interferon 1-beta. The most frequently reported thyroid adverse events in the alemtuzumab group were hyperthyroidism (5.1%) and hypothyroidism (4.8%). Four of the thyroid events were considered serious, all in the alemtuzumab 12 mg treatment group. The annual incidence of thyroid adverse events was 6.9% in year 1 and 13.8% in year 2 in the alemtuzumab group, compared with 3.7% in year 1 and 2.8% in year 2 in the interferon beta-1a group.

Idiopathic thrombocytopenic purpura: In CAMMS223, one patient in each treatment group (0.9% each) met the protocol-defined criteria for ITP. In CAMMS323, three (0.8%) alemtuzumab 12 mg patients and one (0.5%) interferon beta-1a patient, respectively, met the protocol-defined criteria for ITP.

Infusion-associated reactions: The majority of alemtuzumab 12 mg-treated patients (97.2% and 89.9% in CAMMS223 and CAMMS323, respectively) experienced at least one adverse event associated with alemtuzumab 12 mg/day infusions. Two patients (1.8%) in the alemtuzumab 12 mg group in CAMMS223 and 12 (3.2%) in CAMMS323 reported serious infusion-associated reactions that included pyrexia, headache, pruritis, rash, and nausea.

Infections: A greater proportion of patients experienced an infection with alemtuzumab 12 mg than with interferon beta-1a (66.0% versus 45.0%) in CAMMS223 and in CAMMS323 (67.3% versus 45.5%). A greater proportion of patients experienced a serious infection with alemtuzumab 12 mg than with interferon beta-1a (3.7% versus 0.9% in CAMMS223 and 1.9% versus 1.1% in CAMMS323).

TABLE 27: HARMS; SAFETY SET

	CAMMS223		CAMMS323	
	ALZ 12 mg (N = 108) n (%)	INFB-1a (N = 107) n (%)	ALZ 12 mg (N = 376) n (%)	INFB-1a (N = 187) n (%)
AEs				
Subjects with > 0 AEs, N (%)	108 (100.0)	107 (100.0)	361 (96.0)	172 (92.0)
Most common AEs (≥ 10% in either treatment group, by study)				
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Chest discomfort	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Flushing	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
MS relapse	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Paresthesia	[redacted]	[redacted]	[redacted]	[redacted]
Pruritis	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]
UTI	[redacted]	[redacted]	[redacted]	[redacted]

	CAMMS223		CAMMS323	
	ALZ 12 mg (N = 108) n (%)	INFB-1a (N = 107) n (%)	ALZ 12 mg (N = 376) n (%)	INFB-1a (N = 187) n (%)
Uticaria	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
SAEs				
Subjects with > 1 SAEs, N (%)	24 (22.2)	25 (23.4)	69 (18.4)	27 (14.4)
Most common SAEs (> 1% in alemtuzumab 12 mg treatment groups)				
MS relapse	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs				
AEs leading to treatment withdrawal, N (%)	4 (3.7)	13 (12.1)	5 (1.3)	11 (5.9)
AEs leading to study discontinuation, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths				
Number of deaths, N (%)	1 (0.9)	0 (0)	1 (0.3)	0 (0.0)
Reasons				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms				
Thyroid AEs	27 (25.0)	2 (1.9)	68 (18.1)	12 (6.4)
Serious thyroid AEs	1 (0.9)	0 (0.0)	4 (1.1)	0 (0.0)
Idiopathic thrombocytopenic purpura[a]	1 (0.9) [b]	1 (0.9) [c]	3 (0.8) [b]	1 (0.5) [c]
Serious idiopathic thrombocytopenic purpura[a]	1 (0.9)	0 (0.0)	3 (0.8)	0 (0)
Infusion-associated reactions[d]	105 (97.2)	NA	338 (89.9)	NA
Serious infusion-associated reactions[d]	2 (1.8)	NA	12 (3.2)	NA
Infections	142 (66.0)	48 (45.0)	253 (67.3)	85 (45.5)
Serious infections	4 (3.7)	1 (0.9)	7 (1.9)	2 (1.1)

AE = adverse event; ALZ = alemtuzumab; INFB-1a = interferon beta-1a; MS = multiple sclerosis; NA = not applicable; SAE = serious adverse event; UTI = urinary tract infection; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

[a] Idiopathic thrombocytopenic purpura defined as evidence of normal Hgb and WBC, in the absence of splenomegaly; normal peripheral smear except for a decrease in platelets without clumping; and either of the following: a confirmed platelet count ≥ 50,000/µL < 100,000/µL confirmed on ≥ 2 consecutive occasions over one month, or a confirmed platelet count < 50,000/µL without clumping documented ≥ 2 consecutive occasions over any period of time.

[b] Autoimmune thrombocytopenia.

[c] Idiopathic thrombocytopenic purpura.

[d] Infusion-associated reactions were defined post hoc as any AE reported within the two days following an alemtuzumab infusion in CAMMS223, and as any AEs that occurred during or within 24 hours following an alemtuzumab infusion, regardless of relationship to treatment in CAMMS323.

Source: Clinical Study Reports, CAMMS223[26] and CAMMS323.[30]

Summary

Two studies, CAMMS223[26] and CAMMS323,[30] provide evidence for efficacy and harms of alemtuzumab in treatment-naive patients with low levels of disability but active RRMS over two and three years, respectively.

The results of the above studies suggest that, compared with interferon beta-1a, alemtuzumab 12 mg results in a statistically significantly lower ARR over the course of two or three years of treatment in the above patient population. However, the open-label design and differential study withdrawal may have biased these estimates of efficacy. Inconsistent results between the studies on the time to six-month SAD limits the ability to draw conclusions on this end point.

The most common adverse events associated with alemtuzumab 12 mg included headache, rash, and pyrexia. Safety concerns associated with alemtuzumab include immune thrombocytopenia, thyroid disorders, infection, and infusion-associated reactions. No new safety concerns were identified in treatment-naive patients with RRMS.

APPENDIX 7: SUMMARY OF ADDITIONAL STUDIES

Objective

This supplemental issue reviews the long-term safety and efficacy data from alemtuzumab extension studies in patients with relapsing-remitting multiple sclerosis (RRMS). Findings from a long-term observational study are also presented.

Findings

Extension Studies

Two manufacturer-sponsored long-term extension studies of alemtuzumab in patients with RRMS were identified.

The CAMMS03409 study[33] is an open-label, rater-blind, non-randomized extension study to evaluate the long-term safety and efficacy of intravenous (IV) alemtuzumab 12 mg/day. It was open to patients who had participated in one of three manufacturer-sponsored studies: CAMMS223,[26] CAMMS323[30] (CARE-MS I), or CAMMS324[2] (CARE-MS II) and began in January 2010.

The second was the extension data of CAMMS223 patients prior to the opening of the CAMMS03409 study. The three-year CAMMS223 study ended in 2007, approximately two years before the CAMMS03409 extension study was open, in January 2010. During this period, the collection of follow-up safety and efficacy data for CAMMS223 patients was continued. This extension data, which is reported from baseline to month 60 (efficacy) or month 72 (safety), are available in the clinical study report of the original CAMMS223 study, and have been published in manuscript form.[31]

To date, there is no published manuscript or clinical study report for the CAMMS03409 study. Limited data are available in abstract and poster form for patients from the CAMMS323[30] (CARE-MS I) and CAMMS324[2] (CARE-MS II) studies who participated in CAMMS03409. Data on patients from CAMMS223 who were enrolled in CAMMS03409 are not available.

This supplemental issue reports the results of the former alemtuzumab 12 mg group and former interferon beta-1a group, from the extended follow-up period of CAMMS223 (prior to the opening of CAMMS03409), and limited data on patients from CAMMS323[30] (CARE-MS I) and CAMMS324[2] (CARE-MS II) studies who participated in CAMMS03409.

Study design for the three studies and the extension study are outlined in Table 28.

TABLE 28: CAMMS STUDIES

Study	Population	Phase	N	Intervention	Duration	Design
CAMMS223[26]	Treatment-naive patients with RRMS	2	334	INFB-1a 44 mcg 3x/week; alemtuzumab 12 mg/day and 24 mg/day IV for 2 to 3 cycles	3 years (+ extended follow-up, months 36 to up to month 72)	Randomized, open-label, rater-blind
CAMMS323[30] (CARE-MS I)	Treatment-naive patients with RRMS	3	581	INFB-1a 44 mcg 3x/week; alemtuzumab 12 mg/day IV for 2 cycles	2 years	Randomized, open-label, rater-blind

Study	Population	Phase	N	Intervention	Duration	Design
CAMMS324[2] (CARE-MS II)	Treatment-experienced with RRMS; relapsed while on prior treatment[a]	3	840	INFB-1a 44 mcg 3x/week; alemtuzumab 12 mg/day and 24 mg/day IV for 2 cycles	2 years	Randomized, rater- and dose-blind
CAMMS03409[33]	Eligible patients who completed CAMMS223, CAMMS323, CAMMS324	NA	1,320	12 mg/day alemtuzumab IV daily for 3 days as needed	Ongoing	Open-label extension study

INFB-1a = interferon beta-1a; IV = intravenous; NA = not applicable; RRMS = relapsing-remitting multiple sclerosis.
[a] Interferon (interferon beta) or glatiramer acetate.

CAMMS223 Extension Data

The CAMMS223 study underwent numerous protocol changes due to the suspension of alemtuzumab. Patients were required to re-consent for each of the changes. For clarification purposes, the main changes and dates are as follows:

- Original three-year CAMMS223 study ran from December 2002 to July 2004.
- Alemtuzumab dosing suspension was in place between September 16, 2005 and April 7, 2008.
- Amendment 6 (August 2006): during the dosing suspension, the follow-up phase of CAMMS223 was extended for two years to collect additional efficacy and safety data, and to implement a risk-minimization program to detect idiopathic thrombocytopenic purpura (ITP) for alemtuzumab-treated patients.
- Amendment 8 (April 7, 2008): issued after lifting of dose suspension in 2008; alemtuzumab patients were invited to participate in the re-treatment component of the study; consenting patients were re-randomized on a 1:2 ratio to a "fixed" (annual) re-treatment group (maximum two annual cycles of alemtuzumab [12 mg/day]) or an "as-needed" re-treatment group (up to two, three-day cycles of alemtuzumab (12 mg/day). As needed criteria were as follows:
- Had, within the previous year, experienced at least one protocol-defined relapse
- Had, within the previous year or since their last on-study magnetic resonance imaging (MRI), accumulated at least two unique lesions on brain or spinal cord MRIs comprised of either gadolinium-enhancing lesion(s) or new/enlarging MRI-T2 lesion(s).

  Patients who declined re-treatment or did not qualify for re-treatment were permitted alternative disease-modifying therapies (DMTs) at their own expense, and were encouraged to remain on study for follow-up. Interferon beta-1a-treated patients were given the option of continuing with interferon beta-1a during this extension at their own expense or receiving alternative DMTs at their own expense. Alemtuzumab re-treatment was not an option for interferon beta-1a-treated patients at any time.
- Amendment 10 (March 18, 2009): patients invited to re-consent, disregarding the group they were re-randomized to through Amendment 8, and were permitted to choose the re-treatment regimen: fixed annual re-treatment of two annual three-day cycles of alemtuzumab (12 mg/day) or an "as-needed" re-treatment of up to two, three-day cycles of alemtuzumab (12 mg/day), using the same re-treatment criteria as in Amendment 8.
- Patients could have continued to be followed under Amendment 6, Amendment 8, or Amendment 10; patients who did not consent under Amendment 6 could have consented under Amendment 8 or 10. If a patient consented to participate in the study under an amendment, the patient was considered withdrawn from participation under an earlier amendment.
- Patients continued to be followed until January 2010 when CAMMS03409 was opened.

Patient Disposition

Follow-up data of five years (two years of extension) for patients from CAMMS223[63] and three years (one-year extension) for patients from CAMMS323, and four years (two-year extension) for patients from CAMMS324[64] are reported.

CAMMS223 Extension Data (Table 29)

A total of [redacted] patients originally randomized to alemtuzumab 12 mg, and [redacted] patients originally randomized to interferon beta-1a, consented to follow-up under Amendment 6, extending their follow-up of efficacy and safety data for two additional years.

[redacted]

Among patients who consented under Amendment 8, [redacted] were randomized and received re-treatment. Among patients who consented under Amendment 10, [redacted] were treated.

During the extension period of CAMMS223, 27 patients received re-treatment cycles under Amendments 8 and/or 10: two (1.7%) patients received cycle 2, 21 (18.5%) received cycle 3, and four (3.5%) received cycle 4.

A total of 17 (13.8%) alemtuzumab 12 mg-treated patients and 21 (18.9%) interferon beta-1a-treated patients received an alternate multiple sclerosis (MS) medication during the extension.

TABLE 29: EXPOSURE AND DISPOSITION DURING EXTENSION OF CAMMS223, BASED ON RANDOMIZED PATIENTS, MONTHS 36 TO 60

	CAMMS223[a] Treatment-Naive, 36 to 60 Months	
	Former ALZ 12 mg-Treated Patients (N = 113)	Former INFB-1a-Treated Patients (N = 111)
Randomized in original study	[redacted]	[redacted]
Completed original study	[redacted]	[redacted]
Entered extension		
Amendment 6: • Consented n (%) • Completed n (%)	[redacted]	[redacted]
Amendment 8: • Consented, n (%) • Randomized, n (%) • Treated, n (%) • Discontinued, n (%)	[redacted]	[redacted]
Amendment 10: • Consented, n (%) • Treated, n (%) • Discontinued, n (%)	[redacted]	[redacted]
Amendment 8: • Randomized for re-treatment • Received re-treatment[a]	[redacted]	[redacted]

	CAMMS223[a] Treatment-Naive, 36 to 60 Months	
	Former ALZ 12 mg-Treated Patients (N = 113)	Former INFB-1a-Treated Patients (N = 111)
Amendment 10: • Elected for re-treatment • Received re-treatment[a]	[redacted]	[redacted]
Alemtuzumab re-treatment during extension, n (%)	[redacted]	[redacted]
Received other DMT during extension, n (%)	[redacted]	[redacted]

ALZ = alemtuzumab; DMT = disease-modifying therapy; INFB-1a = interferon beta-1a; NR = not reported.
[a] Includes "as-needed" and fixed re-treatments.
[b]†Given 44 to 58 months after the last/prior infusion.

CAMMS03409 Data

During the extension study CAMMS03409, patients previously randomized to interferon beta-1a in the core studies received two annual cycles of IV alemtuzumab (first cycle: 12 mg/day for five days; second cycle: 12 mg/day for three days) and may have received a third cycle (12 mg/day for three days) as needed. Patients previously randomized to alemtuzumab could be re-treated upon evidence of resumed disease activity, defined as ≥ 1 protocol-defined relapse or ≥ 2 new or enlarging brain or spinal lesions on MRI.

All re-treatment cycles consisted of 12 mg/day alemtuzumab IV infused once daily for three days. Patients were also permitted to receive treatment with DMTs during the extension study, although only a small proportion of patients did (2% and 3% of alemtuzumab-treated patients in CARE-MS I and CARE-MS II, respectively).

During CAMMS03409, re-treatment rates were low for patients originally randomized to alemtuzumab 12 mg groups (18% to 20%) (Table 30).

TABLE 30: EXPOSURE AND DISPOSITION, CAMMS03409

	CAMMS323[65] CARE-MS I		CAMMS324[64,65] CARE-MS II	
	ALZ 12 mg	INFB-1a	ALZ 12 mg	INFB-1a
Randomized in original study	[redacted]	[redacted]	[redacted]	[redacted]
Treated in original study	[redacted]	[redacted]	[redacted]	[redacted]
Completed original study	[redacted]	[redacted]	[redacted]	[redacted]
Entered extension	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued extension AE, n (%) Death, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Re-treatment in year 3 in CARE-MS I, or in year 4 in CARE-MS II, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; ALZ = alemtuzumab; INFB-1a = interferon beta-1a; NR = not reported.
[a] 18 of 435 patients who received alemtuzumab have withdrawn from treatment due to AEs.
[b] Six patients withdrew treatment of alemtuzumab.
Source: Lycke,[66] Hartung.[64]

Efficacy

CAMMS223

Efficacy data for CAMMS223 are reported for the period from randomization to month 60 (Table 31). It reflects 102 patients (90.2%) who received two cycles and 24 patients (21%) who received three cycles of alemtuzumab 12 mg during the original three-year time frame, and 27 patients (23.9%) who received re-treatment cycles during the extension phase: two patients (1.7%) who received cycle 2, 21 patients (18.5%) who received cycle 3, and four patients (3.5%) who received cycle 4. Re-treatment cycles were received approximately four years after their last/prior infusion.

CAMMS03409

Efficacy data in CAMMS323 are available only for the patients originally randomized to alemtuzumab. In CAMMS324, efficacy data are available for the patients originally randomized to alemtuzumab as well as interferon beta-1a.

Annualized Relapse Rate

In CAMMS223, the annualized relapse rate (ARR) was analyzed for year 4 and year 5 separately, and was significantly lower in the alemtuzumab 12 mg group compared with the interferon beta-1a group for both years. The rate ratio of ARR of alemtuzumab compared with interferon beta-1a was 0.33 (0.20 to 0.56) for year 4, and 0.34 (0.20–0.57) for year 5.

ARR in the extension year of the two phase 3 CARE studies did not differ from their core studies for patients originally randomized to alemtuzumab therapy. In CAMMS324, for patients who received alemtuzumab in the core study, the ARRs during year 3 (0.22) and year 4 (0.23) were similar to that observed during the core study (0.26); for patients who received prior interferon, the ARRs decreased after switching from interferon to alemtuzumab, 0.52 versus 0.15 (Table 31).

Disability

Time to Six-Month Sustained Accumulation of Disability: The percentage of patients who were six-month sustained accumulation of disability (SAD)-free through to five years was 84% of former alemtuzumab 12 mg patients and 64% of former interferon beta-1a patients in the extension study of CAMMS223. In the CARE studies, patients originally randomized to alemtuzumab 12 mg were also likely to remain six-month SAD free: 88% in CAMMS323 and 76% in CAMMS324, respectively. For patients in the former interferon group in CAMMS324, the proportion of patients six-month SAD-free was 89% two years after switching to alemtuzumab, compared with 79% (or 21% experiencing six-month SAD) during the two years on interferon in the core study.

Kurtzke Expanded Disability Status Scale: Twenty-six per cent of former alemtuzumab 12 mg group patients and 16.7% of former interferon beta-1a group patients reported improvement in Kurtzke Expanded Disability Status Scale (EDSS) from baseline to month 60 in CAMMS223 (Table 31).

Forty per cent of CAMMS323 patients maintained improved EDSS in year 3. In CAMMS324, 67% and 69.2% of patients reported improved or stable EDSS scores in the extension phase, respectively (Table 31).

MRI Outcomes

In CAMMS324, MRI scans were performed at baseline and at year 1, 2, and 3. The results were centrally analyzed by experts blinded to the treatment allocation. The results in year 3 are reported for the former alemtuzumab-treated patients in a poster.[64] At year 3, the mean T2 hyperintense lesion volume remained below baseline (9.7 cm^3 at year 3 versus 10.0 cm^3 at baseline). There was no statistically

significant change at year 3 compared with year 2 (9.5 cm^3). In addition, compared with year 2, there were no statistically significant differences in the proportion of patients with new or enlarging T2 hyperintense lesions (year 3: 31.0%, 95% CI, 26.3 to 35.8; year 2: 23.7%, 95% CI, 19.6 to 27.8), and the proportion of patients with gadolinium (Gd)-enhancing lesions (year 3: 13.5%, 95% CI, 10.0 to 17.0; year 2: 8.7%, 95% CI, 6.0 to 11.5).

TABLE 31: EFFICACY MEASURES DURING THE EXTENSION STUDY

Efficacy Measures	CAMMS223 Baseline – 60[63]		CAMMS323 CARE-MS I Year 3[65]	CAMMS324 CARE-MS II Year 3[64,65]	
	Former ALZ 12 mg-Treated Patients (N = 112)	Former INFB-1a-Treated Patients (N = 11)	Former ALZ 12 mg-Treated Patients (N = 349)	Former ALZ 12 mg-Treated Patients (N = 393)	Former INFB-1a-Treated Patients (N = 146)
ARR year 3 (95% CI)	[redacted]				
Rate ratio (95% CI)					
P value					
ARR year 4 (95% CI)	[redacted]				
Rate ratio (95% CI)					
P value					
ARR year 5 (95% CI)	[redacted]				
Rate ratio (95% CI)					
P value					
6-month SAD-free, % (95% CI)[a]	[redacted]				
Kaplan–Meier estimate, % (95% CI)	[redacted]				
Hazard ratio (95% CI)					
P value					
Change in EDSS, n (%) Improved Stable Worsened	[redacted]				

ALZ = alemtuzumab; ARR = annualized relapse rate; CI = confidence interval; EDSS = Kurtzke Expanded Disability Status Scale; INFB-1a = interferon beta-1a; NA = not applicable; NR = not reported; SAD = sustained accumulation of disability.

[a] In CAMMS223, sustained accumulation of disability (SAD) was defined as a ≥ 1.0 point increase in EDSS score if the baseline EDSS score was ≥ 0 (or a ≥ 1.5 point increase if the baseline EDSS score was 0) sustained for a six-month period. In CARE-MS II, disability during the extension was assessed by EDSS change, either remained stable or improved from baseline.

Safety

Safety data for the extension study of CAMMS223 are reported as follows:

Phase 2 study (CAMMS223):

- Safety data are summarized using data from baseline of core study to complete follow-up (ending January 2010) for patients randomized to alemtuzumab 12 mg and interferon beta-1a (baseline to month 72).
- Safety data of alemtuzumab 12 mg reflect 102 patients (90.2%) who received two cycles and 24 patients (21%) who received three cycles of alemtuzumab 12 mg during the original three-year time frame; and 27 patients (23.9%)who received re-treatment cycles during the extension phase, approximately four years after their last/prior infusion.
- Safety data for interferon beta-1a patients reflect 67 patients (63%) who received treatment for at least 30 months of treatment.

CAMMS03409 — data from phase 3 studies (CARE-MS I; CARE-MS II):[64,65]

- two-year extension data (years 3 and 4) in CARE-MS II
- pooled analysis of year 3 data from former 12 mg alemtuzumab groups from CARE-MS I and II.

In CAMMS223, the safety profile from baseline to month 72 is not dissimilar to the safety profile from baseline to month 36 of the original study.

In CARE-MS II (CAMMS324), 18 patients who were originally randomized to alemtuzumab 12 mg (4.1% of the 435 patients) withdrew from treatment due to adverse events at the end of year 4. The incidence of any adverse events decreased during year 3 and year 4 compared with that in the core study (results were reported graphically in the poster). Six (4.2%) of the 143 former interferon-treated patients withdrew the alemtuzumab therapy in the extension study. Most adverse events were mild to moderate in severity in both groups.

In the pooled alemtuzumab 12 mg groups in the CARE studies during year 3, the incidence of adverse events dropped to 79%, from 97% in the core studies (years 0 to 2) (Table 32). The most common adverse events during year 3 were nasopharygitis (13.3%), urinary tract infection (12%), and hyperthyroidism (11.8%), all having a lower incidence in comparison with years 0 to 2. Only hyperthyroidism had an increased incidence in the extension study (year 3) compared with the core studies (years 0 to 2) (among adverse events occurring in ≥ 5.0% of patients during year 3) (not shown).

Serious adverse events, from baseline to month 72 in CAMMS223, were reported in 27.8% and 27.1% of former alemtuzumab and interferon beta-1a patients, respectively (Table 32). This compares with 22.2% and 23.4% reported in the respective treatment groups from baseline to month 36. One additional death occurred during the extended follow-up in a formerly treated interferon beta-1a group.

Serious adverse events were not separately reported in the extension study of CAMMS324. In the pooled CARE studies, they were reported less frequently in year 3 versus years 0 to 2 (9% versus 19%, respectively) (Table 32). The most frequently reported serious adverse events in the pooled CARE studies were hyperthyroidism (1.9%) and ITP, herpes zoster, headache, sepsis, thyroid cancer, and mental status changes (all 0.3%).

Adverse Events

TABLE 32: INCIDENCE OF SAFETY EVENTS DURING THE EXTENSION STUDY

Adverse Events, n (%)	CAMMS223 Baseline — Month 72[63]		CAMMS324[64]		Pooled CARE-MS I & II ALZ 12 mg[65]	
	Former ALZ 12 mg-Treated Patients (N = 108)	Former INFB-1a-Treated Patients (N = 107)	Former ALZ 12 mg-Treated Patients (N = 393)	Former INFB-1a-Treated Patients (N = 143)	Core Study ALZ 12 mg-Treated Patients Year 0 to2 (N = 811)	Extension Study Former ALZ 12 mg-Treated Patients Year 3 (N = 772[a])
Patients reporting ≥ 1 AE	108 (100)	107 (100)	Data reported in graph	Data reported in graph	[redacted]	[redacted]
Patients reporting ≥ 1 SAE	30 (27.8)	29 (27.1)	NR	NR	[redacted]	[redacted]
Deaths	1 (0.9)	1 (0.9)	0	0	[redacted]	[redacted]
AEs leading to withdrawal	5 (4.6)	13 (12.1)	18 (4.1% of 435 over 4 years)	6 (4.2%) withdrew ALZ	[redacted]	[redacted]

AE = adverse event; ALZ = alemtuzumab; INFB-1a = interferon beta-1a; NR = not reported; SAE = serious adverse event.
[a] Includes 742 prior alemtuzumab 12 mg patients plus 30 patients who did not enter the extension study but were evaluated for AEs.

Adverse Events of Interest: Infusion-Associated Reactions

In CAMMS223, 98% of alemtuzumab treated patients experienced infusion-associated reactions (IARs) between baseline and month 72, 4% of which were serious.

Data of IARs in the extension study of CAMMS324 were graphically reported in a poster.[64] In the pooled alemtuzumab 12 mg groups in the CARE studies, the incidence of IARs decreased in year 3 (62.8%) compared with years 1 to 2 (76%); most were mild to moderate in severity and did not lead to premature discontinuation.

Infections

In CAMMS324, infection rates during years 3 and 4 were reduced to 50% in each year in former alemtuzumab-treated patients, compared with the core study (76.8%). Infection rates in former interferon-treated patients changed from 66.3% in the core study to 72.7% after switching to alemtuzumab in the extension study.

The proportion of patients with infections decreased over time from the last alemtuzumab treatment, with lower incidences reported in the pooled CARE extension study (48%) versus the core studies (73%).

In the pooled analysis of the CARE studies, the most common infections in year 3 were nasopharyngitis (13.3%), urinary tract (12.0%), upper respiratory tract (8.2%), and sinusitis (5.1%)(not shown). Serious infections were not common (< 2% each year).

Autoimmune Diseases

In CAMMS223, thyroid disease continued to be the most frequently reported autoimmune disease reported from baseline to month 72, occurring in 36 (33.3%) former alemtuzumab 12 mg patients and four (3.7%) interferon beta-1a patients. This comprises nine new cases reported after month 36 for former alemtuzumab 12 mg patients and two new cases in former interferon beta-1a patients.

In CAMMS324, among former alemtuzumab-treated patients, the accumulative incidence of thyroid disorders over four years was 34.7% and peaked in year 3 (data were provided in graph format). ITP occurred in six patients in year 4 and no case of nephropathy was reported. For the former interferon-treated patients, the incidence of thyroid disorders was 2.1% during the first year of alemtuzumab therapy and increased to 11.4% during the second year. There was no ITP or nephropathy reported over the two-year extension in this patient group.

In the pooled CARE studies, the incidence of thyroid events increased during the extension study from 16.9% in the core studies to 20.5% in the year 3 extension study.

TABLE 33: ADVERSE EVENTS OF INTEREST REPORTED IN CAMMS223 AND POOLED CARE STUDIES

	CAMMS223 Baseline — Month 72[63]		Pooled CARE-MS I & II ALZ 12 mg[65]	
Incidence, n (%)	Former ALZ 12 mg-Treated Patients (N = 108)	Former INFB-1a-Treated Patients (N = 107)	Core Study Year 0 to 2 (N = 811)	Extension Study Year 3 (N = 772)
IAR Serious	106 (98.1) 4 (3.7)	NA NA	[redacted]	[redacted]
Infections Serious	77 (71.3) 6 (5.6)	54 (50.5) 3 (2.8)	[redacted]	[redacted]
Autoimmune AEs ITP, any Serious Thyroid events Serious Nephropathy Serious	 2 (1.9) 1 (0.9) 36 (33.3) 1 (0.9) NR NR	 1 (0.9) 0 (0) 4 (3.7) 0 (0) NR NR	[redacted]	[redacted]
Malignancies Serious	4 (3.7) 3 (2.7)	1 (0.9) 1 (0.9)	[redacted]	[redacted]

AE = adverse event; ALZ = alemtuzumab; IAR = injection-associated reaction; INFB-1a = interferon beta-1a; ITP = idiopathic thrombocytopenic purpura; NA = not applicable; NR = not reported.
[a] Immune thrombocytopenia

OBSERVATIONAL STUDY

Tuohy et al. conducted a single-group cohort study to explore the long-term clinical benefits and risks of alemtuzumab in patients with RRMS.[25] In this study, disability and safety data of 87 patients from two single-group, open-label studies (67 from CAMMS224, study period: 1999 to 2010; 20 from SM3, study period: 2005 to 2008) were followed during an average period of seven years. The inclusion criteria in both studies were: RRMS, ≥ 1 relapse in the preceding year, EDSS score < 6.0, disease duration < 10 years, and no previous exposure to experimental therapy. Disability was assessed using EDSS by a rater who was blinded to the treatment and previous EDSS sores. Patients received two cycles of alemtuzumab that were administered 12 months apart. Additional cycles were prescribed when a relapse occurred.

At the beginning of the studies, alemtuzumab was administered at 20 mg/day, and increased to 24 mg/day in 2003. The dose was reduced to 12 mg/day from 2006 to be consistent with the phase 3 study dosing. Patients in the SM3 study also received a biologically inert variant of alemtuzumab to prevent the development of anti-alemtuzumab antibodies.

Disability was evaluated using SAD, defined as an increase in EDSS of at least 1.5 points and 1.0 point if the baseline EDSS was 0, and sustained reduction in disability (SRD), defined as a reduction in EDSS score by at least 1.0 or 0.5 for baseline EDSS scores below and above 5.5, respectively. Six-month and 12-month SAD and SRD were measured.

Findings

Forty-five patients (52%) received two planned cycles of alemtuzumab, 31 patients (36%) received three cycles, seven patients (8%) received four cycles, and one patient received five cycles. The mean baseline EDSS score was 3.8 (standard deviation 1.9). Thirty-four patients (39%) received prior disease-modifying therapy, and the majority of them received interferon (31 patients, 35.6%) prior to the treatment of alemtuzumab. The mean ARR after alemtuzumab was 0.16 (standard deviation 0.26) compared with 1.78 (standard deviation 0.82), which was assessed retrospectively for the two pre-treatment years. There was no statistically significant difference in mean EDSS scores between baseline and the last follow-up: 3.8 versus 3.6, *P* = 0.56. More patients had a six-month SRD than a six-month SAD (43.5% versus 32.2%, *P* value was not reported). The proportion of patients with 12-month SRD was higher than those with a 12-month SAD (37.7% versus 21.8%, *P* value was not reported). Secondary autoimmunity (defined as new symptomatic autoimmune disease) was reported in this study. In total, 41 patients (48%) experienced clinical autoimmune disease and another 12 (14%) developed sustained novel autoantibodies with no evidence of associated clinical disease. The reported autoimmunity were:

- thyroid events in 35 patients (41%): 22 hyperthyroidism, one transient thyroiditis, and 12 primary hypothyroidism
- ITP in three patients (3.5%): one occurred 43 months after the third alemtuzumab treatment, one occurred nine months after the third alemtuzumab treatment, and one occurred one month after the second alemtuzumab treatment
- varicella zoster virus reactivation in 11 patients (12.6%): the mean interval from most recent alemtuzumab treatment to the infection was 12 months (standard deviation 13.5).

The study concluded that two cycles of alemtuzumab stabilized disability in RRMS patients over an average seven-year follow-up, and there was no new or late-occurring adverse events reported outside of those previously identified in the literature.

The Tuohy et al. study had the longest follow-up period of alemtuzumab therapy to date. However, several key limitations of the research exist:

- Because of the observational study design and the absence of a comparator group, causal relationships between alemtuzumab therapy and the study outcomes cannot be established.
- The small sample size (N = 87) in this study makes it difficult in result interpretation, although there was no loss to follow-up.

On the other hand, there are also issues of generalizability of the study results:

- Patients in the Tuohy et al. study had higher baseline EDSS scores, indicating more severe disability than those in the CAMMS324 study.
- All patients in CAMMS324 received prior disease-modifying therapy and had inadequate response to the drugs before entering the study, while in the Tuohy et al. study approximately one-third of the cohort failed the previous disease-modifying therapy, mainly interferon.
- During the study period, some patients received higher-dose alemtuzumab (20 mg/day or 24 mg/day), compared with the current treatment standard. It is unclear how many of the 87 patients received alemtuzumab at 12 mg/day. This would have an impact on the benefit-risk assessment of the study drug.

Summary

From CAMMS223, efficacy and safety data are based on 102 patients (90.2%) who received two cycles and 24 patients (21%) who received three cycles of alemtuzumab 12 mg during the original three-year time frame, and 27 patients (23.9%) who received re-treatment cycles during the extension phase: two patients (1.7%) who received cycle 2, 21 patients (18.5%) who received cycle 3, and four patients (3.5%) who received cycle 4. Re-treatment cycles were received approximately four years after their last/prior infusion.

The limited exposure during the extension phase, risk of selection bias of patients into each amended protocol during the extension phase, contamination with alternate MS treatments in 19% and 23% of alemtuzumab 12 mg and interferon beta-1a patients (who received alternate DMTs at some point during the baseline to month 72 period), and the long lag time between prior infusions and re-treatment infusions (range 37 to 58 months after prior infusion) reduce the ability to draw meaningful conclusions from the extension data of CAMMS223.

Limited data are reported in only abstract and poster form for the CAMM3409, putting into question the reliability of these non–peer reviewed data.

Due to these limitations, the results should be interpreted with caution. The significant effects of alemtuzumab 12 mg on ARR during the original CAMMS223 study were maintained during the two-year extension phase, and the time to six-month SAD remained significantly reduced in alemtuzumab patients versus interferon beta-1a patients, among those who were followed. The pooled analysis of the alemtuzumab 12 mg groups of the CARE studies show that the ARR was maintained during the one-year follow-up. In CAMMS324, the two-year follow-up results indicated that the ARR was maintained in the former alemtuzumab-treated patients, and it declined in patients who switched from interferon to alemtuzumab. EDSS scores remained stable in patients who received prior alemtuzumab therapy, while it was improved in patients who switched from interferon to alemtuzumab. The safety profile of alemtuzumab in the original plus extension study of CAMMS223 was consistent with the safety profile from only the original study (months 0 to 36), and no new safety concerns emerged. No new safety issues emerged from the CARE studies during year 3. Given the limited data and risk of bias, it is not possible to draw definitive conclusions on the sustainability of the benefits of alemtuzumab after the medication is stopped in patients with RRMS.

Findings of a long-term observational study suggested that alemtuzumab therapy could help to stabilize disability in patients with RRMS over a seven-year follow-up, and no new safety concerns arose during this extended follow-up. However, design limitations (open-label, no control group, and different drug dosage) limit their usefulness for providing any further information on the risk of harm or efficacy for alemtuzumab.

APPENDIX 8: SUMMARY OF INDIRECT COMPARISON

Objective

The objective of this supplemental issue is to summarize and critically appraise the manufacturer-submitted mixed treatment comparison (MTC)[67] comparing alemtuzumab with other disease-modifying therapies (DMTs) for the management of relapsing-remitting multiple sclerosis (RRMS).

Our summary is focused on the treatment-experienced subpopulation of the MTC analysis, as the Health Canada–approved indication for alemtuzumab is for patients with RRMS who have had an inadequate response to interferon beta or other DMTs.

Summary of Network Meta-Analysis

Rationale

The primary objective of the MTC analysis was to quantitatively examine the efficacy and safety of alemtuzumab when compared with other DMTs for the management of RRMS.

Methods

Literature Search

[redacted]

Interventions and Comparators

Base Case

[redacted]

Subgroup Analysis

[redacted]

Study Eligibility Criteria

Two base case MTCs (1 and 2) were performed.

[redacted]

[redacted]

The study eligibility criteria for inclusion in the subgroup analysis in treatment-experienced patients were:

[redacted]

Outcomes

[redacted]

Data Extraction and Analysis

[redacted]

[redacted]

Critical appraisal of the included studies was performed by the investigators performing the MTC [redacted]

Results

Study and Patient Characteristics

[redacted] In CARE-MS II, all patients had previously received treatment with interferon beta or glatiramer acetate. [redacted]

Results of the MTC Subgroup Analysis

[redacted]

[redacted]

TABLE 34: ANNUALIZED RELAPSE RATE, THREE-MONTH SAD, AND SIX-MONTH SAD RATIOS FOR DISEASE-MODIFYING THERAPIES VERSUS PLACEBO IN MTC ANALYSES IN PREVIOUSLY TREATED PATIENTS

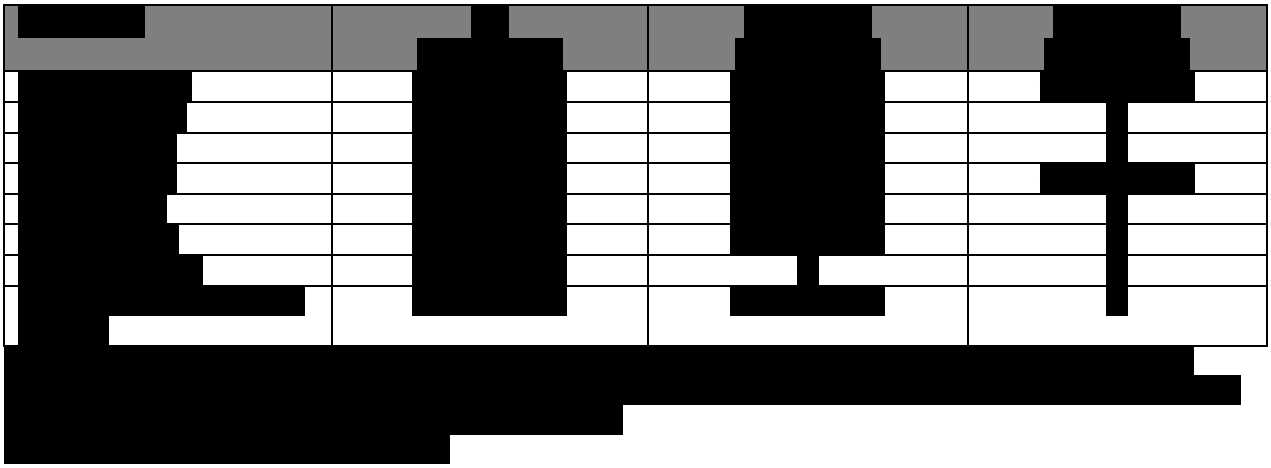

TABLE 35: ANNUALIZED RELAPSE RATE AND THREE-MONTH SAD RATIOS FOR ALEMTUZUMAB VERSUS PLACEBO AND DISEASE-MODIFYING THERAPIES IN MTC ANALYSES IN PREVIOUSLY TREATED PATIENTS

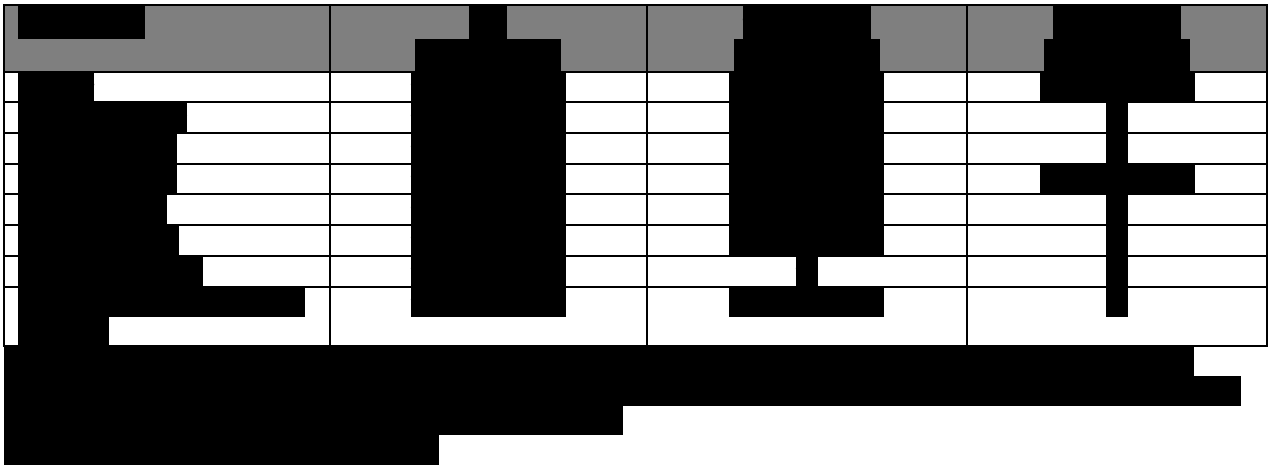

TABLE 36: TRIALS INCLUDED IN THE PREVIOUSLY TREATED SUBGROUP ANALYSES

Study and Design	Patient Characteristics	Intervention Sample Size (Treatment-Experienced Population)	Comparator Sample Size (Treatment-Experienced Population)	Outcomes Measured
AFFIRM[68] Double-blind, placebo-controlled RCT 2 years	[redacted]	[redacted]	[redacted]	[redacted]
CARE-MS II[3] Rater-blind, active-controlled, RCT 2 years	[redacted]	[redacted]	[redacted]	[redacted]
CONFIRM[69] Double-blind, placebo-controlled RCT 2 years	[redacted]	[redacted]	[redacted]	[redacted]

Study and Design	Patient Characteristics	Intervention Sample Size (Treatment-Experienced Population)	Comparator Sample Size (Treatment-Experienced Population)	Outcomes Measured
DEFINE[70] Double-blind, placebo-controlled RCT 2 years	[redacted]	[redacted]	[redacted]	[redacted]
FREEDOMS[71] (D2301) Double-blind, placebo-controlled RCT 2 years	[redacted]	[redacted]	[redacted]	[redacted]
SENTINEL[72] Double-blind, placebo-controlled RCT 2 years	[redacted]	[redacted]	[redacted]	[redacted]
TRANSFORMS[73] (D2302) Double-blind, double-dummy, active-controlled RCT 12 months	[redacted]	[redacted]	[redacted]	[redacted]

Study and Design	Patient Characteristics	Intervention Sample Size (Treatment-Experienced Population)	Comparator Sample Size (Treatment-Experienced Population)	Outcomes Measured
TEMSO[74] Double-blind, placebo-controlled RCT 108 weeks of tx	[redacted]	[redacted]	[redacted]	[redacted]
TOWER[75] Double-blind, placebo-controlled RCT Up to 160 weeks of tx	[redacted]	[redacted]	[redacted]	[redacted]
TENERE[76] Rater-blind, active-controlled, parallel-group RCT Up to 118 weeks of tx	[redacted]	[redacted]	[redacted]	[redacted]

ARR = annualized relapse rate; DMT = disease-modifying therapy; EDSS = Kurtzke Expanded Disability Status Score; IFN = interferon; IM = intramuscular; GA = glatiramer acetate; IV = intravenous; MS = multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SAD = sustained accumulation of disability; SC = subcutaneous; tx = treatment.

Results From the Mixed Treatment Comparison Sensitivity Analysis Used in the Pharmacoeconomic Evaluation

[redacted] (Table 37).

TABLE 37: ANNUALIZED RELAPSE RATE AND THREE-MONTH SUSTAINED ACCUMULATION OF DISABILITY FOR DMTS VERSUS PLACEBO IN MTC SENSITIVITY ANALYSES OF POOLED POPULATION (POST-2000, ≥ 80% RRMS)

Comparator	ARR RR [95% CrI]	3-month SAD HR [95% CrI]
[redacted]		
[redacted]		
[redacted]		

ARR = annualized relapse rate; CrI = credible interval; DMT = disease-modifying therapy; HR = hazard ratio; IFN = interferon; MTC = mixed treatment comparison; RR = rate ratio; RRMS = relapsing-remitting multiple sclerosis; SAD = sustained accumulation of disability; SC = subcutaneous.

Critical Appraisal of Mixed Treatment Comparison

Critical appraisal of the manufacturer-provided MTC was conducted based on the ISPOR (International Society fo Pharmacoeconomics and Outcomes Research) simplified checklist to assist decision-makers in evaluating a reported network meta-analysis.[77] A summary of the primary strengths and limitations is presented; full details are presented in Table 38.

Strengths and Limitations

[redacted]

Population

[redacted]

Trial Inclusion and Exclusion

[redacted]

Treatment Definition

[redacted]

Data Analysis

[redacted]

TABLE 38: SIMPLIFIED CHECKLIST TO ASSIST DECISION-MAKERS IN EVALUATING A REPORTED NETWORK META-ANALYSIS

Checklist Item	Comments
Are the rationale for the study and the study objectives stated clearly?	[redacted]
Does the methods section include the following? • Description of eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction (validity/quality assessment of individual studies)	[redacted]
Are the outcome measures described?	[redacted]
Is there a description of methods for analysis/synthesis of evidence? Do the methods described include the following? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	[redacted]

Checklist Item	Comments
	[redacted]
Are sensitivity analyses presented?	[redacted]
Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	[redacted]
Does the study describe an assessment of model fit? Are competing models being compared?	[redacted]
Are the results of the evidence synthesis presented clearly?	[redacted]
Sensitivity/scenario analyses findings	[redacted]
Does the discussion include the following? • Description/summary of main findings • Internal validity of analysis • External validity • Implications of results for target audience	[redacted]

ARR = annualized relapse rate; DMT = disease-modifying therapy; HR = hazard ratio; MTC = mixed treatment comparison; RR = rate ratio; SAD = sustained accumulation of disability; SD = standard deviation.
Source: Jansen et al. (2011)[77]

Comparison with CADTH Therapeutic Review

The recently published CADTH Therapeutic Review did not perform a subgroup analysis using only patients who had been previously treated. Instead, it performed a subgroup analysis grouping studies that enrolled patients who were treatment-naive, and studies where previous treatment status was unclear, experienced, or mixed. Due to these differences in the analyses performed in the CADTH Therapeutic Review and the manufacturer's MTC, it is difficult to draw any comparisons.

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