Common Drug Review
Clinical Review Report

December 2015

Drug	Peginterferon beta-1a (Plegridy — subcutaneous injection)
Indication (Provisional, Pre-NOC)	Treatment of relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations and to slow the progression of disability.
Listing Request	As per indication
Dosage Form(s)	63, 94, or 125 micrograms of peginterferon beta-1a in a pre-filled syringe or pre-filled pen for subcutaneous administration
NOC Date	August 10, 2015
Manufacturer	Biogen Canada Inc.

Note: At the time of the CADTH Common Drug Review (CDR) submission for Plegridy, the price submitted by the manufacturer to CADTH was confidential. However, the manufacturer advised during the review that the submitted price does not need to remain confidential, as the submitted price is equivalent to the net wholesaler price at launch.

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

TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

AE	adverse event
ARR	annualized relapse rate
CDR	CADTH Common Drug Review
CI	confidence interval
CMSWG	Canadian Multiple Sclerosis Working Group
CNS	central nervous system
DMT	disease-modifying therapy
EDSS	Kurtzke Expanded Disability Status Scale
EQ-5D	EuroQol 5-Dimensions Questionnaire
FDA	US Food and Drug Administration
IDC	indirect comparison
IFN	interferon
INEC	Independent Neurology Evaluation Committee
ITT	intention-to-treat
PegIFN	pegylated interferon (peginterferon) beta-1a
MCID	minimal clinically important difference
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS	Multiple Sclerosis Impact Scale
NEDA	no evidence of disease activity
NMA	network meta-analysis
RRMS	relapsing-remitting multiple sclerosis
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SF-12	Short Form (12) Health Survey
VAS	visual analogue scale

EXECUTIVE SUMMARY

Introduction

Multiple sclerosis (MS) is a chronic, progressive immune-mediated disease of the central nervous system in which the white matter within the brain or spinal cord becomes inflamed and destroyed in a process called demyelination. Relapsing-remitting MS (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-1a/1b, glatiramer acetate, fingolimod, natalizumab, dimethyl fumarate, teriflunomide, and alemtuzumab.

Pegylated interferon (peginterferon) beta-1a is an immunomodulator that binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression, including up-regulation of anti-inflammatory cytokines, down-regulation of pro-inflammatory cytokines and inhibited migration of activated T cells across the blood–brain barrier. Its mechanism of action in MS is unknown.[1] Peginterferon beta-1a is administered by subcutaneous injection of 63 mcg on day 1, 94 mcg at week 2, and then 125 mcg every two weeks.

Indication Under Review
Treatment of relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations and to slow the progression of disability.

The objective of this review is to examine the beneficial and harmful effects of subcutaneous peginterferon beta-1a for the treatment of adults with RRMS.

Results and Interpretation

Included Studies

One randomized, double-blind, parallel-group study met the inclusion criteria for this review. The ADVANCE study (N = 1,516) compared peginterferon beta-1a 125 mcg every two weeks or every four weeks versus placebo. The ADVANCE study was placebo-controlled up to week 48, after which time patients on placebo were randomly allocated to receive either peginterferon beta-1a every two weeks or every four weeks, and blinded treatment continued until week 96. Most patients had mild to moderate disease at baseline (median Kurtzke Expanded Disability Status Scale [EDSS] = 2.5) and most patients (83%) were treatment-naive. The majority of patients (88%) were diagnosed with MS based on McDonald criterion 1 (i.e., two or more relapses, two or more objective lesions). The majority of patients (63%) had two or more relapses in the preceding three years, and 38% of patients had at least one gadolinium-enhancing lesion. The primary end point was annualized relapse rate at the end of the placebo-controlled phase (week 48).

The ADVANCE study was well designed, but there are some limitations to the available evidence, including the absence of trials that directly compare peginterferon beta-1a to other first-line agents used in the treatment of RRMS. The length of the placebo-controlled period was 48 weeks, and this is a relatively short period of time to assess benefit and harm relative to the expected period of time for which patients would use the drug. While the baseline characteristics of the ADVANCE study population

appeared similar to patients who would be treated with peginterferon beta-1a in Canada, less than 3% of the ADVANCE study population was enrolled in North America; therefore, there may be some differences in patient populations between the ADVANCE study population and the Canadian treatment population.

Efficacy

Key outcomes identified in this CADTH Common Drug Review (CDR) were no evidence of disease activity (NEDA), relapse rate, disability, quality of life, and disease symptoms.

In the group taking peginterferon beta-1a every two weeks, 158 patients (34%) achieved NEDA after 48 weeks compared with 73 (15%) in the group taking placebo (relative risk 2.2; 95% confidence interval [CI], 1.8 to 2.9; $P < 0.0001$). Of note, NEDA was defined as part of a post hoc analysis and may therefore have been more prone to bias than the other efficacy outcomes.

Relapse rate was the primary outcome of the ADVANCE study. Ninety patients (18%) in the group taking peginterferon beta-1a every two weeks and 142 patients (28%) in the placebo group experienced a relapse as confirmed by the blinded adjudication committee. The adjusted annualized relapse rate after 48 weeks was 0.256 (95% CI, 0.206 to 0.318) for the peginterferon beta-1a every-two-weeks group and 0.397 (95% CI, 0.328 to 0.481) for the placebo group (rate ratio 0.644; 95% CI, 0.500 to 0.831; $P = 0.0007$). Progression of disability was defined as at least a 1.0-point increase on the EDSS from a baseline EDSS ≥ 1.0 sustained for 12 weeks, or at least a 1.5-point increase on the EDSS from a baseline EDSS of zero sustained for 12 weeks. Thirty-one patients (6%) in the peginterferon beta-1a every-two-weeks group experienced disability progression compared with 50 patients (10%) in the placebo group (hazard ratio 0.62; 95% CI, 0.40 to 0.97; $P = 0.04$).

Changes from baseline in the quality-of-life scales were small for all treatment groups. At week 48, there were no statistically significant differences between the peginterferon beta-1a every-two-weeks and the placebo group on the MSIS-29, the Short Form (12) Health Survey physical or mental component, the EuroQol 5-Dimensions Questionnaire (EQ-5D) index or the EQ-5D visual analogue scale. There was also no statistically significant improvement observed in measures of function (Multiple Sclerosis Functional Composite) and cognition (Symbol Digit Modalities Test).

The magnetic resonance imaging (MRI) results provide evidence for consistency of treatment effect, with comparisons showing less deterioration in the peginterferon beta-1a every-two-weeks group compared with the placebo group at 48 weeks: mean 4.1 versus 13.3 new or newly enlarging T2 hyperintense lesions, respectively ($P < 0.0001$); mean 4.1 versus 13.4 new active lesions, respectively ($P < 0.0001$); mean 0.2 versus 1.4 gadolinium-enhancing lesions, respectively ($P < 0.0001$). The number of patients developing at least one new or newly enlarging T2 hyperintense lesion from baseline to week 48 was lower in the group taking peginterferon beta-1a every two weeks compared with the group taking placebo (59% versus 81%; *P* value not reported).

The results of the second year of the ADVANCE study, in which all patients on placebo were re-randomized to active treatment, suggest that efficacy is maintained among patients who continue with peginterferon beta-1a 125 mcg every two weeks past the first year of treatment.

In the absence of direct comparative trials, the manufacturer submitted a network meta-analysis (NMA) comparing peginterferon beta-1a 125 mcg every two weeks with other first-line injectable treatments for RRMS (Appendix 7: Summary of Indirect Comparisons). Relapse rate and disability progression at

three and six months were assessed in the NMA. There were no statistically significant differences observed between peginterferon beta-1a and the other treatments for these efficacy outcomes, but there was significant heterogeneity across the 16 included trials, as reflected in the wide range of relapse rates in the placebo-treated groups. Due to the heterogeneity in the definitions of relapse and relapse rates across studies, caution is required in interpreting the findings of the NMA. A recent Cochrane NMA also compared the relative effectiveness and harms of 15 immunomodulators and immunosuppressants for RRMS. Alemtuzumab, natalizumab, and fingolimod emerged as the best choices for preventing clinical relapses in this analysis. Relative to the other agents, non-pegylated interferons and peginterferon beta-1a ranked near the bottom from the combined perspective of treatment benefit and acceptability. However, similar to the manufacturer-submitted NMA, there were no significant differences in relapse rate between peginterferon beta-1a and other interferons or glatiramer acetate.

Harms

A total of 11% of patients taking peginterferon beta-1a every two weeks and 15% of patients taking placebo experienced a serious adverse event by week 48. No serious adverse events occurred more than once in the group taking peginterferon beta-1a every two weeks except for the event classified as MS relapse. In year 1, one patient died in the peginterferon beta-1a group (cause unknown) and two patients died in the placebo group (one cause unknown, one subarachnoid hemorrhage).

A total of 94% of patients in the peginterferon beta-1a every-two-weeks group experienced an adverse event compared with 83% of patients in the placebo group. The most common adverse events (incidence ≥ 10% in either peginterferon beta-1a group) that occurred at an incidence ≥ 2% higher in either peginterferon beta-1a group compared with the placebo group included injection-site reactions (injection-site erythema, injection-site pain, injection-site pruritus) and flu-like symptoms (including influenza-like illness, pyrexia, myalgia, chills, asthenia, arthralgia, and headache). Injection-site reactions were reported by 66% of patients who received peginterferon beta-1a every two weeks compared with 11% of patients receiving placebo.

A total of 25 patients (5%) taking peginterferon beta-1a every two weeks withdrew from treatment at 48 weeks because of adverse events, compared with 7 (1%) in the placebo group. The most common adverse effects leading to treatment withdrawal included influenza-like illness, injection-site erythema, and pyrexia.

The NMA submitted by the manufacturer did not include statistical comparisons of the incidence of harms between treatments, but the authors concluded that the incidence of harms was similar to non-pegylated interferons, based on a qualitative comparison. In the recent Cochrane NMA, there were no significant differences between peginterferon beta-1a and interferon beta-1a or glatiramer acetate with respect to treatment discontinuation due to adverse events, although these estimates were associated with a large degree of imprecision (i.e., wide 95% CIs).

There were no new safety events during the second year of ADVANCE compared with the placebo-controlled phase. Patients who completed the 96-week ADVANCE study could enrol in a blinded extension trial (ATTAIN study) (Appendix 6). An interim analysis of this extension study was performed after 21 patients had completed 48 weeks of treatment with peginterferon beta-1a every two weeks. The adverse events observed were similar to those observed in the ADVANCE study.

Conclusions

In one randomized, double-blind, placebo-controlled study (ADVANCE), in patients with relapsing-remitting MS, peginterferon beta-1a was associated with a lower rate of relapse and delayed time to disability progression (sustained for 12 weeks) and less worsening of some MRI outcomes relative to placebo over 48 weeks. Measures of quality of life, function, and cognition did not show any differences between peginterferon beta-1a and placebo. There were no direct comparative trials comparing peginterferon beta-1a with other treatments used for RRMS. Evidence from two NMAs (one submitted by the manufacturer and the other identified in the literature) suggested there was no significant difference in efficacy between peginterferon beta-1a and other treatments for MS; however, caution is required in interpreting these findings due to the limitations of the analysis, particularly the heterogeneity across included trials.

With respect to safety, the results of the ADVANCE study indicate that peginterferon beta-1a is associated with adverse events, such as injection-site reactions and influenza-like symptoms, that occur commonly with other interferon products for MS. The comparative safety of peginterferon beta-1a and other treatments for RRMS is uncertain due to the lack of head-to-head trials and because the manufacturer-submitted NMA did not attempt indirect comparisons for outcomes related to harms.

TABLE 1: SUMMARY OF RESULTS

	Results from Year 1		
	PL N = 500	**PegIFN Q2W N = 512**	**Statistical Comparison**
No evidence of disease progression	73/484 (15%)	158/466 (34%)	Relative risk (95% CI): 2.2 (1.8 to 2.9); $P < 0.0001$
Annualized relapse rate (95% CI)	0.397 (0.328 to 0.481)	0.256 (0.206 to 0.318)	Rate ratio (95% CI): 0.644 (0.500 to 0.831); $P = 0.0007$[a]
Disability progression sustained for 12 weeks, n (%)	50 (10)	31 (6)	Hazard ratio (95% CI): 0.62 (0.40 to 0.97); $P = 0.04$[b]
Mean EDSS score at baseline; mean change (SD); n	2.44; +0.06 (0.67); n = 442	2.46; +0.01 (0.61); n = 456	NR
MSFC score at baseline; mean change (SD)	Baseline NR –0.023 (0.66)	Baseline NR 0.041 (0.39)	$P = 0.22$
SDMT score at baseline; mean change (SD); n	48.7; +1.2 (12.8); n = 499	47.5; +2.4 (11.6); n = 510	$P = 0.23$
QoL: MSIS-29 physical score at baseline, mean change (SD); n	21.5; +1.2 (13.6); n = 497	21.5; +0.1 (13.7); n = 511	$P = 0.15$
QoL: MSIS-29 psychological score at baseline, mean change (SD); n	27.8; –2.2 (16.7) n = 497	27.6; –2.1 (17.5); n = 509	$P = 0.95$
QoL: SF-12 mental score at baseline, mean change (SD); n	47.1; +0.01 (9.2); n = 496	47.7; –0.3 (9.6); n = 511	$P = 0.99$

	Results from Year 1		
	PL N = 500	**PegIFN Q2W N = 512**	**Statistical Comparison**
QoL: SF-12 physical score at baseline, mean change (SD); n	43.9; –0.01 (8.1); n = 496	43.9; +0.4 (7.5); n = 511	*P* = 0.42
QoL: EQ-5D score at baseline, mean change (SD); n	0.74; –0.01 (0.2); n = 498	0.73; 0 (0.2); n = 511	*P* = 0.32
QoL: EQ-5D VAS at baseline, mean change (SD); n	73.0; +0.4 (18.3); n = 495	73.0; +2.1 (16.9); n = 506	*P* = 0.12
Harms, n (%)			
Patients with ≥ 1 AE	417 (83)	481 (94)	
Patients with ≥ 1 SAE	76 (15)	55 (11)	
Deaths	1 (< 1)	1 (< 1)	
AEs leading to treatment withdrawal	7 (1)	25 (5)	

AE = adverse event; CI = confidence interval; EDSS = Kurtzke Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions Questionnaire; MSFC = Multiple Sclerosis Functional Composite; MSIS = Multiple Sclerosis Impact Scale; NR = not reported; PegIFN = peginterferon beta-1a; PL = placebo; QoL = quality of life; Q2W = every two weeks; SAE = serious adverse event; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SF-12 = Short Form (12) Health Survey; VAS = visual analogue scale.

[a] Based on negative binomial regression; adjusted for baseline EDSS (< 4 versus ≥ 4), baseline relapse rate, and age (< 40 years versus ≥ 40 years).

[b] Progression of disability is defined as at least a 1.0-point increase on the EDSS from a baseline EDSS ≥ 1.0 sustained for 74 days or at least a 1.5-point increase on the EDSS from a baseline EDSS of zero sustained for 12 weeks (minimum of 74 days).

Source: Clinical Study Report,[2] Arnold et al.[3]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Multiple sclerosis (MS) is a chronic, progressive, immune-mediated disease of the central nervous system in which the white matter within the brain or spinal cord becomes inflamed and destroyed through a process called demyelination.[4] MS affects up to three times as many women as men and typically has an age of onset of between 20 and 50 years.[5] The Multiple Sclerosis Society of Canada estimates 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 central nervous system tissue.[7] The majority of people (85%) who later develop MS experience an initial episode of neurological disturbance known as clinically isolated syndrome, which may manifest as 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 MS (RRMS); primary-progressive MS, secondary-progressive MS, and progressive-relapsing MS. The RRMS subtype comprises 85% to 90% of MS patients at first presentation, and is characterized by clearly defined relapses with full recovery or with sequelae and residual deficit upon recovery, with lack of progression of disability during the periods between relapses.[5] The relapsing forms of MS are associated with better prognosis than progressive forms of the 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 event profile, dosing schedule, reimbursement, and patient preference.[10] Since these guidelines were published, dimethyl fumarate and teriflunomide were approved for treatment of MS and these are also being used as first-line therapy, according to the clinical expert for this review. In 2013, CADTH published a Therapeutic Review of RRMS.[11] The report concluded that subcutaneous interferons, glatiramer acetate, and teriflunomide all had similar efficacy. Based on this review and accompanying pharmacoeconomic analysis, the CADTH Canadian Drug Expert Committee recommended glatiramer and interferon beta-1b as the initial therapies of choice for RRMS. Peginterferon beta-1a was not included in the Therapeutic Review.

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, disability 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 alemtuzumab, 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, while there are concerns of cardiovascular adverse events with fingolimod.[12,13]

Although no clinical criteria have been established to identify patients that should discontinue treatment, the CMSWG suggests 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

Peginterferon beta-1a is an immunomodulator that binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression, including up-regulation of anti-inflammatory cytokines (e.g., interleukin [IL]-4, IL-10, IL-27), down-regulation of pro-inflammatory cytokines (e.g., IL-2, IL-12, IFN gamma, tumour necrosis factor alpha) and inhibited migration of activated T cells across the blood–brain barrier. Its mechanism of action in MS is unknown.[1] Peginterferon beta-1a is administered by subcutaneous injection of 63 mcg on day 1, 94 mcg at week 2, and then 125 mcg every two weeks. It is supplied as a pre-filled syringe or pre-filled pen.

There are other interferon products used in Canada for the treatment of MS. Interferon beta-1a as Avonex is administered intramuscularly once per week, and as Rebif is administered subcutaneously three times per week. Interferon beta-1b (Betaseron; Extavia) is administered subcutaneously every other day.

Indication Under Review
Treatment of relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations and to slow the progression of disability.

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

	Mechanism of Action	Approved Indications	Route of Administration	Recommended Dose	Contraindications (According to PM)
Peginterferon beta-1a (Plegridy)[1]	Not understood. Influences cytokines and T cells	RRMS	SC injection	125 mcg every 2 weeks	Patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon or any other component of the formulation or the container.
Alemtuzumab (Lemtrada)[14]	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 tuberculosis, 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; at risk for an opportunistic infection; immunocompromised due to treatment or disease; or who 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.

	Mechanism of Action	Approved Indications	Route of Administration	Recommended Dose	Contraindications (According to PM)
Interferon beta-1a (Avonex; Rebif)[17,18]	Not completely understood; likely the up-regulation 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, and pregnant women.
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, and pregnant women.
Natalizumab (Tysabri)[13]	Blocks interaction of α4β7 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; or 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 the following: patients who are hypersensitive to this drug or to leflunomide; patients currently treated with leflunomide; those with severe hepatic impairment; pregnant women or women of child-bearing age who are not using contraception; those with immunodeficiency states such as AIDS; patients with serious active infection, impaired bone marrow function, or with significant anemia, leucopenia, neutropenia, or thrombocytopenia.

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.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of subcutaneous peginterferon beta-1a (Plegridy) 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. 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	Adults with relapsing-remitting multiple sclerosis
Intervention	Subcutaneous peginterferon beta-1a 125 mcg every 2 weeks
Comparators	• Interferon beta-1a (IM or SC) • Interferon beta-1b • Alemtuzumab • Glatiramer acetate • Natalizumab • Fingolimod • Dimethyl fumarate • Teriflunomide • Placebo
Outcomes	**Key efficacy outcomes** • No evidence of disease activity • Relapse rate • Disability progression or improvement using a validated scale (e.g., EDSS, MSFC) • HRQoL using a validated scale (e.g., SF-36)[a] • Symptoms (e.g., fatigue, pain, depression **Other efficacy outcomes** • Brain atrophy (e.g., annualized rate of brain atrophy) • Brain lesions on MRI (gadolinium-enhancing lesions, new or enlarging T2 lesions) • Productivity (ability to attend work or school)[a] • Medication acceptance • Cognition **Harms outcomes** • Mortality, SAEs, WDAEs, AEs Notable harms/harms of special interest: immunogenicity, worsening cardiovascular disease, decreased peripheral blood counts, hepatic/biliary/pancreatic abnormalities, injection-site reactions, depression, suicidal ideation, seizures, neutralizing antibodies
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; DB = double-blind; EDSS = Kurtzke Expanded Disability Status Score; HRQoL = health-related quality of life; IM = intramuscular; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = multiple sclerosis functional composite; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; SF-36 = Short Form (36) Health Survey; WDAE = withdrawal due to adverse event.

[a] Identified as outcomes of interest by patient groups (Appendix 1).

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Plegridy, peginterferon beta 1a, and pegylated interferon beta 1a.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on July 26, 2015. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on November 18, 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 *Grey Matters* checklist (www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials, and 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: Details of Included Studies; excluded studies (with reasons) are presented in Appendix 3: Excluded Studies.

3. RESULTS

3.1 Findings from the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 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

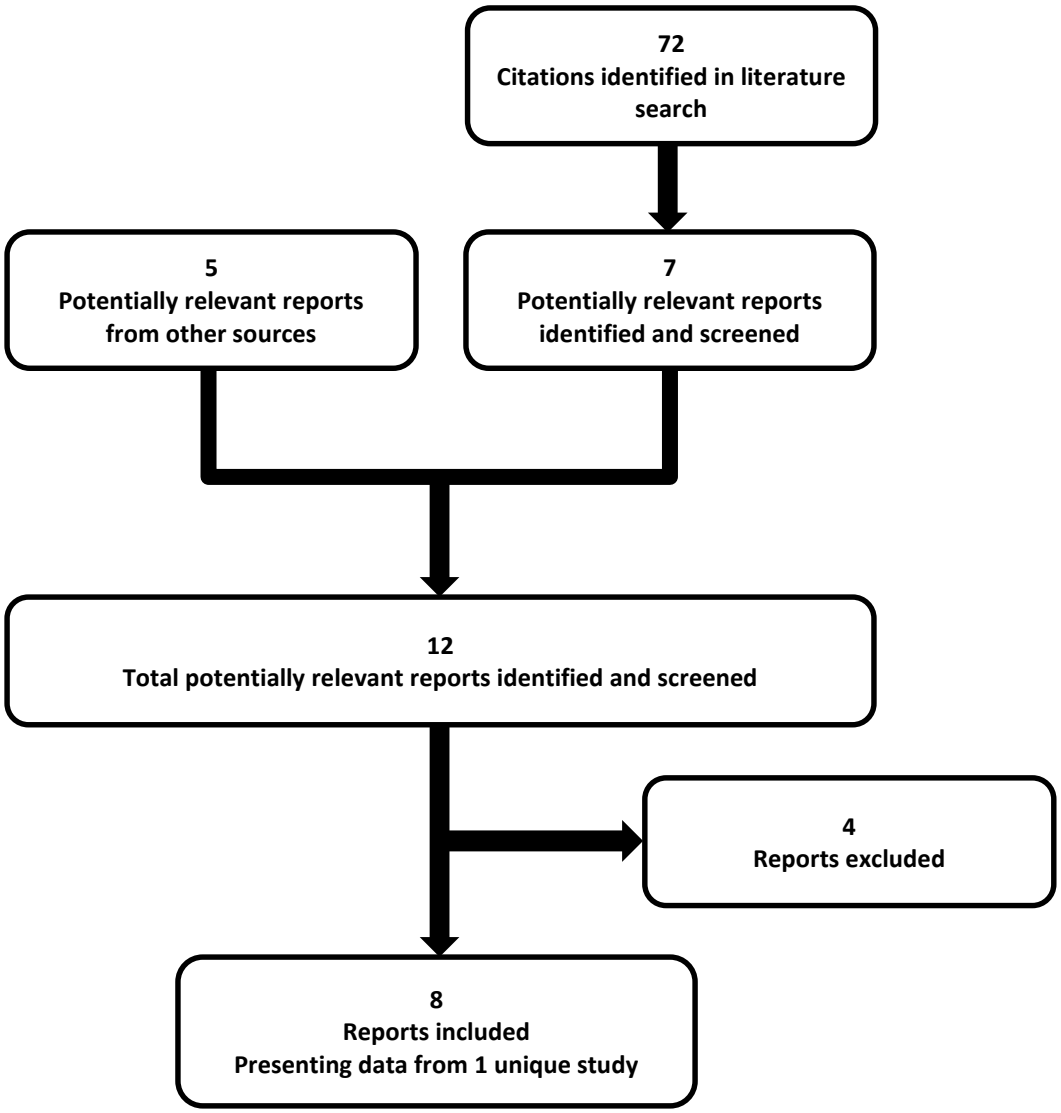


TABLE 4: DETAILS OF INCLUDED STUDIES

		ADVANCE (105MS301)
DESIGNS AND POPULATIONS	**Study design**	Randomized, double-blind, parallel-group, placebo-controlled
	Locations	183 sites in North America, South America, Europe, Russia, Ukraine, India, New Zealand (including 2 sites in Canada and 12 in the USA)
	Randomized (N)	1,516
	Inclusion criteria	• 18 to 65 years old • Relapsing-remitting MS, as defined by McDonald criteria 1 through 4 • EDSS score between 0 and 5.0 • ≥ 2 relapses within the last 3 years with at least one relapse having occurred within 12 months prior to randomization
	Exclusion criteria	• Primary-progressive, secondary-progressive, or progressive-relapsing MS. These conditions required the presence of continuous clinical disease worsening over a period of at least 3 months. Patients with these conditions may also have had superimposed relapse, but were distinguished from relapsing patients by the lack of clinically stable periods or clinical improvement. • Prior treatment with total lymphoid irradiation, cladribine, fingolimod, T cell or T cell receptor vaccination, or any therapeutic monoclonal antibody (e.g., rituximab, natalizumab, alemtuzumab). • Prior treatment with IFN could not exceed 4 weeks and patients must have discontinued interferon treatment at least 6 months prior to baseline.
DRUGS	**Intervention**	First dose: PegIFN 63 mcg SC; second dose: PegIFN 94 mcg SC; then either: PegIFN 125 mcg every 2 weeks SC or PegIFN 125 mcg every 4 weeks SC.
	Comparator(s)	Placebo every 2 weeks SC (up to week 48)
DURATION	**Phase**	
	Weeks 0 to 48	Placebo-controlled phase
	Weeks 49 to 96	Patients on placebo re-randomized at week 48 to PegIFN 125 mcg every 2 or 4 weeks
OUTCOMES	**Primary end point**	Annualized relapse rate at 1 year
	Other end points	Secondary end points: • New or newly enlarging T2 hyperintense lesions on brain MRI at year 1 • Clinical relapse at year 1 • Disability progression by EDSS at 1 year. Tertiary end points: • Relapse over 2 years, lesion assessments, EDSS, MSFC, brain MRI with/without Gd, visual function test, SDMT, SF-12, EQ-5D, MSIS-29, PASAT-3, cognition by SDMT, anti-IFN beta-1a neutralizing antibodies.
NOTES	**Publications**	Calabresi et al.,[22] Arnold et al.,[3] Kieseirer et al.,[23] Newsome et al[24]

EDSS = Kurtzke Expanded Disability Status Score; EQ-5D = EuroQol 5-Dimensions Questionnaire; Gd = gadolinium; MRI = magnetic resonance imaging; MSFC = multiple sclerosis functional composite; MSIS = Multiple Sclerosis Impact Scale; PASAT = Paced Auditory Serial Addition Test; PegIFN = peginterferon beta-1a; SC = subcutaneous; SDMT = Symbol Digit Modality Test; SF-12 = Short Form (12) Health Survey.
Note: Two additional reports were included: FDA Statistical Review[25] and FDA Medical Review.[26]
Source: Clinical Study Report[2] and CADTH Common Drug Review submission.[27]

3.2 Included Studies

3.2.1 Description of Studies

One randomized, double-blinded, placebo-controlled study met the inclusion criteria for this systematic review. All study management and site personnel, investigators, and patients were blinded to treatment assignment.[22] The individuals who performed ratings of relapse were blinded to treatment assignment and were different from the staff involved with treating the study patients. Patients were randomly assigned peginterferon beta-1a 125 mcg every two or four weeks or placebo on a 1:1:1 ratio. Randomization was stratified by site. After a four-week titration period, the target peginterferon beta-1a dosage was reached. At week 48, patients who were originally assigned to placebo were re-randomized to peginterferon beta-1a 125 mcg every two or four weeks. Only data from the group receiving peginterferon beta-1a 125 mcg every two weeks are summarized in this report because this is the dose approved in Canada.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients aged 18 to 65 years who met the McDonald criteria for RRMS and had at least two clinically documented relapses in the previous three years, with at least one having occurred within the past 12 months, were eligible for enrolment in the ADVANCE study. Patients must have had an EDSS of ≤ 5.0 at screening and not have a progressive form of MS. Prior exposure to IFN was not permitted unless treatment duration was less than four weeks.

b) Baseline Characteristics

The majority of patients were from Eastern Europe (70%), which included Russia and the Ukraine; 11% were from India, 8% were from Western Europe and 3% were from North America (Canada: n = 11, US: n = 41).[25] The majority of patients were women. Patients ranged in age from 18 to 61 years and 62% of patients were younger than 40 years of age.

The majority of patients (88%) were diagnosed with MS based on McDonald criterion 1 (i.e., two or more relapses, two or more objective lesions). In the overall study population, the mean number of relapses over the previous three years was 2.5 (range: 1 to 12). Most of the patients had not previously been treated with any MS medications prior to study entry. In the overall population, 17% of patients had used a prior MS therapy, whereas in the small subgroup of patients from the US (n = 41), 41% had previously received treatment for MS.[26] In the overall population, 7% of all patients previously received glatiramer, interferon beta-1b, or interferon beta-1a. A total of 172 patients (11%) had previously received other drug and non-drug therapies for MS that may not have been approved for this indication (e.g., corticosteroids [4%] and azathioprine [1%]). No patients had prior exposure to natalizumab.

Disease severity ranged from mild to moderate as reflected in a median EDSS at baseline of 2.5 (range: 0 to 5.5). The majority of patients (84%) had an EDSS < 4 at baseline. The majority of patients (63%) had ≤ 2 relapses in the past three years. At baseline, 38% of patients had at least one gadolinium-enhancing lesion.

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

Characteristic	PL N = 500	PegIFN Q4W N = 500	PegIFN Q2W N = 512
Mean age, years (SD)	36 (10)	36 (10)	37 (10)
Women, n (%)	358 (72)	352 (70)	361 (71)
Mean weight, kg (SD)	69 (16)	68 (15)	70 (17)
White ethnic origin, n (%)	412 (82)	409 (82)	416 (81)
McDonald criteria, n (%)			
1	445 (89)	428 (86)	450 (88)
2	45 (9)	57 (11)	52 (10)
3	7 (1)	10 (2)	7 (1)
4	3 (< 1)	5 (1)	3 (< 1)
Mean time since first MS symptoms, years (SD)	6.3 (6.3)	6.5 (6.1)	6.9 (6.6)
Mean time since MS diagnosis, years (SD)	3.5 (4.6)	3.4 (4.4)	4.0 (5.1)
Patients without Gd-enhancing lesions, n (%)	296 (59)	297 (59)	334 (65)
Mean number of Gd-enhancing lesions (SD)	1.6 (3.8)	1.8 (5.4)	1.2 (3.4)
Mean number of T2 lesions (SD)	50.6 (35.7)	51.4 (36.0)	48.7 (36.8)
Number who took any prior MS medication, n (%)	86 (17)	85 (17)	89 (17)
Previous treatments, n (%)[a]			
Glatiramer acetate	24 (5)	28 (6)	27 (5)
Interferon beta-1b	6 (1)	5 (1)	8 (2)
Interferon beta-1a	5 (1)	6 (1)	4 (< 1)
Number who took any of the above approved MS treatments	34 (7)	34 (7)	36 (7)
Mean EDSS (SD)	2.44 (1.18)	2.48 (1.24)	2.47 (1.26)
EDSS < 4	432 (86)	413 (83)	423 (83)
EDSS ≥ 4	68 (14)	87 (17)	89 (17)
Number of relapses in the past 3 years, n (%)			
0	0	0	0
1	1 (< 1)	1 (< 1)	2 (< 1)
2	314 (63)	327 (65)	311 (61)
3	119 (24)	129 (26)	147 (29)
≥ 4	66 (13)	43 (9)	52 (10)
Mean number of relapses in the past 3 years, n (%)	2.6 (1.0)	2.5 (0.8)	2.6 (1.0)
Number of relapses in the past 12 months, n (%)			
0	0	0	0
1	266 (53)	278 (56)	259 (51)
2	198 (40)	198 (40)	216 (42)
3	29 (6)	20 (4)	31 (6)
≥ 4	7 (1)	4 (< 1)	6 (1)
Mean number of relapses in the past 12 months, n (%)	1.6 (0.7)	1.5 (0.6)	1.6 (0.7)

EDSS = Kurtzke Expanded Disability Status Scale; Gd = gadolinium; MS = multiple sclerosis; PegIFN = peginterferon beta-1a; PL = placebo; beta-1a; Q2W = every two weeks; Q4W = every 4 weeks; SD = standard deviation.

[a] Patients who took more than one drug were counted more than once.

Source: Clinical Study Report.[2]

3.2.3 Interventions

Patients received peginterferon beta-1a or matching placebo. Patients randomized to peginterferon beta-1a received 63 mcg on day 1, 94 mcg at week 2, and then either 125 mcg every two weeks or 125 mcg every four weeks. Placebo and peginterferon beta-1a were supplied in pre-filled syringes and self-administered by subcutaneous injection into the thigh, abdomen, or arms.

At the end of 48 weeks, patients in the placebo group were randomly reassigned to peginterferon beta-1a 125 mcg every two or every four weeks until week 96. Patients who were originally assigned to peginterferon beta-1a continued their assigned treatment. After week 48, all patients were aware they were receiving peginterferon beta-1a.

a) Concomitant Medications

Other drug treatments for MS such as chronic immunosuppressant therapy or immunomodulatory treatments (e.g., interferons, glatiramer, natalizumab, cyclophosphamide, methotrexate, azathioprine) were not allowed. Systemic steroid therapy was not allowed except for the protocol-approved treatment for relapse: intravenous methylprednisolone 1,000 mg per day for three or five days. Study treatment dosing was to continue uninterrupted during intravenous methylprednisolone treatment. Seventeen per cent of patients in the group taking peginterferon beta-1a every two weeks and 29% of placebo patients took methylprednisolone during year 1.

To relieve flu-like symptoms for the first 26 weeks in the study, all patients were instructed to take acetaminophen, ibuprofen, naproxen, or other nonsteroidal anti-inflammatory drugs prior to, and for 24 hours following, each study treatment injection.

3.2.4 Outcomes

In the ADVANCE study, the primary end point was annualized relapse rate at the end of the placebo-controlled phase (week 48).

The secondary end points were:

- Number of new or newly enlarging T2 hyperintense lesions at year 1
  - proportion of patients relapsed at year 1
- Disability progression by EDSS at year 1.

The tertiary end points were:

- Clinical end points:
  - Annualized relapse rate over two years
  - Proportion of patients relapsed over two years
  - Disability progression by EDSS over two years
  - Number of relapses requiring intravenous steroid therapy
  - MS-related hospitalizations
  - Disability progression by Multiple Sclerosis Functional Composite (MSFC) at year 1 and over two years
  - Time to sustained progression of disability based on the Paced Auditory Serial Addition Test (PASAT-3)
  - Cognitive changes measured by the Symbol Digit Modalities Test (SDMT)
  - Visual function testing
  - Quality of life measured by MSIS-29, the Short Form (12) Health Survey (SF-12), and the EuroQol 5-Dimensions Questionnaire (EQ-5D).

- MRI end points:
  - Number of new or newly enlarging T2 hyperintense lesions at 24 weeks and over two years
  - Number of new active lesions at 24 weeks, one year, and two years
  - Number of gadolinium-enhancing lesions at 24 weeks, one year, and two years
  - Number of new T1 hypointense lesions at 24 weeks, one year, and two years
  - Volume of T2 hyperintense lesions at 24 weeks, one year, and two years
  - Volume of T1 hypointense lesions at 24 weeks, one year, and two years
  - Volume of gadolinium-enhancing lesions at 24 weeks, one year, and two years
  - Brain atrophy at one year, and two years
  - Magnetization transfer ratio at one year, and two years.

a) No Evidence of Disease Activity, Post Hoc Analysis[3]

No evidence of disease activity (NEDA) was defined as absence of both clinical (no relapses and no onset of 12-week confirmed disability progression over the interval) and MRI (no gadolinium-enhancing lesions and no new or newly enlarging T2 hyperintense lesions) disease activity during the respective time periods. MRI-NEDA was defined as no gadolinium-enhancing lesions at weeks 24 and 48 and no new or newly enlarging T2 lesions at week 48 compared with baseline (for data summarized from baseline to week 48), no gadolinium-enhancing lesions at week 24 and no new or newly enlarging T2 lesions at week 24 compared with baseline (for data summarized from baseline to week 24), and no gadolinium-enhancing lesions at week 48 and no new or newly enlarging T2 lesions at week 48 compared with week 24 or the closest previous visit before week 48 (for data summarized from week 24 to week 48). Clinical-NEDA was defined as no relapses and no onset of 12-week confirmed disability progression over the intervals specified (including 12-week confirmation at week 60). NEDA was not part of the original study analysis plan, but was assessed post hoc and reported in a recent publication.[3]

b) Relapse

"All relapses" included any event suspected of being a relapse by a patient whether or not the event met the criteria for protocol-defined or Independent Neurology Evaluation Committee (INEC)-confirmed relapse. "Protocol-defined relapses" were defined as new or recurrent neurologic symptoms not associated with fever or infection lasting at least 24 hours, with onset more than 30 days after the last relapse, and accompanied by new objective neurological findings upon examination by the examining neurologist. Protocol-defined relapses may or may not have been confirmed by the INEC. INEC-confirmed relapses were protocol-defined relapses that were evaluated by three INEC members and confirmed by a majority vote (two out of three members confirmed the event as an MS relapse). Only INEC-confirmed relapses were included in the primary end point analysis. Annualized relapse rate was calculated as the total number of relapses occurring during year 1 for all patients divided by the total number of patient-years followed in year 1, excluding data obtained after patients switched to alternative MS drugs.[2,22]

c) Disability Progression

EDSS is an ordinal scale used to measure disability in MS. It relies on identification of eight functional systems, plus "other." These are pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. Each functional system is graded separately on a scale of 0 (normal) to either 5 or 6.[28] The EDSS score is a composite ranging from 0 to 10 (in increments of 0.5) that incorporates functional system grades as well as the degree of functional disability and ambulation. Scores from 0 to 4.5 represent normal ambulation, while scores of 5 and above represent progressive loss of ambulatory ability. According to clinical experts in MS consulted by CDR, a sustained change of

1.0 in EDSS is clinically relevant; however, a minimal clinically important difference was not identified in the literature for this outcome.

Disability progression was defined as a minimum change (i.e., at least a 1.0-point increase on the EDSS from a baseline EDSS of 1.0 or higher, or at least a 1.5-point increase on the EDSS from a baseline EDSS of 0) that was present on a scheduled or unscheduled study visit. Disability progression was defined as confirmed when this minimum EDSS change was present on the next study visit occurring 12 weeks after the initial observation. Death due to MS was also counted as disability progression.

d) Multiple Sclerosis Functional Composite Z-Score

The MSFC consists of the following three components:

- Average scores from four trials on the nine-hole peg test (the two trials for each hand are averaged and converted to the reciprocals of the mean times for each hand, then the two reciprocals are averaged)
- Average scores of two timed 25-foot walk trials
- Number of correct answers on the Paced Auditory Serial Addition Test (PASAT-3).

The MSFC composite Z-score is calculated by creating Z-scores for each component of the MSFC and averaging them to create an overall composite score. A positive change in the composite Z-score indicates improvement, and a negative change indicates worsening. A 20% change in scores on timed 25-foot walk trials and the nine-hole peg test, and a 0.5 standard deviation (SD) change on PASAT-3 are considered clinically meaningful.[29] A minimal clinically meaningful change for overall MSFC score has not been reported.

e) Symbol Digit Modalities Test

The SDMT is a screening test for cognitive impairment involving a simple substitution task that normal children and adults can easily perform. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures.[30] No minimal clinically meaningful change in the SDMT was identified.

f) Twelve-Item Short Form Health Survey

This 12-item scale is a generic quality-of-life instrument consisting of 12 items to measure functional health and well-being. The 12 items create two summary scores: the physical component and the mental component scales (PCS and MCS). Higher scores indicate better physical and mental function.

g) EuroQoL 5-Dimensions Questionnaire

The EQ-5D is a generic quality-of-life instrument that may be applied to a wide range of health conditions and treatments.[31,32] 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.[31,32]

The second part is a 20 cm visual analogue scale (EuroQol 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. 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 for this scale, although not specific for MS patients, have ranged from 0.033 to 0.074.[33] No studies specifically validating EQ-5D in patients with MS were identified.

h) Multiple Sclerosis Impact Scale

The MSIS-29 measures 20 physical items and nine psychological items that examine the physical and psychological impact of MS from a patient's perspective. A positive change on this scale represents worsening from baseline and a negative change represents improvement from baseline (the range of values for the scale was not identified in the literature). A minimal clinically important difference (MCID) of 7.5[24,33] to ≥ 8 has been suggested for the physical subscale.[34] Based on the standard error of measurement from the ADVANCE trial, a worsening of 6.25 points has been suggested as the MCID for the psychological subscale.[24] The MCID for the total score has not been established.

3.2.5 Statistical Analysis

a) Sample Size Calculation

The sample size calculation was based on the type I error rate of 0.05 and a dropout rate of 10%. It was assumed that the treatment effect for peginterferon beta-1a would be a 32% reduction from placebo in the year 1 annualized relapse rate. In version 1 of the protocol, a sample size of 420 per treatment group was planned to provide approximately 90%, 87%, and 85% power when the placebo year 1 annualized relapse rate is 0.6, 0.55, or 0.5, respectively. The pooled year 1 annualized relapse rate was monitored over the course of the trial in a blinded fashion, and the placebo year 1 annualized relapse rate was estimated by back-calculating from the pooled annualized relapse rate and the assumed treatment effect. As a result of this monitoring, the sample size was increased from 420 to 500 patients per group in a protocol modification.

b) Statistical Testing

Multiple Testing

A sequential closed testing procedure was used to control the type I error rate. For the primary end point, the peginterferon beta-1a every-two-weeks group was compared with placebo; if this comparison was statistically significant ($P \leq 0.05$), a comparison of the peginterferon beta-1a every-four-weeks group versus placebo could also be performed and considered statistically significant if $P \leq 0.05$. However, if statistical significance was not achieved with the peginterferon beta-1a every-two-weeks group versus placebo, the comparison of the peginterferon beta-1a every-four-weeks group versus placebo was not considered statistically significant, regardless of the *P* value.

Secondary end points were ranked as listed in section 3.2.4 and, for each secondary end point, the comparison of peginterferon beta-1a every two weeks versus placebo was made first, followed by the comparison of peginterferon beta-1a every four weeks versus placebo. In addition, if statistical significance was not achieved for an end point for a particular dose-frequency group, all comparisons for end point(s) of lower rank for that dose-frequency group were considered statistically non-significant.

c) Methods of Analysis

The primary analysis method for the annualized relapse rate was negative binomial regression. As a sensitivity analysis, the Poisson regression method was also used to analyze the primary end point. Logarithmic transformation of the time on study was included as an independent variable in the model

as the "offset" parameter. The model was to include a term for treatment, the baseline relapse rate, age (< 40 years versus ≥ 40 years), and EDSS (< 4 or ≥ 4). Baseline relapse rate was defined as the number of relapses over the three years prior to the day of screening, divided by 3. The rate ratio for each group as compared with placebo was also presented.

For annualized relapse rate at one year, the total number of days on study was defined as the number of days from the date of the first dose to the date of the week 48 visit if subjects stayed on the study for longer than a year. If subjects withdrew from the study or switched to an alternative MS medication prior to one year, the total number of days was defined as the number of days from the date of the first dose to the last date on study, or last date prior to the switch. The unadjusted relapse rate for each treatment group was calculated as the total number of relapses experienced in the group divided by the total number of days in the study for the group, and the ratio multiplied by 365.

Other end points were analyzed as follows:[22]

- Negative binomial regression was used to analyze new or newly enlarging hyperintense lesions on T2-weighted images (adjusted for baseline number of T2 lesions) and new active lesions (adjusted for baseline number of gadolinium-enhancing lesions).
- Multiple logit regression was used to analyze the number of gadolinium-enhancing and new T1-hypointense lesions (adjusted for baseline number of respective lesions).
- Analysis of covariance (ANCOVA) was used to analyze lesion volumes (adjusted for respective baseline lesion volumes) and brain atrophy (adjusted for baseline normal brain volume).
- Cox proportional hazards model was used to analyze time to first clinical relapse (adjusted for baseline EDSS score, age, baseline relapse rate, and baseline gadolinium-enhancing lesions) and time to first disability progression (adjusted for baseline EDSS score and age).
- Comparison between the treated and placebo groups for MSFC Z-score was based on analysis of covariance on rank data, adjusted for MSFC Z-score at baseline.
- Quality-of-life scales were assessed using an ANCOVA model with treatment effect and adjusted for baseline scores.

d) Sensitivity Analyses

Multiple sensitivity analyses were performed on the data from the ADVANCE study. Sensitivity analyses on the primary outcome included the following reanalyses:[2]

- Using the per-protocol population
- Using a Poisson regression model
- Using all relapses regardless whether they met protocol criteria and regardless whether they were confirmed by the INEC
- Using protocol-defined objective relapses recorded on the unscheduled relapse assessment
- Adding baseline gadolinium-enhancing lesion (presence versus absence) as a covariate in the model.

e) Analysis Populations

All efficacy end points were evaluated on the intention-to-treat (ITT) population. In addition, the primary and secondary efficacy end points were analyzed based on the per-protocol population. The ITT population was defined as all patients who were randomized and received at least one dose of study treatment. The per-protocol population was defined as patients from the ITT population without any major protocol deviations (e.g., major inclusion/exclusion criteria violation, study treatment non-compliance, taking prohibited medications). Safety data were analyzed based on the safety population, defined as all patients who received at least one dose of study treatment.

3.3 Patient Disposition

The disposition of patients in the ADVANCE study is presented in Table 6. A total of 1,936 patients were screened for this study but no information was provided regarding reasons for screening failures. A greater proportion of patients randomized to the peginterferon beta-1a every-two-weeks group discontinued the study early in the first year, relative to placebo (14% versus 9%). The most common reason for discontinuation was adverse events. Study withdrawal rates for the peginterferon beta-1a treatment groups were slightly higher during the first 12 weeks of year 1 than in subsequent 12-week periods. Of patients taking peginterferon beta-1a every two weeks who discontinued in the first year, approximately one-third (25 out of 74) discontinued during the first 12 weeks of the study.

TABLE 6: PATIENT DISPOSITION IN ADVANCE, YEAR 1

	Year 1		
	PL	PegIFN Q4W	PegIFN Q2W
Randomized, N	500	501	515
ITT (received ≥ 1 dose), N (%)	500 (100)	500 (> 99)	512 (99)
Per-protocol population, n (%)	482 (96)	486 (97)	497 (97)
Safety population, n (%)	500 (100)	500 (> 99)	512 (99)
Patients completing year 1 study treatment, n (%)	456 (91)	438 (88)	438 (86)
Patients discontinuing study treatment in year 1, n (%)	44 (9)	62 (12)	74 (14)
Adverse event	5 (1)	24 (5)	24 (5)
Protocol-defined disability progression	0	0	0
Lost to follow-up	3 (< 1)	4 (< 1)	2 (< 1)
Consent withdrawn	30 (6)	30 (6)	35 (7)
Investigator decision	0	1 (< 1)	4 (< 1)
Death	2 (< 1)	1 (< 1)	1 (< 1)
Other	4 (< 1)	2 (< 1)	8 (2)

ITT = intention-to-treat; PegIFN = peginterferon beta-1a; PL = placebo; Q2W = every two weeks; Q4W = every 4 weeks.
Source: Clinical Study Report.[2]

3.4 Exposure to Study Treatments

The percentage of study medication taken in year 1 was greater than 99% for all three treatment groups (calculated by using the actual number of injections/number of injections the patient was expected to take, during year 1). The mean number of weeks on study treatment was 46.2, 44.8, and 43.9 in the placebo, peginterferon beta-1a every-four-weeks, and peginterferon beta-1a every-two-weeks arms, respectively.

3.5 Critical Appraisal

3.5.1 Internal Validity

- In the ADVANCE study, demographic characteristics, previous treatment history, and disease characteristics were generally well balanced between treatment groups, but there was a slight imbalance in the mean number of gadolinium-enhancing lesions at baseline. This was adjusted for in a sensitivity analysis of the primary outcome and did not appear to have a substantial impact on the results.[2]
- Blinding is difficult to maintain in a trial with an interferon product because of the common and widely known adverse effects of these agents (e.g., influenza-like illness). As well, it was not stated in the Clinical Study Report whether matching placebo was used during the titration phase; if not, this could have also resulted in some degree of unblinding. Compromised blinding due to these

factors may have particularly affected patient-reported outcomes such as quality-of-life measurements.

- It appears that reasonable procedures were incorporated in the ADVANCE study design to minimize evaluation bias, including use of separate examining neurologists and treating neurologists to increase the likelihood that blinding would be maintained.[22] However, there was potential for biased referral of relapse events because it was the treating neurologist who decided whether an event should be examined by the evaluating neurologist.[26] Sensitivity analyses of relapse events were performed using "all relapses" or "protocol-defined relapses," which were not necessarily adjudicated as relapses by the INEC. The results of these analyses corroborated the results of the primary outcome.
- If patients discontinued the study prior to one year, or took another medication for MS, they were censored at that time point for the calculation of annualized relapse rate (primary outcome). There was a slightly higher proportion of patients in the peginterferon beta-1a every-two-weeks group who discontinued medication in the first year, relative to the placebo group. However, sensitivity analyses performed by the manufacturer (Appendix 4) and the FDA did not contradict the findings of the main analysis of the primary outcome.[2,25]
- The enrolment target was increased during the course of the study to ensure sufficient power based on the accrued relapse rate, but this did not appear to adversely impact the trial's integrity.[25]
- The NEDA results corroborate the direction of the results observed for relapse rate and disability progression, but NEDA was not part of the predefined analysis plan for the ADVANCE study. It was defined post hoc and may therefore be more prone to bias than predefined end points.
- The number of new or newly enlarging T2 hyperintense lesions at year 1 was a secondary outcome and was subject to the hierarchical statistical analysis, but all other MRI outcomes were tertiary outcomes and statistical comparisons for these outcomes were not adjusted for multiplicity.

3.5.2 External Validity

- According to the clinical expert consulted for this review, the population enrolled in this study was similar to a treatment-naive population in Canada that would be eligible for treatment with peginterferon beta-1a. However, less than 3% of the enrolled population was based in North America. There may be some differences in patient populations across geographic regions; for example, there are differences in the treatment approaches in North America compared with other regions, and this was reflected in the higher rate of previous MS treatment in the subgroup of patients from the US.
- The definition of relapse used in the ADVANCE study is reasonable and commonly used in MS trials, according to the clinical expert consulted for this review.
- The protocol for using methylprednisolone to treat relapse is a common procedure in MS studies and reflects current practice in Canada, according to the clinical expert consulted for this review.

3.6 Efficacy

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

The results from the placebo-controlled phase (up to week 48) for the approved dose of peginterferon beta-1a are the focus of this report. A brief summary of the year 2 results can be found in Appendix 4.

3.6.1 No Evidence of Disease Activity Week 0 to Week 48

This outcome was not part of the original study analysis plan, but was assessed post hoc and reported in a recent publication.[3] NEDA was defined as absence of both clinical (no relapses and no onset of 12-week confirmed disability progression over the 48 weeks) and MRI (no gadolinium-enhancing lesions and no new or newly enlarging T2 hyperintense lesions) disease activity; data from patients with complete MRI results during the time interval were used for analysis of MRI disease activity. In the group taking peginterferon beta-1a every two weeks, 158/466 patients (34%) had NEDA compared with 73/484 patients (15%) in the group taking placebo (CDR-calculated relative risk: 2.2 [95% confidence interval (CI), 1.8 to 2.9; *P* < 0.0001]).

3.6.2 Relapse

As summarized in Table 7, there were 90 patients (18%) in the group taking peginterferon beta-1a every two weeks and 142 patients (28%) in the placebo group who experienced a relapse as confirmed by the blinded adjudication committee. The adjusted annualized relapse rate after year 1 for the peginterferon beta-1a every-two-weeks group was 0.256 (95% CI, 0.206 to 0.318) versus 0.397 (95% CI, 0.328, 0.481) for the placebo group (rate ratio: 0.644 [95% CI, 0.500 to 0.831]; *P* = 0.0007).

TABLE 7: NUMBER OF CONFIRMED RELAPSES AND NUMBER OF PATIENTS WITH CONFIRMED RELAPSE IN YEAR 1, ITT

	PL N = 500	PegIFN Q2W N = 512	Statistical Comparison
Number of confirmed relapses, n (%)			
0	358 (72)	422 (82)	
1	110 (22)	71 (14)	
2	26 (5)	13 (3)	
3	5 (1)	5 (< 1)	
≥ 4	1 (< 1)	1 (< 1)	
Total number of INEC-confirmed relapses	181	116	
Total patient-years	445	436	
Number of patients with INEC-confirmed relapse, n (%)	142 (28)	90 (18)	Hazard ratio (95% CI) 0.61 (0.47 to 0.80); *P* = 0.0003[a]
Annualized relapse rate (95% CI)	0.397 (0.328 to 0.481)	0.256 (0.206 to 0.318)	Rate ratio [95% CI] 0.644 [0.500 to 0.831]; *P* = 0.0007)[b]

CI = confidence interval; EDSS = Kurtzke Expanded Disability Status Scale; INEC = Independent Neurology Evaluation Committee; ITT = intention-to-treat; PL = placebo; PegIFN = peginterferon beta-1a; Q2W = every two weeks; vs. = versus.

[a] Based on Cox proportional hazards model, adjusted for baseline EDSS (< 4 vs. ≥ 4), age (< 40 vs. ≥ 40 years), baseline relapse rate, and baseline gadolinium-enhancing lesions (presence vs. absence).

[b] Based on negative binomial regression; adjusted for baseline EDSS (< 4 vs. ≥ 4), baseline relapse rate, and age (< 40 vs. ≥ 40 years).

a) Sensitivity Analyses

The manufacturer performed sensitivity analyses of the primary outcome using different populations, statistical models and definitions of relapse. In general, the results of these analyses were similar to the main analysis for the primary outcome (see Appendix 4 for sensitivity analyses).

3.6.3 Disability Progression and Function

Disability (EDSS) and function (MSFC) data are summarized in Table 8. Progression of disability was defined as an increase of at least 1.0 point on the EDSS from a baseline EDSS ≥ 1.0 sustained for

12 weeks (minimum of 74 days) or an increase of at least 1.5 points on the EDSS from a baseline EDSS of 0 sustained for 12 weeks (minimum of 74 days). Thirty-one patients (6%) in the peginterferon beta-1a every-two-weeks group had disability progression, compared with 50 patients (10%) in the placebo group (hazard ratio: 0.62 [95% CI, 0.40 to 0.97; *P* = 0.04]).

The mean increase (worsening) in EDSS score from baseline was 0.01 (SD ± 0.61) for the peginterferon beta-1a every-two-weeks group, compared with 0.06 (SD ± 0.67) for the placebo group.

For the MSFC Z-scores, there was a mean increase (indicating improvement) from baseline of 0.041 (SD ± 0.39) in patients taking peginterferon beta-1a and a mean decrease of 0.023 (SD ± 0.66) in patients taking placebo (*P* = 0.22). Baseline scores were not reported.

3.6.4 Quality of Life

Quality-of-life data are summarized in Table 8. Changes from baseline in quality-of-life scales were small for all treatment groups. There were no statistically significant differences between placebo and peginterferon beta-1a every two weeks in mean changes from baseline on the MSIS-29 physical or psychological scores, SF-12 physical or mental components, EQ-5D index, or EQ-5D VAS score.

3.6.5 Symptoms

Symptoms such as fatigue, pain, or depression were not systematically monitored in the ADVANCE study.

3.6.6 Brain Atrophy

The per cent decreases (SD) in brain volume were similar in the group taking peginterferon beta-1a every two weeks (–0.72 [0.75]) and the placebo group (–0.62% [0.90]). There were no statistically significant differences for this outcome at the end of year 1 (Table 8).

3.6.7 Brain Lesions

Data on brain lesions are summarized in Table 8. The number of new or newly enlarging T2 hyperintense lesions from baseline to week 48 was lower in the group taking peginterferon beta-1a every two weeks compared with the group taking placebo (mean 4.1 versus 13.3, respectively; *P* < 0.0001). The number of patients developing at least one new or newly enlarging T2 hyperintense lesion from baseline to week 48 was lower in the group taking peginterferon beta-1a every two weeks compared with the group taking placebo (59% versus 81%; *P* value not reported).

The number of new active lesions from baseline to week 48 was lower in the group taking peginterferon beta-1a every two weeks compared with the group taking placebo (mean 4.1 versus 13.4, respectively; *P* < 0.0001).

The number of gadolinium-enhancing lesions detected at year 1 was lower in the group taking peginterferon beta-1a every two weeks compared with the group taking placebo (mean 0.2 versus 1.4, respectively; *P* < 0.0001).

3.6.8 Cognition

Data on cognition are summarized in Table 8. The mean change (± SD) in SDMT score from baseline to the end of year 1 was 2.4 (± 11.6) in the group taking peginterferon beta-1a every two weeks compared with 1.2 (± 12.8) in the placebo group, and the difference was not statistically significant (*P* = 0.23).

3.6.9 Productivity and Medication Acceptance

These outcomes were not reported in the ADVANCE study.

TABLE 8: KEY EFFICACY OUTCOMES

	Results at 1 Year		
	PL N = 500	PegIFN Q2W N = 512	Statistical Comparison
NEDA	73/484 (15%)	158/466 (34%)	CDR-calculated relative risk (95% CI): 2.2 (1.8 to 2.9); $P < 0.0001$
Annualized relapse rate (95% CI)	0.397 (0.328 to 0.481)	0.256 (0.206 to 0.318)	Rate ratio (95% CI) 0.644 (0.500 to 0.831); $P = 0.0007$[a]
Disability progression sustained for 12 weeks, n (%)	50 (10)	31 (6)	Hazard ratio (95% CI) 0.62 (0.40 to 0.97); $P = 0.04$[b]
Mean EDSS score at baseline; mean change (SD); n	2.44; +0.06 (0.67); n = 442	2.46; +0.01 (0.61); n = 456	NR
MSFC score at baseline; mean change (SD)	baseline NR –0.023 (0.66)	baseline NR 0.041 (0.39)	$P = 0.22$
SDMT score at baseline; mean change (SD); n	48.7; +1.2 (12.8); n = 499	47.5; +2.4 (11.6); n = 510	$P = 0.23$
QoL: MSIS-29 physical score at baseline, mean change (SD); n	21.5; +1.2 (13.6); n = 497	21.5; +0.1 (13.7); n = 511	$P = 0.15$[h]
QoL: MSIS-29 psychological score at baseline, mean change (SD); n	27.8; -2.2 (16.7) n = 497	27.6; -2.1 (17.5); n = 509	$P = 0.95$[h]
QoL: SF-12 mental score at baseline, mean change (SD); n	47.1; +0.01 (9.2); n = 496	47.7; –0.3 (9.6); n = 511	$P = 0.99$
QoL: SF-12 physical score at baseline, mean change (SD); n	43.9; –0.01 (8.1); n = 496	43.9; +0.4 (7.5); n = 511	$P = 0.42$
QoL: EQ-5D score at baseline, mean change (SD); n	0.74; –0.01 (0.2); n = 498	0.73; 0 (0.2); n = 511	$P = 0.32$
QoL: EQ-5D VAS at baseline, mean change (SD); n	73.0; +0.4 (18.3); n = 495	73.0; +2.1 (16.9); n = 506	$P = 0.12$
MRI: new or newly enlarging T2 hyperintense lesions, mean (SD); n	13.3 (19.5); n = 476	4.1 (8.6); n = 457	$P < 0.0001$[c]
MRI: number of patients developing new or newly enlarging T2 hyperintense lesions, n/N (%)	385/476 (81%)	270/457 (59%)	NR
MRI: volume of T2 hyperintense lesions at baseline – cm^3;	11.0; +0.8 (2.5);	9.8; –0.3 (1.7);	$P < 0.0001$[d]

	Results at 1 Year		
	PL N = 500	PegIFN Q2W N = 512	Statistical Comparison
mean change, (SD); n	n = 476	n = 457	
MRI: new active lesions, mean (SD); n	13.4 (19.7); n = 476	4.1 (8.6); n = 457	$P < 0.0001$[e]
MRI: Gd-enhancing lesions, mean (SD); n	1.4 (3.7); n = 477	0.2 (1.0); n = 457	$P < 0.0001$[f]
Whole brain volume percentage change from baseline (SD); n	–0.62 (0.90); n = 476	–0.72 (0.75); n = 457	$P = 0.08$[g]

CDR = CADTH Common Drug Review; CI = confidence interval; EDSS = Kurtzke Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions Questionnaire; Gd = gadolinium; MSFC = Multiple Sclerosis Functional Composite; MRI = magnetic resonance imaging; MSIS = Multiple Sclerosis Impact Scale; NEDA = no evidence of disease activity; NR = not reported; PegIFN = peginterferon beta-1a; PL = placebo; Q2W = every two weeks; QoL = quality of life; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SF-12 = Short Form (12) Health Survey; VAS = visual analogue scale.
[a] Based on negative binomial regression; adjusted for baseline EDSS (< 4 vs. ≥ 4), baseline relapse rate, and age (< 40 vs. ≥ 40 years).
[b] Progression of disability is defined as at least a 1.0-point increase on the EDSS from a baseline EDSS of ≥ 1.0 sustained for 12 weeks (minimum of 74 days) or at least a 1.5-point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks (minimum of 74 days).
[c] *P* value based on negative binomial regression, adjusted for baseline number of T2 lesions.
[d] *P* value based on analysis of covariance on ranked data, adjusted for baseline T2 lesion volume.
[e] *P* value based on negative binomial regression, adjusted for baseline number of gadolinium lesions.
[f] *P* value based on multiple logit regression, adjusted for baseline number of gadolinium-enhancing lesions.
[g] *P* value based on analysis of covariance, adjusted for baseline normal brain volume.
[h] *P* value based on analysis of covariance model, adjusted for the baseline MSIS-29 score.
Note: population size for analyses are PL N = 500 and PegIFN N = 512, unless otherwise stated.
Source: Clinical Study Report.[2]

3.6 Harms

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

3.6.1 Adverse Events

A total of 94% of patients in the peginterferon beta-1a every-two-weeks group experienced an adverse event compared with 83% of patients in the placebo group. The most common adverse events (incidence ≥ 10% in either the peginterferon beta-1a every-two-weeks group or every-four-weeks group) that occurred at an incidence ≥ 2% higher in either peginterferon beta-1a group compared with in the placebo group, included injection-site reactions (injection-site erythema, injection-site pain, injection-site pruritus), flu-like symptoms (including influenza-like illness, pyrexia, myalgia, chills, asthenia, arthralgia, and headache). Injection-site reactions (e.g., injection-site erythema, pain, pruritus, or edema) were reported by 66% of patients who received peginterferon beta-1a every two weeks compared with 11% of patients receiving placebo.

The incidence of severe events was numerically higher in the peginterferon beta-1a every-two-weeks group compared with placebo for: headache (5% peginterferon beta-1a versus 2% placebo), myalgia (2% peginterferon beta-1a versus < 1% placebo), influenza-like illness (5% peginterferon beta-1a versus < 1% placebo), pyrexia (3% peginterferon beta-1a versus 0% placebo) and injection-site erythema (2% peginterferon beta-1a versus 0% placebo).

3.6.2 Serious Adverse Events

In year 1, a total of 11% taking peginterferon beta-1a every two weeks and 15% of patients taking placebo experienced a serious adverse event. No serious adverse events occurred more than once in the group taking peginterferon beta-1a every two weeks, except for the event classified as MS relapse.

3.6.3 Withdrawals Due to Adverse Events

A total of 25 patients (5%) taking peginterferon beta-1a every two weeks withdrew treatment because of adverse events, compared with 7 (1%) in the placebo group during year 1. The most common adverse event leading to treatment withdrawal included influenza-like illness, injection-site erythema and pyrexia.

3.6.4 Mortality

In year 1, one patient died taking peginterferon beta-1a (cause unknown) and two patients died taking placebo (one cause unknown, one subarachnoid hemorrhage).

3.6.5 Other Notable Harms

The incidence of seizures, suicidal ideation, and depression was similar in the peginterferon beta-1a every-two-weeks group compared with the placebo group at year 1. The incidence of cardiovascular events was similar in the group taking peginterferon beta-1a every two weeks and the placebo group.

a) Hematology

Decreases in white blood cell counts of less than 3.0×10^9/L were observed in 7% of patients receiving peginterferon beta-1a every two weeks and in 1% receiving placebo. The incidence of decreases in lymphocyte counts ($< 0.8 \times 10^9$/L) was slightly higher in patients taking peginterferon beta-1a every two weeks (5%) compared with placebo (3%). The incidence of decreases in neutrophils ($\leq 1.5 \times 10^9$/L) was higher in patients taking peginterferon beta-1a every two weeks compared with placebo. The incidence of red blood cell decreases ($\leq 3.3 \times 10^9$/L) was similar between the two groups. The incidence of low platelets ($\leq 100 \times 10^9$/L) was slightly higher in patients taking peginterferon beta-1a every two weeks (n = 3[< 1%]) compared with placebo (n = 6 [1%]).

b) Antibody Tests

Binding antibodies to interferon beta-1a were observed in 8% of patients taking peginterferon beta-1a every two weeks and in 3% of patients taking placebo. The incidence of neutralizing antibodies to interferon beta-1a was < 1% in both groups. The incidence of anti–polyethylene glycol antibodies was similar in the two groups (5% to 6%). Positive antibody findings in the placebo group may be attributable to false-positive assays.

TABLE 9: HARMS; SAFETY POPULATION, YEAR 1

	Placebo (N = 500)	PegIFN Every 2 Weeks (N = 512)
AEs		
Patients with > 0 AEs, n (%)	417 (83)	481 (94)
Most common AEs[a]		
Injection-site erythema	33 (7)	315 (62)
Influenza-like illness	63 (13)	239 (47)
Pyrexia	76 (15)	228 (45)
Headache	165 (33)	224 (44)
Myalgia	30 (6)	97 (19)

	Placebo (N = 500)	PegIFN Every 2 Weeks (N = 512)
Chills	23 (5)	88 (17)
Injection-site pain	15 (3)	77 (15)
Asthenia	38 (8)	68 (13)
Injection-site pruritus	6 (1)	68 (13)
Arthralgia	35 (7)	57 (11)
Nausea	31 (6)	44 (9)
Body temperature increased	14 (3)	31 (6)
Vomiting	11 (2)	26 (5)
Pain	16 (3)	25 (5)
ALT increased	13 (3)	29 (6)
Hyperthermia	6 (1)	21 (4)
Injection-site edema	0	15 (3)
AST increased	8 (2)	18 (4)
Pruritus	6 (1)	19 (4)
GGT increased	7 (1)	15 (3)
Injection-site warmth	0	16 (3)
Injection-site rash	0	8 (2)
SAEs		
Patients with > 0 SAEs, n (%)	76 (15)	55 (11)
Deaths, n (%)	1 (< 1)	1 (< 1)
Most common SAEs, n (%)		
Multiple sclerosis relapse	57 (11)	34 (7)
Dengue fever	0	1 (< 1)
Intervertebral disc disorder	0	1 (< 1)
Multiple sclerosis	0	1 (< 1)
Paraparesis	0	1 (< 1)
Pneumonia	1 (< 1)	0
Urinary tract infection	1 (< 1)	0
WDAEs		
AEs leading to treatment withdrawal, n (%)	7 (1)	25 (5)
Most common reasons		
Influenza-like illness	0	4 (< 1)
Injection-site erythema	0	3 (< 1)
Pyrexia	0	4 (< 1)
Suicidal ideation	1 (< 1)	2 (< 1)
Depression	0	1 (< 1)
Fatigue	0	2 (< 1)
Headache	0	1 (< 1)
Transaminases increased	0	2 (< 1)
Notable harms		
Seizures	1 (< 1)	3 (< 1)
Suicidal ideation	1 (< 1)	2 (< 1)
Depression	20 (4)	21 (4)

	Placebo (N = 500)	PegIFN Every 2 Weeks (N = 512)
Cardiovascular disorders	16 (3)	18 (4)
Antibody tests positive at any time, n (%)		
IFN binding antibody positive	13/481 (3)	38/483 (8)
IFN neutralizing antibody positive	2/489 (< 1)	4/491 (< 1)
Anti-PEG antibody positive	24/456 (5)	30/474 (6)
Hematologic abnormalities		
WBC total < 3.0×10^9/L, n (%)	5 (1)	34 (7)
Lymphocytes < 0.8×10^9/L, n (%)	17 (3)	27 (5)
Neutrophils ≤ 1.5×10^9/L, n (%)	15 (3)	45 (9)
Red blood cells ≤ 3.3×10^9/L, n (%)	1 (< 1)	2 (< 1)
Platelets ≤ 100×10^9/L, n (%)	3 (< 1)	6 (1)
ALT > 5 × ULN, n (%)	5 (1)	12 (2)
AST > 5 × ULN, n (%)	3 (< 1)	3 (< 1)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; IFN = interferon; PEG = polyethylene glycol; PegIFN = peginterferon beta-1a; SAE = serious adverse event; ULN = upper limit of normal; WBC = white blood cell; WDAE = withdrawal due to adverse event.

[a] Adverse events at least 2% higher in incidence for PegIFN every two weeks compared with placebo.

Source: Clinical Study Report.[2]

4. DISCUSSION

4.1 Summary of Available Evidence

One randomized, double-blind, parallel-group study met the inclusion criteria for this review. The ADVANCE study (N = 1,516) compared peginterferon beta-1a 125 mcg every two weeks or every four weeks versus placebo. The study was placebo-controlled up to week 48. Most of the enrolled patients were treatment-naive (83%).

The ADVANCE study was generally of adequate design to ensure internal validity. The absence of trials that directly compare peginterferon beta-1a to other first-line agents used in the treatment of RRMS, particularly interferon beta-1a, represents a limitation. As well, the length of the placebo-controlled period was 48 weeks, and this is a short period of time to assess benefit and harm relative to the expected period of time for which patients would use the drug.

4.2 Interpretation of Results

4.2.1 Efficacy

The primary end point of the ADVANCE study was achieved: peginterferon beta-1 given every two weeks was superior to placebo with respect to the annualized relapse rate and the results of the sensitivity analyses of the primary end point were congruent with the main analysis (Appendix 4, Table 11). It is noteworthy that the study incorporated detailed procedures for adjudication of relapse. These were designed to reduce bias and heterogeneity in outcome assessment across the many countries represented in the ADVANCE trial. Many earlier MS drug trials did not use such rigorous procedures, therefore, the relapse results reported in the ADVANCE trial may not be comparable with other older studies.

Another outcome of interest for this systematic review identified in collaboration with a clinical expert was NEDA. The NEDA results corroborate the direction of the results observed for relapse rate and disability progression, but NEDA was not part of the predefined analysis plan for the ADVANCE study, possibly because it was developed relatively recently. Because of the post hoc nature of the analysis for NEDA, it may be more prone to bias than the other efficacy outcomes.

Studies investigating the correlation of MRI outcomes and clinical outcomes suggest that conventional MRI may be a useful tool for predicting disease relapses and disability progression for patients with RRMS, although the correlations between MRI outcomes and clinical outcomes are not consistent across studies (Appendix 5: Validity of Outcome Measures). The MRI results from ADVANCE provide evidence for consistency of treatment effect, with most comparisons showing less deterioration in the peginterferon beta-1a every-two-weeks group compared with placebo. This included the outcome of new or newly enlarged T2 lesions, which is an important clinical outcome according to the expert consulted for this review.

While there was improvement seen in the outcome of disability sustained for 12 weeks based on EDSS, the mean EDSS change from baseline for peginterferon beta-1a every two weeks compared with placebo was similar. Sustained disability progression at six months is considered a more rigorous assessment of disability progression. This outcome was not found in the ADVANCE Clinical Study Report; however, the manufacturer indicated as part of its feedback on the draft CDR reports that a post hoc analysis was conducted for this outcome. It found that peginterferon beta-1 every two weeks significantly reduced the risk of progression by 54% compared with placebo (hazard ratio: 0.46, 95% CI

0.26 to 0.81; *P* = 0.0069).[35] There were no statistically significant improvements observed for measures of cognition (SDMT), function (MSFC) or quality of life (MSIS-29, EQ-5D, SF-12) for peginterferon beta-1a every two weeks compared with placebo. The study was not powered to detect differences in these tertiary outcomes; hence, it is not clear whether peginterferon beta-1a lacks effect on these outcomes, or whether the observed results reflect type II error. The ADVANCE trial was shorter than some of the other interferon beta-1a trials, which were 24 and 36 months long (see Appendix 7, Table 18). It is therefore possible that the ADVANCE trial may not have been long enough to achieve substantive differences in these outcomes.

In 2013, CADTH published a Therapeutic Review of RRMS.[11] Peginterferon beta-1a was not included in this report. The report concluded that subcutaneous interferons, glatiramer acetate, and teriflunomide had activity similar to one another. The ADVANCE study was placebo-controlled and therefore did not resolve the uncertainties regarding the relative effectiveness of peginterferon beta-1a among the first-line agents used to treat RRMS. The manufacturer performed a network meta-analysis (NMA) comparing peginterferon beta-1a 125 mcg every two weeks with other first-line injectable treatments for RRMS (Appendix 7: Summary of Indirect Comparisons). Relapse rate and disability progression at three and six months were assessed in the NMA. There were no statistically significant differences observed between peginterferon beta-1a and the other treatments for these efficacy outcomes, but there was evidence of significant heterogeneity across the 16 included trials. This was reflected in the variable definitions used for relapse across studies, and the wide range of relapse rates across the placebo treatment groups of included studies. There was no adjustment in the NMA for these sources of heterogeneity; therefore, the results of the analysis should be interpreted with caution.

A recent Cochrane NMA also compared the relative effectiveness and harms of 15 immunomodulators and immunosuppressants for RRMS.[36] It included one study with peginterferon beta-1a (ADVANCE) and 38 other studies (N = 25,113). Alemtuzumab, natalizumab, and fingolimod emerged as the best choices for preventing clinical relapses in this analysis. Relative to the other agents, non-pegylated interferons and peginterferon beta-1a ranked near the bottom from the combined perspective of treatment benefit and acceptability. However, similar to the manufacturer-submitted NMA, there were no statistically significant differences in relapse rate between peginterferon beta-1a and other agents typically considered as first-line (interferons, glatiramer acetate). There were also no significant differences with respect to treatment discontinuation due to adverse events, although these estimates were associated with a large degree of imprecision (i.e., wide 95% CIs).

According to the patient input received by CADTH for this review (Appendix 1), the impact of MS on quality of life, physical activity, work performance, social well-being, and caregivers were key issues for patients. Several instruments were used in the ADVANCE study to quantify the effects on quality of life (MSIS-29, SF-12, and EQ-5D), function (MSFC), and cognition (SDMT), but there was no improvement observed in these outcomes in patients taking peginterferon beta-1a compared with placebo. Social well-being and impact on caregivers were not measured in the ADVANCE trial.

The patient group providing input also indicated that reduced frequency of administration resulting in simplifying compliance would be a desirable feature of a new treatment for MS. It is not known if the reduction in dose frequency for peginterferon beta-1a relative to non-pegylated interferons would result in improved compliance because this was not measured in the ADVANCE study. The clinical expert consulted for this review indicated that dosing every two weeks may be marginally more convenient than weekly intramuscular injections with interferon beta-1a; however, this was not perceived to be a great advantage in the absence of a clear improvement in efficacy or tolerability.

The results of the second year of the ADVANCE study, in which all patients on placebo were re-randomized to active treatment, suggest that efficacy is maintained among patients that continue with peginterferon beta-1a 125 mcg every two weeks past the first year of treatment. There were no new safety events during the second year of ADVANCE. Patients who completed the ADVANCE study could enrol in a blinded extension study (Appendix 6). An interim analysis of the ATTAIN study was performed after 21 patients had completed 48 weeks of treatment with peginterferon beta-1a every two weeks (i.e., a total of 144 weeks after ADVANCE baseline). Adverse events were similar to those in ADVANCE. No conclusions could be made regarding efficacy outcomes due to the small number of patients having completed the 48 weeks.

4.2.2 Harms

Input received from patient groups for this review indicated that adverse effects of concern include flu-like symptoms, injection-site reactions, flushing, and headaches. The most common adverse events in the ADVANCE trial included injection-site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection-site pain, asthenia, injection-site pruritus and arthralgia. Influenza-like illness and injection-site erythema were the most common reasons for withdrawal due to adverse events and occurred infrequently (< 1% of patients taking peginterferon beta-1a every two weeks). Serious adverse events occurred at a low frequency and there were none that occurred at a frequency greater than once, except for events related to MS.

The NMA submitted by the manufacturer did not include statistical comparisons of the incidence of harms between treatments, but the authors concluded that the incidence of harms was similar to non-pegylated interferons.

The results of antibody testing at one year showed a small increase in rate of positive results in the group taking peginterferon beta-1a every two weeks compared with placebo. The proportion of patients with positive tests was low (< 8%) and the clinical significance of these findings is uncertain.

In the ATTAIN study, the adverse events observed were similar to those observed in the ADVANCE study.

4.2.3 Potential Place in Therapy[1]

Based on the ADVANCE trial and submitted NMA, peginterferon beta-1a does not appear to provide any benefits over other first-line treatments with respect to effectiveness in terms of relapse rate, disability progression and MRI outcomes, and safety, particularly with respect to skin reactions and flu-like symptoms. Dosing every two weeks could be perceived as more convenient than daily oral, once weekly intramuscular peginterferon beta-1a, or three times per week subcutaneous interferon beta-1a. Peginterferon beta-1a could therefore be appropriate as a first-line DMT option for early RRMS patients. It would also be a reasonable consideration for patients having tolerability issues on another non-interferon first-line DMT. It would not be an appropriate choice for patients failing another first-line DMT due to ongoing disease activity, and is unlikely to be of benefit for patients who do not tolerate interferons in general.

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

5. CONCLUSIONS

In one randomized, double-blind, placebo-controlled study (ADVANCE), in patients with relapsing-remitting MS, peginterferon beta-1a was associated with a lower rate of relapse and delayed time to disability progression (sustained for 12 weeks) and less worsening of some MRI outcomes relative to placebo over 48 weeks. Measures of quality of life, function, and cognition did not show any differences between peginterferon beta-1a and placebo. There were no direct comparative trials comparing peginterferon beta-1a with other treatments used for RRMS. Evidence from two NMAs (one submitted by the manufacturer and the other identified in the literature) suggested there was no significant difference in efficacy between peginterferon beta-1a and other treatments for MS; however, caution is required in interpreting these findings due to the limitations of the analysis, particularly the heterogeneity across included trials.

With respect to safety, the results of the ADVANCE study indicate that peginterferon beta-1a is associated with adverse events, such as injection-site reactions and influenza-like symptoms, that occur commonly with other interferon products for MS. The comparative safety of peginterferon beta-1a and other treatments for RRMS is uncertain due to the lack of head-to-head trials and because the manufacturer-submitted NMA did not attempt indirect comparisons for outcomes related to harms.

APPENDIX 1: PATIENT INPUT SUMMARY

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

1. Brief Description of Patient Group Supplying Input

One patient group supplied input for this submission.

The Multiple Sclerosis Society of Canada (MS Society) is a national voluntary organization that supports research and services related to multiple sclerosis (MS) for patients with MS and their families. The MS Society received unrestricted educational grants between 2014 and 2015 from the following pharmaceutical companies: Bayer, Biogen Idec, EMD Serono, Novartis, Pfizer, Genzyme, Allergan, and Teva Neuroscience. All contributions are subject to policies that prevent any control or influence by the donor on the Society's decision-making.

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

2. Condition-Related Information

Information for this submission was obtained from an online survey (posted from July 8 to 17, 2015) targeted at MS patients and their caregivers. The survey respondents (N = 158) included patients (90%) and caregivers (10%); the majority were women (76%). The length of diagnosis varied from two to more than 20 years, with ages ranging from 20 to more than 70 years. Respondents indicated their various types of MS, which included clinically isolated syndrome (2%), relapsing-remitting (71%), secondary-progressive (15%), primary-progressive (10%), or unknown (2%). In addition to the online survey, information for this submission was obtained using publicly available information.

MS is an unpredictable, disabling disease of the central nervous system (CNS) that is characterized by a wide variety of symptoms depending on what areas of the CNS are affected. Symptoms can include fatigue, MS-related pain, cognition problems, bladder problems, numbness or weakness in one or more body parts, tingling, heat intolerance, problems with balance, dizziness, difficulties walking, sexual dysfunction, tremor, spasticity, and difficulties swallowing and/or speaking. There is tremendous variation in disease severity and symptomatology, with no one-size-fits-all therapy. Quality of life for MS patients and their caregivers is often negatively affected due to the aforementioned symptoms, especially when patients suffer from moderate to severe disease. Physical and cognitive limitations can interfere with employment, education, family commitments, interpersonal relationships, and physical, social, and recreational activities. In addition, treatment regimens can also affect a patient's quality of life through resulting side effects and administration issues. As stated by one respondent, *"MS sucks. It costs the patients, their families, and their caregivers enormous amounts of money to cope with the disease. Many people living with MS must work fewer hours or leave the work force entirely because of symptoms and the negative social effects of chronic illness."*

Caregivers also suffer both emotionally and physically due to the burden of MS. They are often required to administer disease-modifying therapies (DMTs), help their loved one travel to appointments with the medical teams, and provide regular assistance, which can subsequently impact their daily routines and lifestyles. An example can be found in this quote by a caregiver, *"She is always tired; my time is dedicated to be there for her; she is stable but not independent."*

3. Current Therapy-Related Information

Patients living with relapsing-remitting MS (RRMS) and secondary-progressive MS with relapses have seven "first-line" treatment options available. These include the interferon beta-1a and beta-1b injectables (Avonex, Rebif, Betaseron, Extavia), Copaxone injectable, and two oral options (Tecfidera and Aubagio). Subsequent treatment is available for those patients who do not respond to initial treatment and include oral Gilenya and two infusion options (Tysabri and Lemtrada). Of the respondents to the online survey, 63% were currently taking DMTs, with Tecfidera (24%), Avonex (22%), and Copaxone (18%) being the top three. While most (81%) of those on DMTs had been on therapy for five years or less, the remainder had been taking therapy for over six years. Although more than half of the respondents claimed DMT effectiveness, less than half reported that all of their needs were met.

Common side effects from taking DMTs included flu-like symptoms, injection-site reactions, flushing, and headaches. These side effects were reported to interfere with regular physical activity, work performance, and attending social events.

Most respondents reported no challenge in accessing their therapy. Some patients experienced challenges with cost, accessibility, and administration of therapy, with one person indicating that, *"The stress of having to worry about how you are going to pay for the cost of these drugs can take a toll on people. It's also a hassle to have to frequently go through the reimbursement approval process."* When choosing an MS therapy, the majority of patients desired the ability to maintain physical activity, remain at work, meet family commitments, have the ability to travel, and have the ability to start a family. Complex administration routines associated with therapies along with the side effects are undesirable; hence patients want more treatment options. With regard to longer times between administrations, one individual stated, *"It provides an option for those with compliance issues as the dosing is less often or, as in my case, it would mean I would not be impacted by the side effects of the medication as often."* In general, patients are seeking more options for their treatment: *"There are some therapies that do not work for everyone. The more options there are, the better it is and the more likely people living with MS will find something that works."*

4. Expectations About Plegridy

The majority of respondents had no experience with Plegridy, nor had they been informed about it by their physician. In patients informed by their physicians, the main highlight included the reduced dosing schedule. As such, MS patients indicated that this initial therapy would provide a treatment option with a more convenient dosing regimen, thus enhancing their quality of life and potentially increasing adherence. Patients with MS acknowledged that the side effects of Plegridy would not be expected to differ from the other interferon beta-1a medications currently available, and would also be similarly priced.

MS patients with Plegridy experience (2% of respondents) did not provide any details regarding their experience.

APPENDIX 2: LITERATURE SEARCH STRATEGY

For more details on literature search methods, see section 2.2: Methods.

Database Search

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:	July 26, 2015
Alerts:	Bi-weekly search updates until project completion
Study types:	No study design filters used
Limits:	Date limit: none Language limit: none Conference abstracts: excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.nm	Name of Substance Word
.ot	Original title
.pt	Publication type
.rn	CAS registry number
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Plegridy* or "BIIB 017" or BIIB017 or UNII-I8309403R0).ti,ab,ot,hw,rn,nm.
2	((Polyethyleneglycol or polyethylene glycol) adj3 (beta1* or beta 1 or beta 1a* or "B1 or B1a" or "B1 a" or "B 1 a")).ti,ab,ot,hw,rn,nm.
3	(peg* adj3 (interferon* or ifn) adj3 (beta* or B1 or B1a or B1 a or B 1 a)).ti,ab,ot,hw,nm.
4	(peginterferon* adj3 (beta1* or beta 1 or beta 1a* or "B1" or "B1a" or "B1 a" or "B 1 a")).ti,ab,ot,hw,nm.
5	(1211327-92-2 or "1211327922").rn,nm.

MULTI-DATABASE STRATEGY	
#	Searches
6	or/1-5
7	6 use pmez
8	*peginterferon beta1a/
9	(Plegridy* or "BIIB 017" or BIIB017 or UNII-I8309403R0).ti,ab.
10	((Polyethyleneglycol or polyethylene glycol) adj3 (beta1* or beta 1 or beta 1a* or "B1 or B1a" or "B1 a" or "B 1 a")).ti,ab.
11	(peg* adj3 (interferon* or ifn) adj3 (beta* or B1 or B1a or B1 a or B 1 a)).ti,ab.
12	(peginterferon* adj3 (beta1* or beta 1 or beta 1a* or "B1" or "B1a" or "B1 a" or "B 1 a")).ti,ab.
13	or/8-13
14	13 not conference abstract.pt.
15	14 use oemezd
16	7 or 15
17	remove duplicates from 16

OTHER DATABASES	
PubMed	Same MeSH, keywords and limits as per MEDLINE search, with appropriate syntax used. PubMed is searched for citations not found in MEDLINE.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Date of Search:	July 2015
Keywords:	Multiple sclerosis, peginterferon beta-1a, and Plegridy
Limits:	No date limit, English only

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine), were searched:

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Clinical study report: 105MS302. A dose-frequency blinded, multicenter, extension study to determine the long-term safety and efficacy of pegylated interferon beta-1a (BIIB017) in subjects with relapsing multiple sclerosis [CONFIDENTIAL internal manufacturer's report]. Cambridge (MA): Biogen Idec Inc.; 2013 Apr 23.	Inappropriate comparator
Seddighzadeh A, Hung S, Selmaj K, Cui Y, Liu S, Sperling B, et al. Single-use autoinjector for peginterferon-beta1a treatment of relapsing-remitting multiple sclerosis: safety, tolerability and patient evaluation data from the Phase IIIb ATTAIN study. Expert Opin Drug Deliv. 2014 Nov;11 (11):1713-20.	Inappropriate Comparator
Hu X, Seddighzadeh A, Stecher S, Zhu Y, Goyal J, Matson M, et al. Pharmacokinetics, pharmacodynamics, and safety of peginterferon beta-1a in subjects with normal or impaired renal function. J Clin Pharmacol [Internet]. 2015 Feb [cited 2015 Jul 29];55 (2):179-88. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4303928/pdf/jcph0055-0179.pdf	Inappropriate outcomes
Hu X, Cui Y, White J, Zhu Y, Deykin A, Nestorov I, et al. Pharmacokinetics and pharmacodynamics of peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis in the randomized ADVANCE study. Br J Clin Pharmacol [Internet]. 2015 Mar [cited 2015 Jul 29];79 (3):514-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4345961/	Inappropriate outcomes

APPENDIX 4: ADDITIONAL OUTCOME DATA (ADVANCE STUDY)

TABLE 10: NUMBER OF REPORTED RELAPSES AT YEAR 1

	PL	PegIFN Q2W
All relapses	213	132
Protocol-defined relapses	204	126
INEC-confirmed relapses	181	116

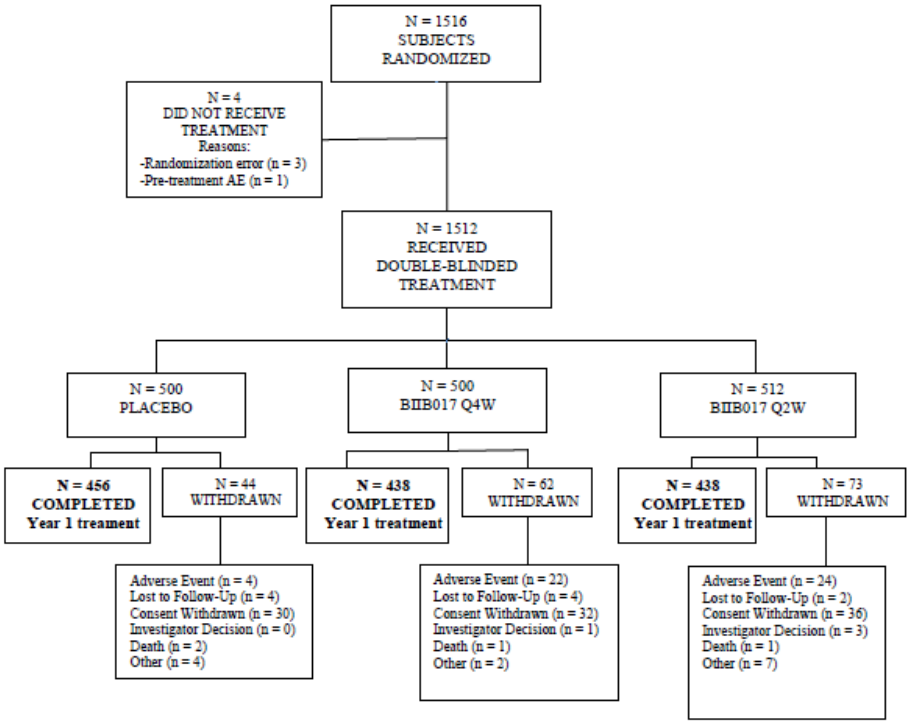
INEC = Independent Neurology Evaluation Committee; PegIFN = peginterferon beta-1a; PL = placebo; Q2W = every two weeks.

TABLE 11: SENSITIVITY ANALYSES OF PRIMARY OUTCOME OF THE ADVANCE STUDY, YEAR 1

	Adjusted Relapse Rate (95% CI)		
	PL N = 500	PegIFN Q2W N = 512	Statistical Comparison
Relapse rate using INEC-confirmed relapses in the per-protocol population	0.397 (0.327 to 0.482)	0.248 (0.199 to 0.310)	0.625 (0.482 to 0.809), *P* = 0.004
Relapse rate using INEC-confirmed relapses and a Poisson regression model[a]	0.394 (0.324 to 0.480)	0.255 (0.203 to 0.320)	0.646 (0.497 to 0.841), *P* = 0.011
Relapse rate using all relapses	0.469 (0.392 to 0.560)	0.293 (0.239 to 0.359)	0.625 (0.493 to 0.792), *P* < 0.0001
Relapse rate using protocol-defined relapses (but not INEC-confirmed)	0.456 (0.379 to 0.547)	0.282 (0.229, 0.348)	0.620 (0.485 to 0.792), *P* = 0.0001
Relapse rate using INEC-confirmed relapses, adjusted for baseline Gd-enhancing lesions	0.407 (0.335 to 0.493)	0.269 (0.217 to 0.334)	0.662 (0.514 to 0.854), *P* = 0.0015

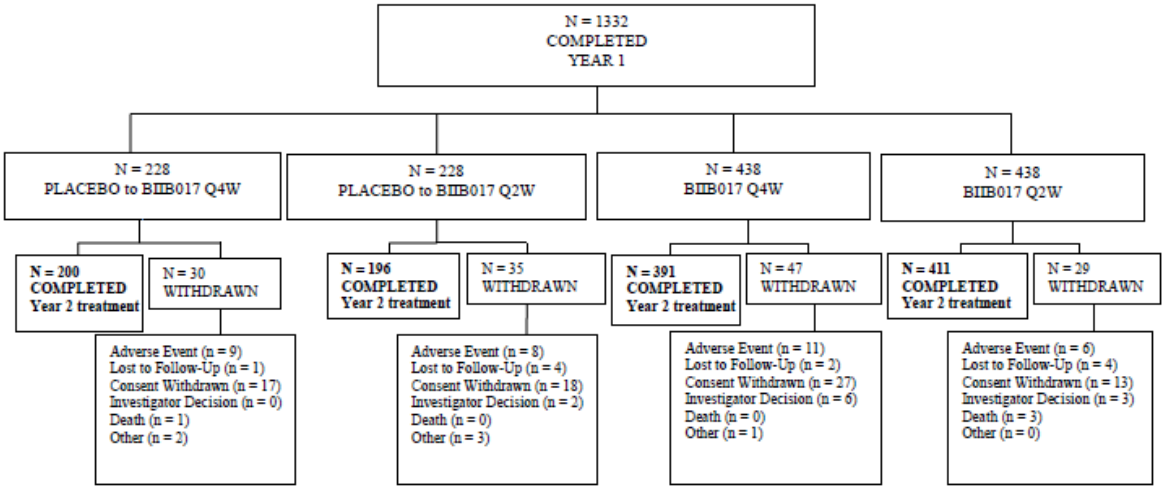
CI = confidence interval; INEC = Independent Neurology Evaluation Committee; EDSS = Kurtzke Expanded Disability Status Scale; Gd = gadolinium; PegIFN = peginterferon beta-1a; PL = placebo; Q2W = every two weeks.
[a] Based on Poisson regression.
Note: unless indicated, all analyses were based on negative binomial regression, with adjustment for baseline EDSS (< 4 versus ≥ 4), baseline relapse rate, age (< 40 years versus ≥ 40 years).

FIGURE 2: PATIENT DISPOSITION IN YEAR 1 OF ADVANCE



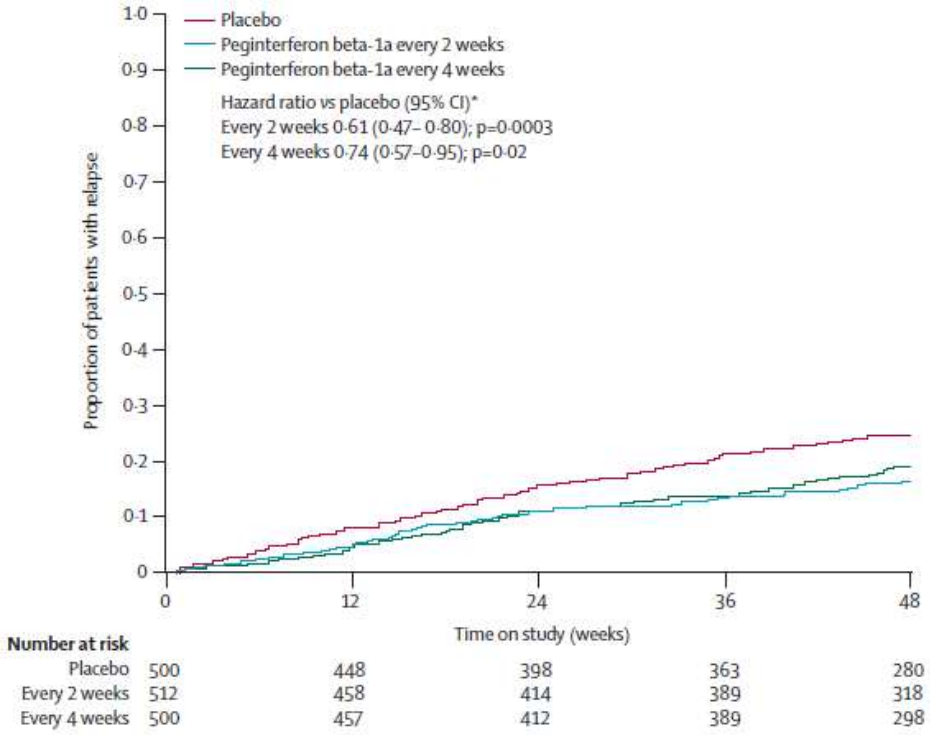
Q2W = every two weeks; Q4W = every four weeks.
Source: Clinical Study Report.[2]

FIGURE 3: PATIENT DISPOSITION IN YEAR 2 OF ADVANCE



Q2W = every two weeks; Q4W = every four weeks.
Source: Clinical Study Report.[2]

FIGURE 4: TIME TO FIRST RELAPSE IN YEAR 1 OF ADVANCE



CI = confidence interval; vs = versus.
Reprinted from Lancet Neurol. 2014 Jul;13(7):661, with permission from Elsevier.
Source: Calabresi et al.[22]

Data from Year 2 of the ADVANCE Study

After week 48 of the ADVANCE study, patients taking placebo were re-randomized to peginterferon beta-1a every two weeks or every four weeks. The following section summarizes selected data from the second year of the study.

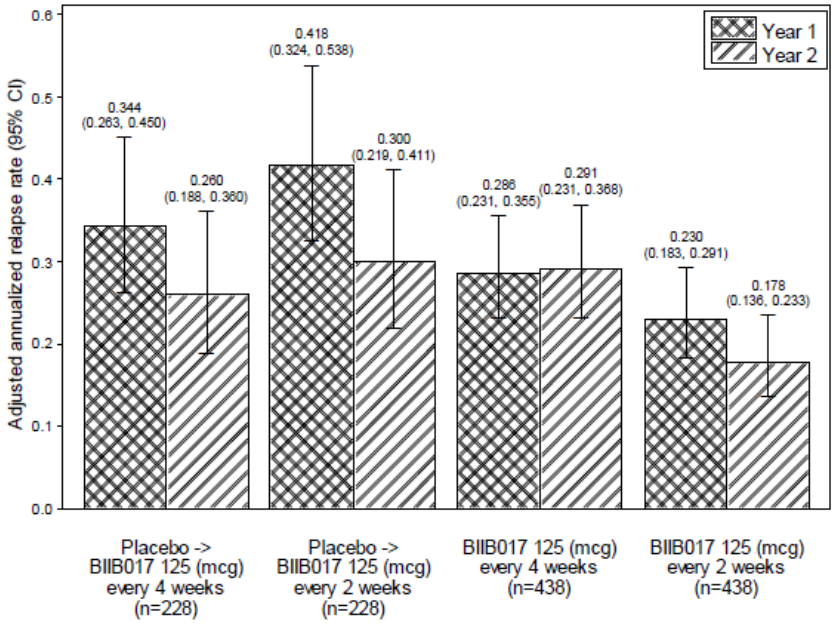
TABLE 12: PATIENT DISPOSITION IN ADVANCE, YEAR 2

	ADVANCE Year 2			
	PL→ PegIFN Q4W	PL→ PegIFN Q2W	PegIFN Q4W	PegIFN Q2W
Patients dosed in year 2, n (%)	228	228	438	438
Patients completing year 2, n (%)	200 (88)	196 (86)	391 (89)	411 (94)
Patients discontinuing in year 2, n (%)	28 (12)	32 (14)	47 (11)	27 (6)
Adverse event	9 (4)	8 (4)	9 (2)	7 (2)
Protocol-defined disability progression	0	0	0	0
Lost to follow-up	1 (< 1)	4 (2)	2 (< 1)	1 (< 1)
Consent withdrawn	14 (6)	17 (7)	28 (6)	12 (3)
Investigator decision	0	1 (< 1)	5 (1)	3 (< 1)
Death	0	0	0	3 (< 1)
Other	4 (2)	2 (< 1)	3 (< 1)	1 (< 1)

PegIFN = peginterferon beta-1a; PL = placebo; Q2W = every two weeks; Q4W = every 4 weeks.

In the group of patients randomized to peginterferon beta-1a every two weeks at the beginning of the study, 411 out of 512 patients (80%) were still taking their originally assigned treatment after two years. During the first year, 24 out of 512 patients (5%) randomized to peginterferon beta-1a every two weeks at the beginning of the study discontinued due to an adverse event. During the second year, seven out of 512 (1%) discontinued due to an adverse event. Five of the patients taking peginterferon beta-1a during the first year discontinued due to influenza-like illness.

FIGURE 5: SUMMARY OF ANNUALIZED RELAPSE RATE (INEC-CONFIRMED RELAPSES) BY STUDY YEAR— ITT POPULATION DOSED IN YEAR 2



CI = confidence interval; INEC = Independent Neurology Evaluation Committee; ITT = intention-to-treat.
Note: The rates in the above figure are the adjusted annualized relapse rates based on negative binomial regression, adjusted for baseline EDSS (< 4 versus ≥ 4), baseline relapse rate and age (< 40 years versus ≥ 40 years).
Source: Clinical Study Report.[2]

Figure 5 provides a summary of the annualized relapse rates during the second year of the ADVANCE study and divides the group that originally received placebo into two groups. For patients who received peginterferon beta-1a every two weeks in year 1 and year 2, the annualized relapse rate in year 2 was 0.178 (95% confidence interval [CI], 0.136 to 0.233), and in year 1 it was 0.230 (95% CI, 0.183 to 0.291). The adjusted annualized relapse rate for patients who received peginterferon beta-1a every two weeks over two years was 0.203 (95% CI, 0.167 to 0.247)

For patients who received placebo in year 1 and were re-randomized to peginterferon beta-1a every two weeks in year 2, the adjusted annualized relapse rate at year 1 was 0.418 (95% CI, 0.324 to 0.538). The adjusted annualized relapse rate at year 2 was 0.300 (95% CI, 0.219 to 0.411) in the placebo to peginterferon beta-1a every-two-weeks group.

The results of the second year of the ADVANCE study suggest that the relapse rate does not increase during the second year of treatment with peginterferon beta-1a. There were no new adverse event findings during the second year of ADVANCE. The main limitation with the data from the second year of the ADVANCE trial is that there was no appropriate control group; therefore, conclusions based on these data must be made cautiously.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Objective

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

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

Findings

Kurtzke Expanded Disability Status Scale

The EDSS is an ordinal scale used to measure disability in multiple sclerosis (MS). It relies on identification of eight functional systems (FS) (plus "other"). These are pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. Each functional system is graded separately on a scale of 0 (normal) to either 5 or 6.[37] 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 13). 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 to 7 points, indicating that patients do not stay equally long at each step of the scale. There are many criticisms of the EDSS, including the fact that it has only modest intra-rater reliability, it has low reproducibility, it is a poor assessment of upper limb and cognitive function, and it lacks linearity.[38,39] Other limitations 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 previous reviews, a sustained change of 1.0 in EDSS is considered clinically relevant.

TABLE 13: SCORING OF KURTZKE EXPANDED DISABILITY STATUS SCALE

	Normal Neurological Exam (All Grade 0 in Functional Systems; Cerebral Grade 1 Acceptable)
1.0	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; others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2; others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3; others 0 or 1), or mild disability in three or four FS (three/four FS grade 2; others 0 or 1), though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2, or two FS grade 3, or five FS grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relative severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 metres

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

FS = functional system; MS = multiple sclerosis.
Source: Potter et al.[37]

European Quality-of-Life Scale

The EQ-5D is a generic quality-of-life instrument that may be applied to a wide range of health conditions and treatments.[31,32] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged 12 years or older) 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.[31,32] The second part is a 20 cm visual analogue scale (EuroQol 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 for this scale, although not specific for MS patients, have ranged from 0.033 to 0.074.[33] The clinically important differences were derived from patients with a variety of chronic and acute conditions, including rheumatoid arthritis, osteoarthritis, irritable bowel syndrome, and acute myocardial infarction.[40,41]

Validity

No studies specifically validating EQ-5D in patients with MS were identified. As with any generic health-related quality-of-life 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 over-estimated utility scores compared with a disease-specific measure.[40]

Minimal Clinically Important Difference

The EQ-5D MCID for people with MS is estimated to range from 0.050 to 0.084.[42] The MCID is higher for patients with more severe disability than patients with mild to moderate disability.[42]

Multiple Sclerosis Functional Composite

The MSFC is a measure of disability developed in 1994 by a task force convened by the US National Multiple Sclerosis Society.[43,44] The MSFC assesses different clinical dimensions: arm (9HPT = time to insert nine pegs into holes and remove them), leg (T25FW = time to walk 25 feet) and cognition (Paced Auditory Serial Addition Test [PASAT-3] = number of correct additions). The raw scores for each item are transformed into Z-scores to achieve a common metric in SD units. A Z-score represents the number of SD units a patient's test result is higher ($Z > 0$) or lower ($Z < 0$) than the average test result ($Z = 0$) of the reference population. To create the Z-scores for each component of the composite, the mean and SD of the test results at the baseline visit for all patients in a study are used as the values for the reference population. The Z-score is calculated by subtracting the mean of the reference population from the test result and then dividing by the SD of the reference population. For T25FW and 9HPT, a higher test result means the patient worsened from baseline. For PASAT-3, a higher test result means the patient improved from baseline. To ensure that all measures align 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.[43-45] Psychometric properties and MCID in MS patients are provided below.

Test–Retest Reliability
Intra-class coefficients (ICC) of 0.96 to 0.98 have been reported for the inter-rater ICC and intra-rater ICC, respectively.[29]

Convergent Validity (Correlation With Kurtzke Expanded Disability Status Scale)
A study by Ozakbas et al. (N = 38) found a significant correlation between the EDSS and MSFC.[38] Another study found that the MSFC and EDSS are moderately correlated (r = –0.41 to –0.83).[29] In looking at individual components, the EDSS had the lowest correlation (r = 0.31) with PASAT-3, and the authors suggested this might confirm the observation of poor assessment of cognitive function by EDSS. The strongest correlation was between EDSS and T25FW (r = 0.84) followed by 9HPT (r = 0.51), which was only moderately correlated, consistent with the observation of poor assessment of upper limb function by EDSS.[38]

Minimal Clinically Important Difference
A 20% change in scores on T25FW and 9HPT, and a 0.5 SD change on PASAT-3 are considered clinically meaningful.[29] A clinically meaningful value for overall MSFC score has not been reported.

Twelve-Item Short Form Health Survey
The SF-12 is a multi-item generic health-related quality-of-life questionnaire that was developed from the SF-36.[46] It has been used in clinical trials to study the impact of chronic disease on health-related quality of life but can be used for patients of any age, with any disease, and for any treatment, since it involves general health concepts.[47] The SF-12 is composed of the physical component summary score and the mental component summary score, which measure the physical and psychological burden of disease, respectively.[46] Scores range between 0 and 100, with higher scores indicating better health-related quality of life.[46]

Like the SF-36, the SF-12 measures eight individual health domains: general health (which measures the patient's perception of their overall health), vitality (whereby fatigue and energy levels are assessed), bodily pain (which measures both the frequency of pain and how much pain interferes with normal functioning), social functioning (which measures how much a patient's illness affects social functioning), physical functioning (extent to which daily life is affected), role-physical (which measures limitations in roles due to problems with physical health), mental health (measures psychological distress), and role-emotional (which assesses role limitation due to emotional issues).[47] The 12 items that make up the SF-12 are derived from the eight domains and include the following:

- General health, one item
- Vitality, one item
- Bodily pain, one item
- Social functioning, one item
- Physical functioning, two items
- Role-physical, two items
- Mental health, two items
- Role-emotional, two items.[47]

The SF-12 has been shown to have 90% of the variance of the full SF-36.[48] Moderate reliability for the SF-12 was obtained in one study whereby generic quality-of-life assessments were compared with MS-specific quality-of-life assessments (MSIS-29 and Patient-Determined Disease Steps [PDSS]) in patients with various types of MS.[46] In this study, the physical and mental components of the SF-12 were strongly correlated with the physical and mental components of the MSIS-29, respectively. This provides further evidence regarding the validity of the SF-12 in patients with MS.[46]

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

Magnetic Resonance Imaging Outcomes

MRI techniques play an important role in the diagnosis of MS; in addition, they are valuable in monitoring treatment response and predicting disease progression. However, the correlation between the burden of lesions observed on MRI scans and the clinical manifestations of the disease remains controversial.[49-51]

Conventional MRI outcomes such as new and enlarging T2 hyperintense lesion count, T2 hyperintense lesion volume, and gadolinium-enhancing lesions are widely used to monitor treatment effects in clinical trials of MS.[52] Their roles as a surrogate for clinical outcomes such as relapses and disability progression in relapsing-remitting MS have been investigated in previous research. Findings from systematic reviews and large randomized controlled trials reporting the correlations between the treatment effect on relapses and disability progression and the treatment effect on MRI lesions are presented in Table 14. 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 14: SUMMARY OF CORRELATIONS BETWEEN MRI OUTCOMES AND CLINICAL OUTCOMES

	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
Sormani 2013[53]	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 arm and in the control arm REL effect: ratio between the relapse rate in the experimental arm and in the control arm 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[54]	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 arm and in control arm. REL effect: ratio between the annualized relapse rate in the experimental arm and in the control arm. DIS effect: ratio between % of patients with disability progression (≥ 1 point on EDSS at month 3) in experimental and control arm 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 predicted by MRI active lesions.	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[52]	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 reduced the number of new T2 lesions by 60% over 2 years, and reduced the number of relapses by 30%. The 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[55]	Patients in natural-course studies or who were treated with placebo or observed in the pre-treatment phase of controlled clinical trials 77% of the patients had RRMS; 23% had secondary-progressive MS. Follow-up: 6 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 progression; EDSS = Kurtzke Expanded Disability Status Scale; Gd = gadolinium; MRI = magnetic resonance imaging; MS = multiple sclerosis; OR = odds ratio; PTE = proportion of treatment effect; RCT = randomized controlled trial; REL = relapse; RR = relative risk; RRMS = relapsing-remitting multiple sclerosis; vs. = versus.

Multiple Sclerosis Impact Scale

The MSIS-29 is a patient-reported measure comprising 29 questions measuring the physical (questions 1 to 20) and psychological (questions 21 to 29) impact of MS. The two stem questions are, "In the past two weeks, how much has your MS limited your ability to . . ." and, "In the past two weeks, how much have you been bothered by . . ." The response options for each item in the scale are: not at all, a little, moderately, quite a bit, and extremely.[56] Among the physical items, concepts of balance, gripping, movement, stiffness, and spasm are captured, while the psychological items include social/leisure activities, work, mental fatigue, anxiety, and confidence. High total or subscale scores indicate greater disease impact, while a negative change on either of the subscales indicates improvement.[56]

This scale has been studied extensively and validated in a variety of settings (e.g., hospital- and community-based)[57,58] and has been shown to be psychometrically robust. Initial testing demonstrated adequate test–retest reliability[56] and construct validity has been substantiated against predicted correlations with other outcome measures, such as quality of life[56] and change in EDSS scores.[57] It has been shown to be responsive,[56] and an MCID of 7.5[24,33] to 8.0 or higher has been suggested for the physical subscale.[34] A worsening of 6.25 points has been suggested as the MCID for the psychological subscale based on the standard error of measurement in the ADVANCE trial.[24] The MCID for the total score has not been established.

Symbol Digit Modalities Test

Cognitive impairment is a significant potential consequence of MS. The Symbol Digit Modalities Test (SDMT) is a screening test for cognitive impairment that takes little time to administer and score.[30] Like the PASAT-3, the SDMT measures processing speed, which tends to decline with MS progression.[30] In addition, the SDMT and PASAT-3 are similar in terms of practice effect and reliability when performed at one-week intervals in patients with MS; however, the SDMT is superior in its sensitivity when discriminating between healthy controls and patients with MS.[30] It is suggested that this test would be an acceptable complementary test when examining cognitive impairment in patients with MS.[30]

No MCID was identified for SDMT in patients with MS.

Conclusion

With respect to the reliability and validity of the instruments used in the ADVANCE trial:

- MSFC shows good construct validity and is moderately correlated with EDSS.
- The reliability and validity of EQ-5D have not been determined specifically for MS patients.
- The SF-12 has moderate reliability when compared with the MSIS-29 and Patient-Determined Disease Steps in patients with MS. In addition, there was good correlation between the physical and mental SF-12 scores and those of MSIS-29.
- The SDMT is a reliable screening test for cognitive impairment in patients with MS and would be best administered as a complementary test to the PASAT.

No MCID information specific to MS was identified for EDSS, SF-12, or SDMT. A 20% change in scores on the T25FW and 9HPT, and a 0.5 SD change on PASAT-3 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 for predicting disease relapses and disability progression for patients with RRMS; however, the correlations between MRI outcomes and clinical outcomes were not consistent across studies.

APPENDIX 6: SUMMARY OF EXTENSION STUDY (ATTAIN)

1. Objective

To summarize the results from an interim assessment of the ATTAIN study,[59] which is an ongoing, global, multi-centre, parallel-group, dose frequency–blinded study that includes patients who have completed 96 weeks of the ADVANCE study. The aim of this extension study is to determine the long-term tolerability, safety, and outcomes of pegylated interferon (peginterferon beta-1a administered at 125 mcg once every two weeks for up to two additional years. The following summary is based on unpublished data from the Clinical Study Report.

2. Findings

Study Design

Patients with relapsing-remitting multiple sclerosis who participated and completed study treatment through week 96 of the ADVANCE study were eligible to enter the ATTAIN extension study. The primary objective was to determine the long-term safety and tolerability of peginterferon beta-1a 125 mcg once every two weeks; the secondary objective was to assess the efficacy outcomes related to the aforementioned treatment. A total of 517 patients from 101 sites in 24 countries had enrolled in the extension study as of the cut-off date for this interim analysis. Year 1 information consisted of data from day 1 through week 48 (i.e., 144 weeks from ADVANCE baseline), while year 2 data were obtained from week 48 through week 96 (i.e., 192 weeks from ADVANCE baseline). The total follow-up was two years and one month (an additional four weeks were added for follow-up). Patients in group 1 were administered peginterferon beta-1a 125 mcg once every two weeks, while patients in group 2 were administered peginterferon beta-1a 125 mcg once every four weeks, alternating between placebo and peginterferon injections every two weeks. This extension study did not randomize patients to the treatment groups as they received the same treatment they had while participating in the ADVANCE study.

Dose frequency was blinded and there was also rater-blinding (which referred to the fact that different study personnel were assigned to treat patients and conduct efficacy assessments). Protocol-defined relapses were not assessed by an Independent Neurology Evaluation Committee in this extension study. Rescue medication was available for those patients who experienced relapse or disease progression. In addition, patients switching to an alternate multiple sclerosis (MS) treatment discontinued the peginterferon treatment regimen but remained in the study for 24 weeks on a modified evaluation schedule in order for investigators to obtain as much follow-up data as possible.

Assessment

The assessment of safety and tolerability of peginterferon beta-1a 125 mcg once every two weeks was the primary objective of the ATTAIN study, with observations of MS efficacy outcomes being the secondary objective. Clinic visits occurred every 12 weeks up to week 96 and, if necessary, an unscheduled relapse assessment visit occurred within 72 hours of any new neurological symptoms that suggested relapse.

The clinical assessments used to evaluate the long-term safety profile of peginterferon beta-1a 125 mcg once every two weeks included the following:

- Adverse events (AEs)
- Serious adverse events

- The Beck Depression Inventory-II, which was used to assess the severity of depressive symptoms along two dimensions, cognitive affective and somatic, with higher scores indicating greater severity of symptoms (scores ranging from 0 to 63).

The MS outcomes that were assessed over the two-year period included the following:

- Annualized relapse rate
- Proportion of patients who relapsed (with relapse defined as new or recurrent neurologic symptoms lasting for at least 24 hours)
- Number of relapses requiring intravenous steroid use
- Number of MS-related hospitalizations
- Progression of disability as measured by the Kurtzke Expanded Disability Status Scale
- Cognitive changes measured by the Symbol Digit Modalities Test
- Patient-reported outcomes (Short Form [12] Health Survey [SF-12], EuroQol 5-Dimensions Questionnaire [EQ-5D], Multiple Sclerosis Impact Scale [MSIS]).

Results

The total number of patients entering the ATTAIN study was 517; however, those who received dosing every four weeks are not reported in this summary (n = 253). Therefore, 264 patients in total received peginterferon beta-1a 125 mcg once every two weeks: 92 patients originally randomized to placebo in ADVANCE, and 172 patients originally randomized to peginterferon beta-1a 125 mcg. Of these patients, 261 were continuing treatment at the cut-off point of this interim analysis, while 4% (n = 11) discontinued treatment. The main reasons for discontinuation included consent withdrawal (3%) and AEs (1%). The mean exposure to peginterferon beta-1a 125 mcg was 22.3 weeks (standard deviation [SD] of 16.2 weeks), with a minimum of two weeks and a maximum of 80 weeks. Only one patient at data cut-off had exposure to another MS medication (methotrexate). Most other patients had received at least one dose of other concomitant medications, the most common of which included acetaminophen (47%), ibuprofen (21%), and methylprednisolone (9%).

Safety

Out of the 203 patients in the safety population, 70 were from the original placebo group of ADVANCE, and 133 were from the original peginterferon beta-1a 125 mcg once every-two-weeks group. In the two aforementioned groups, 77% and 78% of patients, respectively, experienced AEs, with AEs remaining almost unchanged in incidence and type when compared with the ADVANCE study. The most common AEs included injection-site erythema (41%), influenza-like illness (34%), pyrexia (24%), and headache (23%), with the majority of AEs reported as mild or moderate in severity. Ten per cent (n = 21) of AEs were perceived as severe in patients receiving the two-week regimen. Of note, the incidence of MS relapse in patients receiving peginterferon every two weeks was 7%.

Serious adverse events occurred in 4% of patients originally randomized to placebo in ADVANCE, , and in 3% in the group originally randomized to peginterferon beta-1a 125 mcg once every two weeks, with MS relapse occurring at an incidence rate of 2% when these groups were combined. Of the injection-site reactions, most were considered mild to moderate; however, one patient in the two-week-regimen groups did experience severe injection-site pruritus. Cardiovascular disorders were reported by 4% (n = 8) of patients receiving the two-week regimen; the majority of cardiovascular events were reported by two individuals (< 1%). No hepatic disorders, autoimmune disorders, or seizures were reported by the cut-off date. The incidence of depression, suicidal ideation, and suicide attempt (according to the Beck Depression Inventory-II) decreased steadily through week 48. Two patients (3%) receiving the two-week

regimen were positive for interferon beta-1a antibodies; however, no patients were positive for neutralizing antibodies to interferon beta-1a. Withdrawals due to AEs were minimal at approximately 1%, and there were no deaths reported by the cut-off date. Detailed harms data are presented in Table 15.

TABLE 15: HARMS IN THE ATTAIN EXTENSION STUDY

	PegIFN 125 mcg[a]
Safety population, n (%)	N = 203
AEs, n (%)	158 (78)
AEs occurring in ≥ 5% of patients[b]	
Injection-site erythema	83 (41)
Influenza-like illness	69 (34)
Pyrexia	49 (24)
Headache	46 (23)
Myalgia	23 (11)
MS relapse	15 (7)
Chills	19 (9)
Asthenia	11 (5)
Injection-site pain	16 (8)
Arthralgia	13 (6)
Fatigue	12 (6)
Nasopharyngitis	13 (6)
Back pain	11 (5)
Pain in extremity	14 (7)
Injection-site pruritus	12 (6)
Depression, suicidal ideation, and suicide attempt, BDI-II > 18[c]	
Baseline, n (%)	37 (18)
Day 1	40 (20)
Week 12	13 (6)
Week 24	12 (6)
Week 36	7 (3)
Week 48	0
SAEs, n (%)	7 (3)
WDAEs, n (%)	2 (< 1)

AE = adverse event; BDI-II = Beck Depression Inventory-II; MSIS = Multiple Sclerosis Impact Scale; PegIFN = peginterferon beta-1a; SAE = serious adverse event; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SF-12 = Short Form (12) Health Survey; WDAE = withdrawal due to adverse event.
Note: For patients who switched to alternative MS medications, data after switch and 14 days after last dose of study treatment are excluded.
[a] Only reported PegIFN beta-1a 125 mcg dosing of once every two weeks, not every four weeks.
[b] Combined all patients taking PegIFN beta-1a 125 mcg once every two weeks.
[c] N and percentage of patients with > 18 BDI-II score; higher scores indicate greater depression severity (range from 0 to 63).

Multiple Sclerosis Efficacy Outcomes

While MS efficacy outcomes were assessed, only 46 patients in total (including those from both the two- and four-week regimens) had received at least 48 weeks of peginterferon beta-1a 125 mcg treatment; therefore, meaningful conclusions could not be deciphered from this interim analysis. There is a suggestion of improvement in clinical outcomes and magnetic resonance imaging measures in patients receiving the two-week regimen, with numerical improvements in annualized relapse rate, time to

relapse, disability progression, and magnetic resonance imaging measures. Detailed MS efficacy outcome data are presented in Table 16.

TABLE 16: MULTIPLE SCLEROSIS EFFICACY OUTCOMES FOR THE ATTAIN EXTENSION STUDY

	PegIFN 125 mcg[a] Once Every Two Weeks
Sustained disability progression[b]	
ITT population, n (%)	N = 261
Patients who progressed, n (%)	16 (6)
Relapse and relapse rates	
Patients with relapse at year 1, n (%)	
0	247 (95)
1	12 (5)
2	1 (< 1)
3	0
≥ 4	1 (< 1)
Adjusted annualized relapse rate[c] (95% CI)	0.203 (0.116 to 0.355)
Annualized relapse rate requiring IV steroid use (95% CI)[d]	0.166 (0.097 to 0.284)
Hospitalizations	
MS-related hospitalizations, n (%)	
0	257 (98)
1	4 (2)
Annualized rate of MS-related hospitalizations (95% CI)	0.039 (0.011 to 0.139)
Cognitive function[e]	
Baseline mean SDMT	51.853
Mean decrease in SDMT at 24 weeks	0.171
MRI outcomes[f]	
New or newly enlarging T2 lesions, mean (SD)	1.1 (2.67)
Number Gd-enhancing lesions	
Baseline mean number	0.3
n/N (%) Week 48 mean number	2/18 (11.1%) 0.1
New T1 hypointense lesions	
Week 48, n/N (%)	2/18 (11.1)
Week 48, mean number of lesions	0.2
Brain atrophy	
N	17
Mean change from ATTAIN baseline (%)	–0.29
Patient-reported outcomes	
MSIS-29	
Baseline mean physical score	21.235
Week 48 mean increase	0.595
Baseline mean psychological score	22.769
Week 48 mean decrease	1.944
SF-12	

	PegIFN 125 mcg[a] Once Every Two Weeks
Baseline mean mental score	48.925
Week 24 mean decrease	1.386
Baseline mean physical score	44.581
Week 24 mean increase	0.454
EQ-5D index	
Baseline mean	0.76
Week 24 mean decrease	0.02

CI = confidence interval; EDSS = Kurtzke Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions Questionnaire; Gd = gadolinium; ITT = intention-to-treat; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS = Multiple Sclerosis Impact Scale; PegIFN = peginterferon beta-1a; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SF-12 = Short Form (12) Health Survey.

[a] Only reported dosing of PegIFN beta-1a 125 mcg once every two weeks, not every four weeks.

[b] As measured by an increase in EDSS. Sustained progression of disability is defined as at least a 1.0-point increase on the EDSS from the Study 301 baseline EDSS of ≥ 1.0, sustained for 24 weeks, or at least a 1.5-point increase on the EDSS from the Study 301 baseline EDSS of 0, sustained for 24 weeks. Estimated proportion of patients with progression and time to progression of up to 144 weeks based on the Kaplan-Meier product limit method. Estimated proportion is not calculated if the number of patients at risk is less than 30.

[c] Based on negative binomial regression, with adjustment for baseline EDSS (< 4 versus ≥ 4), baseline relapse rate, and age (< 40 years versus ≥ 40 years).

[d] Based on Poisson regression for each treatment group.

[e] Measured by SDMT.

[f] A total of only 37 patients had post-baseline MRI data at data cut-off; of these, only 18 were receiving PegIFN every two weeks. Therefore, no meaningful conclusion can be provided.

Limitations

The main limitations inherent in this extension study are the lack of a control group. There were 52 patients who completed the ADVANCE trial (n = 569 completed) who did not continue into the ATTAIN trial (n = 517 entering). It is likely that the patients with the best response and tolerability would have entered ATTAIN and that, over time, attrition would result in progressive enrichment of the study population with the best outcomes on therapy. While MS outcomes were assessed in ATTAIN, no definitive conclusions could be made due to the small number of patients who had actually received 48 weeks of peginterferon beta-1a 125 mcg once every two weeks.

3. Summary

The safety and tolerability results were similar across the ADVANCE and ATTAIN studies. The most common AEs experienced by ≥ 10% of patients included injection-site erythema, influenza-like illness, pyrexia, headache, and myalgia. Serious adverse events were experienced by few patients, with 2% experiencing MS relapse by the cut-off date. No deaths were reported. MS efficacy outcomes were assessed; however, due to the small number of patients who received 48 weeks of peginterferon 125 mcg, definitive conclusions regarding efficacy were not appropriate.

APPENDIX 7: SUMMARY OF INDIRECT COMPARISONS

1. Objective

To provide a summary and critical appraisal of two network meta-analyses (NMAs): one provided by the manufacturer that compared pegylated interferon (peginterferon) beta-1a with other first-line injectable treatments for relapsing-remitting multiple sclerosis (RRMS),[60] and a second that compared all available pharmaceutical treatments for people with RRMS.[36]

2. Methods

One indirect comparison (IDC) was provided by the manufacturer as part of the CADTH Common Drug Review submission package.[60] A search was also performed to identify other potentially relevant IDCs of peginterferon beta-1a 125 mcg once every two weeks with appropriate comparators. While none were initially identified in the comprehensive search, a relevant study was identified from the September 2015 monthly alert. Therefore, both the manufacturer-submitted IDC by Tolley et al.[60] and the other IDC, by Tramacere et al.,[36] were summarized and critically appraised.

3. Description of Indirect Comparisons Identified

Inclusion criteria for the randomized controlled trials (RCTs) included in both the Tolley[60] and Tramacere[36] IDCs are presented in Table 17.

TABLE 17: INCLUSION CRITERIA FOR THE NETWORK META-ANALYSES

Inclusion Criteria	Tolley 2015	Tramacere 2015
Patient population	Patients with RRMS (trials with subgroup consisting of ≥ 80% patients with RRMS were eligible for inclusion)	Adults ≥ 18 years of age with RRMS according to the Poser or McDonald diagnostic criteria
Interventions and comparators	At least one of the following injectable DMTs: • IFN beta-1a • IFN beta-1b • Glatiramer acetate • PegIFN beta-1a.	Included the following irrespective of dose: • IFN beta-1a (Avonex, Rebif) • IFN beta-1b • PegIFN beta-1a • Glatiramer acetate • Natalizumab • Mitoxantrone • Fingolimod • Teriflunomide • Dimethyl fumarate • Alemtuzumab • Daclizumab • Ocrelizumab • Laquinimod • Azathioprine • Immunoglobulins.

Inclusion Criteria	Tolley 2015	Tramacere 2015

Outcomes	**Efficacy outcomes**
	• Annualized relapse rate
	• Disability progression sustained for 3 months
	• Disability progression sustained for 6 months
	
	Harms outcomes
	• Discontinuations
	• AEs (most common AEs in the ADVANCE trial)
		Efficacy outcomes
		Primary outcome:
		• Clinical benefit as measured according to the following:
		  ○ New relapses over 12, 24, and 36 months after randomization or at study end
		  ○ Disability worsening over 24 or 36 months after randomization or at study end
		• Acceptability as measured by discontinuations due to AEs
		Secondary outcome:
		• Total SAEs

Study designs	RCTs ≥ 6 months in duration	RCTs > 6 months in duration

AE = adverse event; DMT = disease-modifying therapy; IFN = interferon; PegIFN = peginterferon beta-1a; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SAE = serious adverse event.
Source: Tolley, 2015[60] and Tramacere, 2015.[36]

Objectives and Rationale of the Indirect Comparisons

The objective of the Tolley[60] IDC was to compare, through NMA, the efficacy of peginterferon beta-1a 125 mcg once every two weeks with other approved first-line injectable disease-modifying therapies (DMTs) (as stated by the Canadian Multiple Sclerosis Working Group).[10] While there have been some past direct comparisons between injectable DMTs for patients with RRMS, this systematic review with NMA was performed due to the paucity of direct comparative evidence for peginterferon beta-1a versus interferon beta-1a, interferon beta-1b, and glatiramer acetate.[60] The objective of the Tramacere[36] IDC was to compare, through NMA, the benefits (measured as the number of new relapses after 12, 24, and 36 months and disability worsening over 24 and 36 months) and acceptability (measured as discontinuations due to adverse events [AEs]) of the interventions listed in Table 17, regardless of their dosing regimens.

The patient population of interest in both IDCs consisted of patients with RRMS.[36,60] While the main efficacy outcomes of interest in the Tolley IDC[60] included the annualized relapse rate, disability progression sustained for three months, and disability progression sustained for six months, the Tramacere IDC[36] focused on the number of new relapses after 12, 24, and 36 months; disability worsening over 24 and 36 months; and discontinuations due to AEs. The secondary outcome for the Tramacere[36] IDC was the total number of serious adverse events (SAEs).

Methods for the Indirect Comparisons

Study Eligibility and Selection Process

Tolley[60]

The eligibility criteria included RCTs of patients with RRMS or a subgroup of ≥ 80% of patients with RRMS who had been treated with at least one of the approved first-line injectable DMTs (interferon beta-1a, interferon beta-1b, glatiramer acetate, or peginterferon beta-1a) for six months or longer. Detailed inclusion criteria were previously presented in Table 17. In 2014, Tolley et al.[60] conducted a systematic search of MEDLINE, Embase, and The Cochrane Library databases (with no date limitation) to ascertain any relevant literature. In addition to supplementary searches in clinical trial registries, they also searched abstracts from the proceedings of relevant US and European scientific meetings held between 2009 and 2013. Exclusion criteria included retrospective studies, case reports, reviews, letters, prognostic studies, and phase 1 or pre-clinical studies.

Based on the aforementioned inclusion and exclusion criteria, first-level selection was performed by reviewing titles and abstracts; however, there was no distinct discussion pertaining to the number of reviewers involved in this step. A subsequent selection of full-text publications was performed by two independent reviewers with any discrepancies reconciled using a third, independent reviewer.

***Tramacere*[36]**

The eligibility criteria included RCTs of patients with RRMS treated with at least one of the aforementioned treatments listed in Table 17 (regardless of dose) for more than six months. Exclusion criteria included: combination treatments, trials that compared only the different doses of the same drug (i.e., no other active treatment or placebo arm), non-pharmacological treatments, and comparisons of over-the-counter drugs. The authors conducted a search of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Groups Trial Register which includes, but is not limited to, the following databases: Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL, LILACS, clinicaltrials.gov, and the World Health Organization International Clinical Trials Registry Platform Search Portal. In addition, they attempted to contact principal authors when warranted, and searched FDA reports.

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

Data Extraction

In both IDCs, data extraction was performed in parallel by two independent reviewers, with any discrepancies reconciled using a third reviewer.[36,60] Baseline patient characteristics, study design, and key efficacy outcomes were extracted.

***Tolley*[60]**

Sixteen trials were included in the IDC. There were nine placebo-controlled trials and seven direct-comparison trials. Trials involved one or more of the following treatments: glatiramer acetate, interferon beta-1a, interferon beta-1b, or peginterferon beta-1a. All trials included patients with RRMS (or a subgroup consisting of at least 80% RRMS patients), with mean ages ranging from 27.4 to 39 years. The majority of patients were female (range 56% to 80%) and Caucasian (range 61.5% to 100%, in studies that reported this characteristic [11 out of 16 trials]). All but four included trials enrolled more than 100 patients per treatment group. Most trials reported similar baseline mean disease duration (range 2.9 to 6.7 years), while two trials enrolled patients with median disease duration of 0.9 years and mean duration of 1.4 years, and the European and Canadian glatiramer acetate trial reported mean disease duration of approximately 8 years. All trials reported either baseline mean or median Kurtzke Expanded Disability Status Scale (EDSS) scores (range 1.9 to 3.3). Out of the 16 included trials, only seven reported either the mean or median number of relapses in the year prior to the start of the trial. Detailed baseline characteristics and demographics are provided in Table 18.

***Tramacere*[36]**

Thirty-nine studies published between 1987 and 2014 involving a total of 25,113 patients with RRMS were included in the IDC. Of the included trials, 24 (60%) were placebo-controlled and 15 (40%) were head-to-head trials. The median follow-up was 24 months; 12 studies had a 12-month follow-up, 25 studies had a 24-month follow-up, and two studies had a 36-month follow-up. Ages in the included studies ranged from 13 years (the majority of studies specified that patients were at least 18 years of age) to 65 years. Mean disease duration ranged from 4 to 11 years; however, few studies reported this, or reported only the median disease duration.

TABLE 18: OVERVIEW OF STUDIES INCLUDED IN THE TOLLEY NETWORK META-ANALYSIS[60] AND/OR TRAMACERE[36]

Trial, Year	Included In	Trial Duration (Months)	Treatment	Sample Size	Age in Years, Mean (SD)	Duration of Disease in Years, Mean (SD)	EDSS Baseline Score, Mean (SD)	No. of Relapses One Year Prior to Baseline, Mean (SD)
Placebo-Controlled Trials (Alphabetical Order According to Brand Name)								
Teriflunomide								
TEMSO, 2011	Tramacere[36]	24	Teriflunomide 14 mg OD Teriflunomide 7 mg OD PL OD	359 366 363	18 to 55[a]	9 (NR)	2.7 (NR)	NR
TOWER, 2014	Tramacere[36]	12	Teriflunomide 14 mg OD Teriflunomide 7 mg OD PL OD	372 408 389	18 to 55[a]	8 (NR)	2.7 (NR)	NR
IFN beta-1a								
MSCRG	Tolley[60] Tramacere[36]	24	IFN beta-1a 30 mcg QW PL QW	158 143	36.7 36.9	6.6 (NR) 6.4 (NR)	2.4 (0.8) 2.3 (0.8)	NR NR
Azathioprine[b]								
Goodkin, 1991[b]	Tramacere[36]	24	Azathioprine 3.0 mg/kg OD PL OD	30 29	18 to 65[a]	6 (NR)	3.5 (NR)	NR
IFN beta-1b								
IFNB MS, 1993	Tolley[60] Tramacere[36]	60	IFN beta-1b 250 mcg EOD IFN beta-1b 50 mcg EOD PL EOD	124 125 123	35.2 NR[c] 36	4.7 (NR) NR[c] 3.9 (NR)	3 (NR) NR[c] 2.8 (NR)	NR NR NR
Glatiramer acetate								
Bornstein, 1987	Tolley[60] Tramacere[36]	24	GA 20 mg OD PL OD	25 25	30 (NR) 31 (NR)	4.9 (NR) 4.6 (NR)	2.9 (NR) 3.2 (NR)	NR NR
CONFIRM, 2012	Tolley[60]	24	GA 20 mg OD PL (unspecified)	350 363	36.7 (9.1) 36.9 (9.2)	4.4 (4.7) 4.8 (5.01)	2.57 (1.22) 2.59 (1.17)	1.4 (0.64) 1.4 (0.8)
Copolymer 1 MS	Tolley[60]	24	GA 20 mg OD PL (unspecified)	125 126	34.6 (6.0) 34.3 (6.5)	7.25 (4.85) 6.64 (5.09)	2.82 (1.19) 2.42 (1.28)	NR NR
Comi, 2001	Tramacere[36]	9	GA 20 mg OD PL (unspecified)	119 120	18 to 50[a]	8 (NR)	2.4 (NR)	NR

Trial, Year	Included In	Trial Duration (Months)	Treatment	Sample Size	Age in Years, Mean (SD)	Duration of Disease in Years, Mean (SD)	EDSS Baseline Score, Mean (SD)	No. of Relapses One Year Prior to Baseline, Mean (SD)
European and Canadian GA	Tolley[60]	9	GA 20 mg OD PL (unspecified)	113 114	34.1 (7.4) 34 (7.5)	7.9 (5.5) 8.3 (5.5)	2.3 (1.1) 2.4 (1.2)	NR NR
GALA, 2003	Tramacere[36]	12	GA 40 mg TIW PL TIW	943 461	18 to 55[a]	8 (NR)	2.8 (NR)	NR
Johnson, 1995	Tramacere[36]	24	GA 20 mg OD PL (unspecified)	125 126	18 to 45[a]	7 (NR)	2.6 (NR)	NR
Daclizumab[b]								
SELECT, 2013	Tramacere[36]	12	Daclizumab 300 mg every 4 weeks Daclizumab 150 mg every 4 weeks PL every 4 weeks	209 208 204	18 to 55[a]	3 (NR)	2.7 (NR)	NR
Fingolimod								
FREEDOMS, 2010	Tramacere[36]	24	Fingolimod 1.25 mg OD Fingolimod 0.5 mg OD PL OD	429 425 418	18 to 55[a]	8 (NR)	2.4 (NR)	NR
FREEDOMS II, 2014	Tramacere[36]	24	Fingolimod 1.25 mg OD Fingolimod 0.5 mg OD PL OD	370 358 355	18 to 55[a]	11 (NR)	2.4 (NR)	NR
Immunoglobulins								
Achiron, 1998	Tramacere[36]	24	Immunoglobulins 0.4 g/kg body weight[d] PL	20 20	19 to 60[a]	4 (NR)	3.0 (NR)	NR
Fazekas, 1997	Tramacere[36]	24	Immunoglobulins 0.15 to 0.2 g/kg QMT PL QMT	75 75	15 to 64[a]	7 (NR)	3.3 (NR)	NR
Fazekas, 2008	Tramacere[36]	12	Immunoglobulins 0.2 g/kg QMT Immunoglobulins 0.4 g/kg QMT PL QMT	45 42 41	18 to 55[a]	3 (NR)	2.0 (NR)	NR
Lewanska, 2002	Tramacere[36]	12	Immunoglobulins 0.2 g/kg QMT Immunoglobulins 0.4 g/kg QMT PL QMT	17 16 18	18 to 55[a]	9 (NR)	3.0 (NR)	NR

Trial, Year	Included In	Trial Duration (Months)	Treatment	Sample Size	Age in Years, Mean (SD)	Duration of Disease in Years, Mean (SD)	EDSS Baseline Score, Mean (SD)	No. of Relapses One Year Prior to Baseline, Mean (SD)
Laquinimod[b]								
ALLEGRO, 2012	Tramacere[36]	24	Laquinimod 0.6 mg OD PL OD	550 556	18 to 55[a]	9 (NR)	2.6 (NR)	NR
PegIFN beta-1a								
ADVANCE, 2014	Tolley[60] Tramacere[36]	12	Peginterferon beta-1a 125 mcg every 2 weeks Peginterferon beta-1a 125 mcg every 4 weeks PL every 2 weeks	512 500 500	36.9 (9.8) 36.4 (9.9) 36.3 (9.7)	4.0 (5.09) 3.4 (4.36) 3.5 (4.63)	2.47 (1.26) 2.48 (1.24) 2.44 (1.18)	1.6 (0.67) 1.5 (0.62) 1.6 (0.67)
IFN beta-1a								
OWIMS, 1999	Tramacere[36]	12	IFN beta-1a 22 mcg TIW IFN beta-1a 44 mcg TIW PL TIW	95 98 100	18 to 50[a]	7 (NR)	2.6 (NR)	NR
PRISMS, 1998	Tolley[60] Tramacere[36]	24	IFN beta-1a 22 mcg TIW IFN beta-1a 44 mcg TIW PL TIW	189 184 187	34.8[c] 35.6[c] 34.6[c]	5.4[c] 6.4[a] 4.3[c]	2.5 (1.2) 2.5 (1.3) 2.4 (1.2)	NR NR NR
Dimethyl fumarate								
DEFINE, 2012	Tramacere[36]	24	DF 240 mg TID DF 240 mg BID PL TID	416 411 410	18 to 55[a]	6 (NR)	2.4 (NR)	NR
Natalizumab								
AFFIRM, 2006	Tramacere[36]	24	Natalizumab 300 mg once every 4 weeks PL (unspecified)	627 315	18 to 50[a]	5 (0 to 34)[a]	2.3 (NR)	NR
Mitoxantrone[b]								
Millefiorini, 1997	Tramacere[36]	24	Mitoxantrone 8 mg/m^2 QMT PL QMT	27 24	18 to 45[a]	5 (NR)	3.6 (NR)	NR

Trial, Year	Included In	Trial Duration (Months)	Treatment	Sample Size	Age in Years, Mean (SD)	Duration of Disease in Years, Mean (SD)	EDSS Baseline Score, Mean (SD)	No. of Relapses One Year Prior to Baseline, Mean (SD)
Active-Comparator Trials (Alphabetical Order According to Brand Name)								
Teriflunomide vs. IFN beta-1a								
TENERE, 2014	Tramacere[36]	12	Teriflunomide 14 mg OD Teriflunomide 7 mg OD IFN beta-1a 44 mcg TIW	111 109 104	≥ 18	7 (NR)	2.1 (NR)	NR
Avonex vs. Betaseron								
INCOMIN, 2002	Tramacere[36]	24	IFN beta-1a 30 mcg QW IFN beta-1b 250 mcg EOD	92 96	18 to 50[a]	6 (NR)	2.0 (NR)	NR
IFN beta-1a vs. IFNs beta-1b								
Etemadifar, 2006	Tolley[60]	24	IFN beta-1a 30 mcg QW IFN beta-1a 44 mcg TIW IFN beta-1b 250 mcg EOD	30 30 30	28.1 (1.2) 27.4 (1.2) 29.9 (1.4)	2.9 (2.3) 3 (2.2) 3.7 (2.3)	1.9 (1.1) 2.1 (1) 1.9 (0.7)	2 (0.8) 2.4 (1) 2.2 (0.7)
IFNs beta-1a vs. glatiramer acetate								
Calabrese 2011	Tolley[60]	24	GA 20 mg OD FN beta-1a 30 mcg QW IFN beta-1a 44 mcg TIW	48 47 46	38.9 (10.2) 34.8 (9.6) 35.9 (9.1)	5.5 (6.1) 5.3 (5.1) 5.7 (4.9)	2.1 (1.1) 1.9 (0.8) 1.9 (1)	NR NR NR
CombiRx, 2013	Tolley[60] Tramacere[36]	36	GA 20 mg OD IFN beta-1a 30 mcg QW	259 250	39 (9.5) 37.6 (10.2)	1 (2.9) 1.4 (4)	1.9 (1.2) 2 (1.2)	1.6 (0.7) 1.7 (0.9)
REGARD, 2008	Tolley[60] Tramacere[36]	24	GA 20 mg OD IFN beta-1a 44 mcg TIW	378 386	36.8 (9.5) 36.7 (9.8)	– 3.7	2.33 (1.31) 2.35 (1.28)	NR 1[c]
IFN beta-1a vs. fingolimod								
TRANSFORMS, 2010	Tramacere[36]	12	IFN beta-1a 30 mcg QW Fingolimod 1.25 mg OD Fingolimod 0.5 mg OD	435 426 431	18 to 55[a]	7 (NR)	2.2 (NR)	NR
IFN beta-1a vs. IFN beta-1a								
EVIDENCE, 2007	Tolley[60] Tramacere[36]	12	IFN beta-1a 30 mcg QW IFN beta-1a 44 mcg TIW	338 339	37.4 38.3	6.7 (NR) 6.5 (NR)	2.3 (NR) 2.3 (NR)	NR NR

Trial, Year	Included In	Trial Duration (Months)	Treatment	Sample Size	Age in Years, Mean (SD)	Duration of Disease in Years, Mean (SD)	EDSS Baseline Score, Mean (SD)	No. of Relapses One Year Prior to Baseline, Mean (SD)
IFN beta-1a vs. laquinimod[b]								
BRAVO, 2014	Tolley[60] Tramacere[36]	24	IFN beta-1a 30 mcg QW Laquinimod 0.6 mg OD PL OD	447 434 450	38.5[a] (NR) NR[c] 37.5[a] (NR)	5.3[a] (NR) NR[c] 4.7[c] (NR)	2.5[a] (NR) NR[c] 2.5[a] (NR)	1.0[c] (NR) NR[e] 1.0[c] (NR)
IFN beta-1b vs. glatiramer acetate								
BECOME, 2009	Tolley[60] Tramacere[36]	24	GA 20 mg OD IFN beta-1b 250 mcg EOD	39 36	36 (NR) 36 (NR)	1.2 (0.2 to 34)[a] 0.9 (0.1 to 24)[a]	2[a] (NR) 2[a] (NR)	NR NR
BEYOND, 2009	Tolley[60] Tramacere[36]	24	GA 20 mg OD IFN beta-1b 250 mcg EOD IFN beta-1b 500 mcg EOD	448 897 899	35.2 (NR) 35.8 (NR) NR[c]	5.1 (NR) 5.3 (NR) NR[c]	2.28 (NR) 2.35 (NR) NR[c]	1.6 (NR) 1.6 (NR) NR[d]
IFN beta-1b vs. IFN beta-1a								
Koch-Henriksen, 2006	Tramacere[36]	24	IFN beta-1b 250 mcg EOD IFN beta-1a 22 mcg QW	158 143	18 to 55[a]	8 (NR)	2.9 (NR)	NR
Glatiramer acetate vs. dimethyl fumarate								
CONFIRM, 2012	Tramacere[36]	24	DF 240 mg TID DF 240 mg BID GA 20 mg OD PL TID	345 362 350 363	18 to 55[a]	5 (NR)	2.6 (NR)	NR
Azathioprine[b] vs. IFN beta-1b vs. IFN beta-1a								
Etemadifar, 2007	Tramacere[36]	12	Azathioprine 3 mg/kg OD IFN beta-1b 250 mcg EOD IFN beta-1a 30 mcg QW IFN beta-1a 44 mcg TIW	47 47 19 13	13 to 50[a]	NR	1.5 (NR)	NR
MAIN	Tramacere[36]	24	Azathioprine 36 mg/kg OD IFN beta-1a 30 mcg QW IFN beta-1a 22 mcg TIW IFN beta-1a 44 mcg TIW IFN beta-1b 250 mcg EOD	77 26 35 7 5	18 to 55[a]	6 (NR)	1.9 (NR)	NR

Trial, Year	Included In	Trial Duration (Months)	Treatment	Sample Size	Age in Years, Mean (SD)	Duration of Disease in Years, Mean (SD)	EDSS Baseline Score, Mean (SD)	No. of Relapses One Year Prior to Baseline, Mean (SD)
Alemtuzumab vs. IFN beta-1a								
CAMMS223, 2008	Tramacere[36]	36	Alemtuzumab 24 mg OD[e] Alemtuzumab 12 mg OD[f] IFN beta-1a 44 mcg TIW	110 113 111	18 to 50[a]	NR	1.9 (NR)	NR
CARE-MS I, 2012	Tramacere[36]	24	Alemtuzumab 12 mg OD[f] IFN beta-1a 44 mcg TIW	386 195	18 to 50[a]	2 (NR)	2.0 (NR)	NR
CARE-MS II, 2012	Tramacere[36]	24	Alemtuzumab 24 mg OD[e] Alemtuzumab 12 mg OD[f] IFN beta-1a 44 mcg TIW	170 436 231	18 to 55[a]	5 (NR)	2.7 (NR)	NR

DF = dimethyl fumarate; EDSS = Kurtzke Expanded Disability Status Scale; EOD = every other day; GA = glatiramer acetate; IFN = interferon; IV = intravenous; MS = multiple sclerosis; MSCRG = Multiple Sclerosis Collaborative Research Group; NR = not reported; OD = once daily; PL = placebo; QMT = monthly; QW = once a week; SD = standard deviation; TID = three times daily; TIW = three times a week; vs. = versus.

[a] Median and/or range.

[b] Not approved or indicated by Health Canada for the treatment of MS.

[c] Not reported separately in Tolley[60] and reported only as a total across all groups in Tramacere.[36]

[d] Immunoglobulins 0.4 g/kg body weight IV daily for five consecutive days followed by additional booster doses of immunoglobulins 0.4 g/kg body weight IV daily every 2 months

[e] Alemtuzumab 24 mg OD IV on five consecutive days during first month and on 3 consecutive days at months 12 and 24.

[f] Alemtuzumab 12 mg OD IV on five consecutive days during first month and three consecutive days at month 12.

for 24 months; placebo in the Achiron study also had the same dosing regimen.

Sources: Tolley, 2015[60] and Tramacere, 2015.[36]

Comparators

Tolley[60]

The Tolley IDC[60] included the following relevant injectable DMT comparators that have been approved for use in Canada for the treatment of RRMS:

- Interferon beta-1a 22 mcg three times a week
- Interferon beta-1a 44 mcg three times a week
- Interferon beta-1a 30 mcg once a week
- Interferon beta-1b 250 mcg every other day
- Glatiramer acetate 20 mg once a day.

The comparators are considered standard first-line treatment for RRMS according to the clinical expert consulted for this review. Other first-line oral treatments are also available; however, this IDC focused on those with a similar route of entry and, hence, oral formulations were not included.

Tramacere[36]

The Tramacere IDC[36] included the following comparators (irrespective of dose) for the treatment of RRMS:

- Interferon beta-1a (Avonex, Rebif)
- Interferon beta-1b
- Peginterferon beta-1a
- Glatiramer acetate
- Natalizumab
- Mitoxantrone
- Fingolimod
- Teriflunomide
- Dimethyl fumarate
- Alemtuzumab
- Daclizumab
- Ocrelizumab
- Laquinimod
- Azathioprine
- Immunoglobulins.

The Tramacere IDC[36] examined all treatments available for the treatment of RRMS. Of these, mitoxantrone, ocrelizumab, laquinimod, daclizumab, and azathioprine do not have Health Canada marketing approval for the treatment of RRMS.

Outcomes

Tolley[60]

The efficacy outcomes of interest described by Tolley et al.[60] included:

- Annualized relapse rate for each treatment group and a rate ratio, which was used to compare treatment groups
- Disability progression sustained at three months, measured as a hazard ratio
- Disability progression sustained at six months, measured as a hazard ratio.

While disability progression sustained at three months is commonly reported in clinical trials, the clinical expert consulted for this review highlighted that this timeframe is often not indicative of true disability progression, and that sustained disability progression at six months or later is preferable. Individual study data on annualized relapse rate, disability progression sustained at three months, and disability progression sustained at six months that were used in the NMA are provided in Table 19.

Harms of interest included:

- Discontinuations
- Common AEs occurring in ≥ 5% of patients in the full two years of the ADVANCE trial, or ≥ 3% of AEs occurring in year 1 of the ADVANCE trial:
    - Annual incidence of any AEs (arthralgia, back pain, depression, diarrhea, fatigue, flu-like symptoms, headache, injection-site reaction, leucopenia, nausea, pain in extremity, pruritus, urinary tract infection)
    - Anti-interferon–neutralizing antibodies (regardless of incidence)
- SAEs.

None of the harms were included in the NMA; the authors noted that this would not be methodologically sound because clinical trials are rarely powered to accurately detect statistical significance with regard to AEs.

TABLE 19: SUMMARY OF STUDY-LEVEL OUTCOME DATA FROM TRIALS INCLUDED IN THE TOLLEY INDIRECT COMPARISON[60]

Studies	Treatments	ARR			DPS3M	DPS6M
		Total Number of Relapses	Person-Years	Relapse Rate[a]	Patients With Disability Progression n/N (%)[a]	Patients With Disability Progression n/N (%)
ADVANCE trial	PegIFN beta-1a 125 mcg once every 2 weeks PL	116 181	435.74 445.25	0.27 0.41	31/515 (6) 50/500 (10)	18/515 (3) 39/500 (8)
BECOME trial	IFN beta-1b 250 mcg EOD GA 20 mg OD	25 23	67.57 69.7	0.37 0.33	– –	4/36 (11) 6/39 (15)
BEYOND trial	IFN beta-1b 250 mcg EOD GA 20 mg OD	814 374	2,260 1,099.5	0.36 0.34	188/897 (21) 90/448 (20)	– –
Bornstein, 1987	GA 20 mg OD PL	8 38	23.67 27.59	0.34 1.38	– –	– –
BRAVO trial	IFN beta-1a, 30 mcg QW PL	215 275	825 809	0.26 0.34	47/447 (11) 60/450 (13)	35/447 (8) 46/450 (10)
Calabrese, 2011	GA 20 mg OD IFN beta-1a 30 mcg QW IFN beta-1a 44 mcg TIW	52 51 40	103 102 101	0.50 0.50 0.40	– –	– –
CombiRx trial	IFN beta-1a 30 mcg QW GA 20 mg OD	97 70	604.4 650.7	0.16 0.11	– –	– –
CONFIRM trial	GA 20 mg OD PL	105 146	300.91 312.62	0.35 0.47	48/360 (13) 52/363 (14)	34/360 (9) 39/363 (11)
Copolymer 1 trial	GA 20 mg OD PL	161 210	272.88 250	0.59 0.84	27/125 (22) 31/126 (25)	– –
Etemadifar, 2006	IFN beta-1a 30 mcg QW IFN beta-1a 44 mcg TIW IFN beta-1b 250 mcg EOD	57 66 65	60 60 60	0.95 1.1 1.1	– –	– –
European/ Canadian GA trial	GA 20 mg OD PL	61 91	75.31 75.21	0.81 1.21	– –	– –
EVIDENCE trial	IFN beta-1a 30 mcg QW IFN beta-1a 44 mcg TIW	195 165	304.2 304.71	0.64 0.54	49/338 (14) 43/339 (13)	28/338 (8) 20/339 (6)
IFNB MS trial	IFN beta-1b 250 mcg EOD PL	173 266	207 209.2	0.84 1.27	43/124 (35) 56/123 (46)	– –

Studies	Treatments	ARR			DPS3M	DPS6M
MSCRG trial	IFN beta-1a 30 mcg QW	104	170	0.61	–	20/158 (13)
	PL	157	174	0.90	–	31/143 (22)
PRISMS trial	IFN beta-1a 22 mcg TIW	344	366	0.94	56/189 (30)	–
	IFN beta-1a 44 mcg TIW	318	363	0.88	49/184 (27)	–
	PL	479	364	1.32	72/187 (39)	
REGARD trial	GA 20 mg OD	194	669.5	0.29	–	33/378 (9)
	IFN beta-1a 44 mcg TIW	201	669.5	0.30	–	45/386 (12)

ARR = annualized relapse rate; DPS3M = disability progression sustained at three months; DPS6M = disability progression sustained at six months; EDSS = Kurtzke Expanded Disability Status Scale; EOD = every other day; GA = glatiramer acetate; IFN = interferon; MS = multiple sclerosis; MSCRG = Multiple Sclerosis Collaborative Research Group; NR = not reported; OD = once daily; PegIFN = peginterferon beta-1a; PL = placebo; QW = once a week; TIW = three times a week.

[a] Calculated by CADTH.

Source: Tolley et al.[60]

Tramacere[36]
The primary efficacy outcomes of interest described by Tramacere et al.[60] included:

- Proportion of patients experiencing new relapses after 12, 24, and 36 months, and proportion of patients experiencing disability worsening over 24 and 36 months
- Discontinuations due to AEs.

The secondary outcome included the total number of SAEs.

Quality Assessment of Included Studies
Tolley[60]
Quality assessment included assessment of whether randomization and allocation concealment were carried out appropriately; whether the care providers, patients, and outcome assessors were appropriately blinded to the treatment allocation; whether the baseline characteristics were similar between patients in the treatment groups; whether follow-up was appropriate; whether more outcomes were reported than originally outlined in the respective trial protocols; and whether the analysis was intention-to-treat along with what methods (if any) were used to account for missing data.

Study quality was examined by two independent reviewers, with any discrepancies reconciled by a third independent reviewer. Sensitivity analyses were additionally performed on studies that were perceived as having inherent bias.

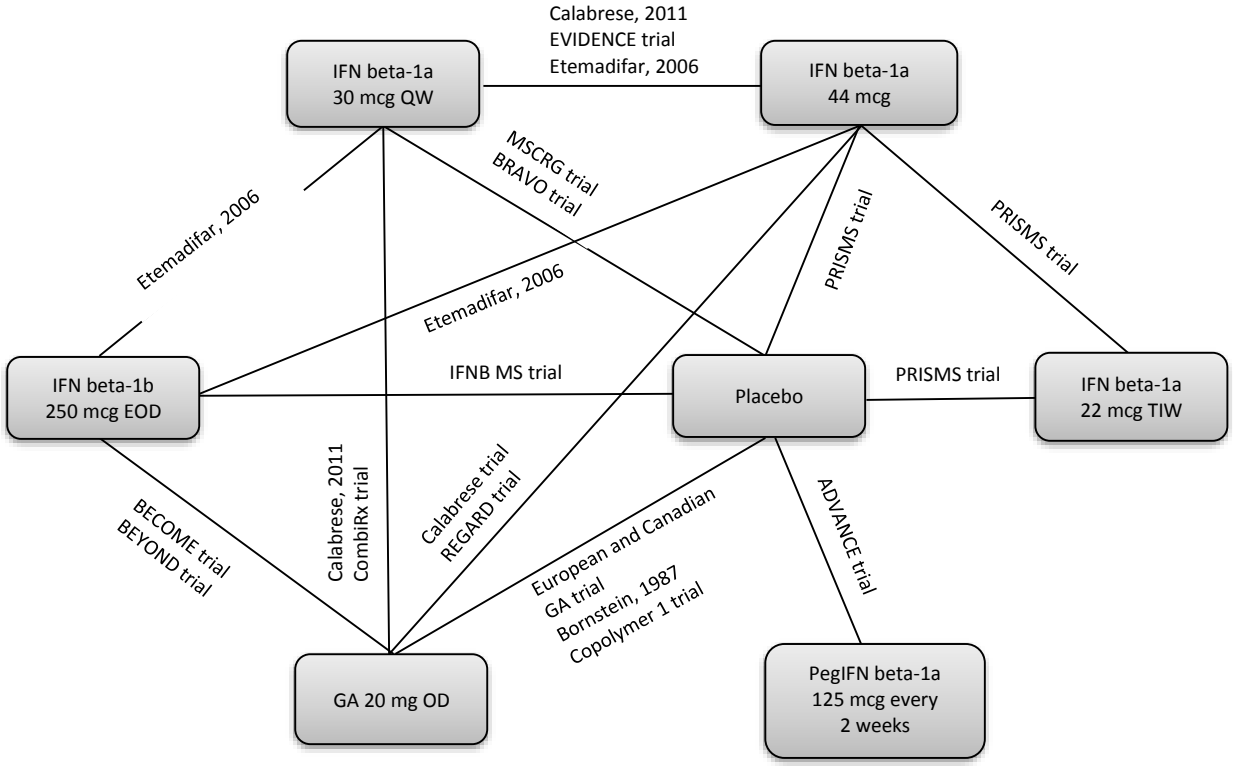
Tramacere[36]
Risk of bias of individual studies was assessed using the Cochrane Collaboration criteria, of which the following were included: random sequence generation, allocation concealment, participant blinding, outcome assessor blinding, incomplete outcome data, and reporting of selective outcomes. The sponsor's role was also assessed. Three individuals assessed risk of bias for each study, with any discrepancies reconciled through consensus.

Evidence Networks
Tolley[60]
The evidence networks for the pre-specified outcomes of interest in the Tolley IDC are presented in Table 6, Figure 7, and Figure 8. The network for annualized relapse rate was the largest, with all trials examining this outcome (Table 6). The networks for disability progression sustained at three months and six months were less intricate and involved fewer studies (Figure 7 and Figure 8, respectively). In addition, there were fewer direct comparisons between drugs for disability progression.

Tramacere[36]
The evidence networks for the pre-specified outcomes of interest are presented in Figure 4 and Figure 5.

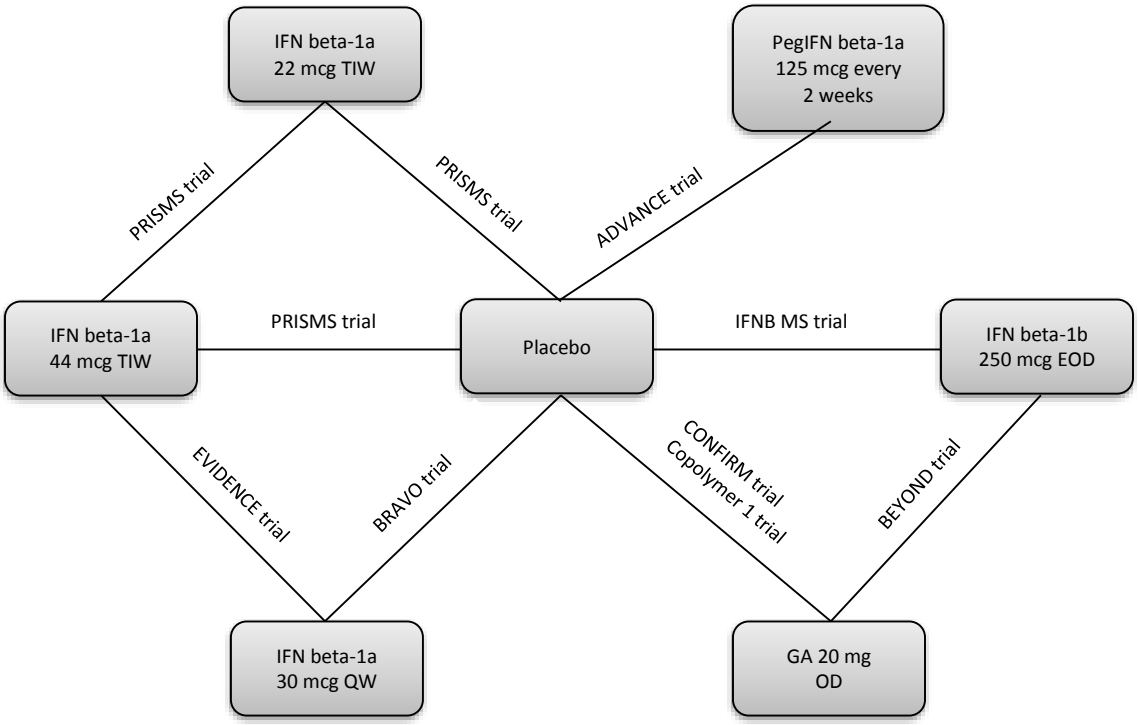
The network for relapses over 12 months (Figure 9) was the largest network that included peginterferon beta-1a (other networks that did not include peginterferon beta-1a are not considered in this summary and critical appraisal). It included a total of 29 studies (n = 17,897 patients), with 19 placebo-controlled studies (n = 12,100), nine active-comparator trials (n = 4,367 patients), and one study having both two active-treatment groups and one placebo arm (n = 1,430). The network for discontinuations due to AEs over 12 months (Figure 10) included 13 studies on 10 treatments (n = 8,105 patients), with nine studies of seven treatments examined in placebo-controlled trials (n = 5,718), and four studies of six treatments examined in active-comparator trials (n = 2,387). However, the individual studies included in the analysis were not reported for this outcome.

FIGURE 6: NETWORK OF TRIALS IN TOLLEY NMA, ANNUALIZED RELAPSE RATE



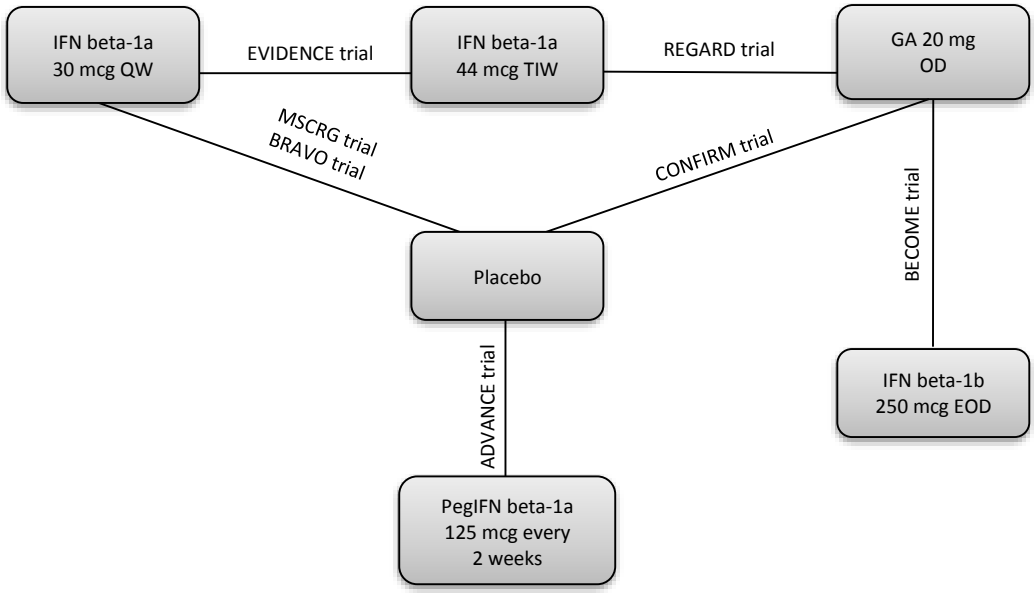
EOD = every other day; GA = glatiramer acetate; IFN = interferon; MS = multiple sclerosis; MSCRG = Multiple Sclerosis Collaborative Research Group; NMA = network meta-analysis; PegIFN = peginterferon beta-1a; OD = once daily; QW = once a week; TIW = three times a week.
Source: Tolley, 2015.[60]

FIGURE 7: NETWORK OF TRIALS IN TOLLEY NMA: DISABILITY PROGRESSION SUSTAINED FOR THREE MONTHS



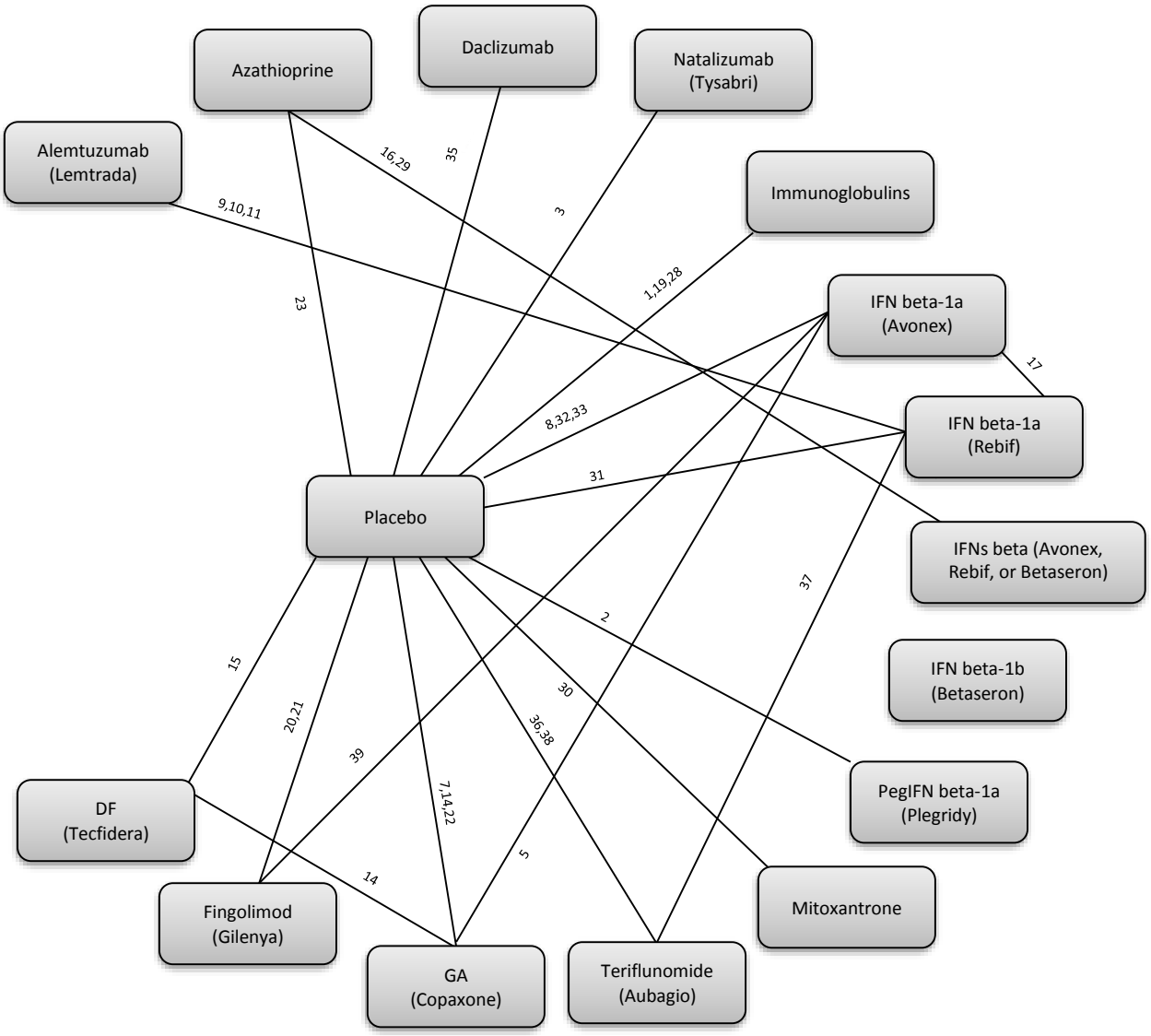
EOD = every other day; GA = glatiramer acetate; IFN = interferon; MS = multiple sclerosis; NMA = network meta-analysis; OD = once daily; PegIFN = peginterferon; QW = once a week; TIW = three times a week.
Source: Tolley, 2015[60]

FIGURE 8: NETWORK OF TRIALS IN TOLLEY NMA: DISABILITY PROGRESSION SUSTAINED FOR SIX MONTHS



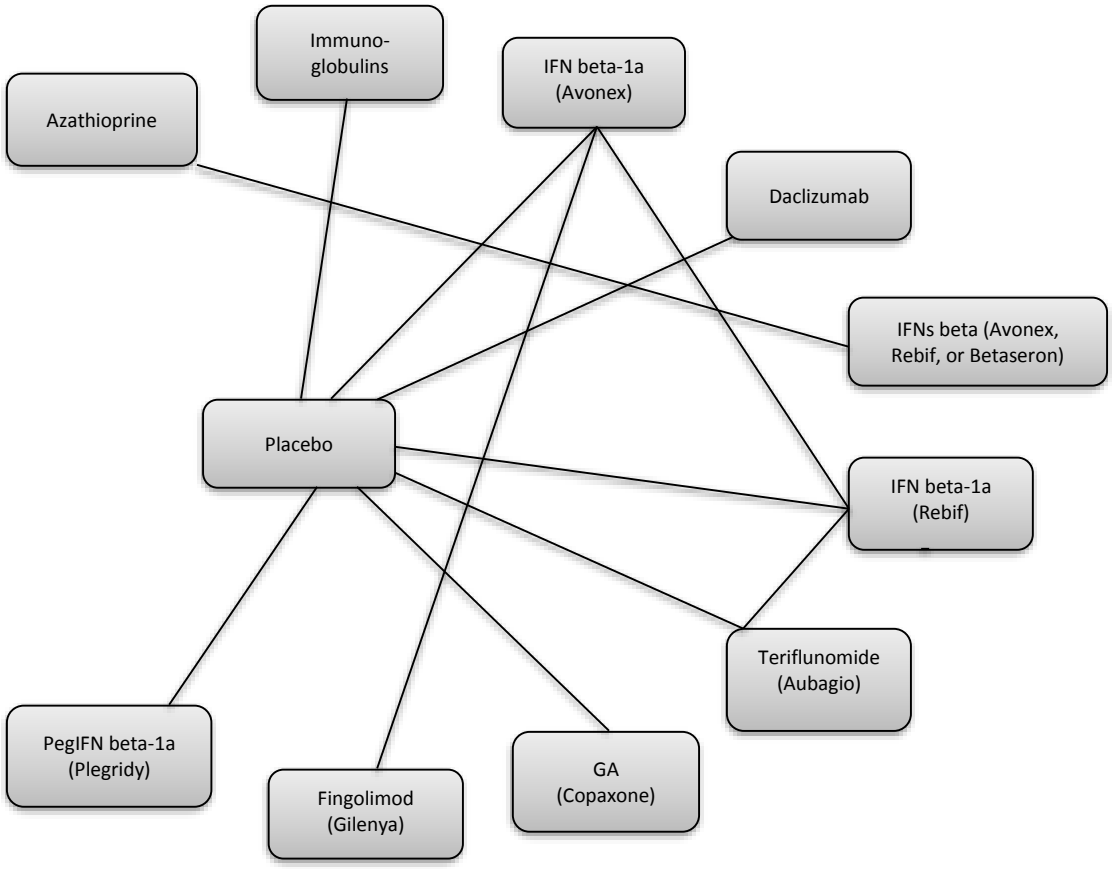
EOD = every other day; GA = glatiramer acetate; IFN = interferon; MSCRG = Multiple Sclerosis Collaborative Research Group; NMA = network meta-analysis; OD = once daily; PegIFN = pegylated interferon; QW = once a week; TIW = three times a week.
Source: Tolley, 2015.[60]

FIGURE 9: NETWORK OF TRIALS IN TRAMACERE NMA: RELAPSES OVER 12 MONTHS



1 = Achiron; 2 = ADVANCE; 3 = AFFIRM; 5 = BECOME; 7 = Bornstein; 8 = BRAVO; 9 = CAMMS223; 10 = CARE-MS I; 11 = CARE-MS II; 14 = CONFIRM; 15 = DEFINE; 16 = Etemadifar; 17 = EVIDENCE; 19 = Fazekas, 2008; 20 = FREEDOMS; 21 = FREEDOMS II; 22 = GALA; 23 = Goodkin; 28 = Lewanska; 29 = MAIN; 30 = Millefiorini; 31 = Multiple Sclerosis Collaborative Research Group (MSCRG); 32 = OWIMS; 33 = PRISMS; 35 = SELECT; 36 = TEMSO; 37 = TENERE; 38 = TOWER; 39 = TRANSFORMS; DF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; NMA = network meta-analysis; PegIFN = peginterferon beta-1a.
Note: Only those networks that included PegIFN beta-1a are provided in this review; therefore, not all networks were included.
Source: Tramacere, 2015.[36]

FIGURE 10: NETWORK OF TRIALS IN TRAMACERE NMA: DISCONTINUATION DUE TO ADVERSE EVENTS OVER 12 MONTHS



GA = glatiramer acetate; IFN = interferon; NMA = network meta-analysis; PegIFN = peginterferon beta-1a.
Notes: Of the 13 studies that reported the acceptability over 12 months, none of the individual studies were listed; rather, only differing line and node thickness were provided. Only those networks that included peginterferon beta-1a are provided in this review; therefore, not all networks were included.
Source: Tramacere, 2015.[36]

Indirect Comparison Methods

Tolley[60]

Annualized relapse rate (ARR), confirmed disability progression at three months (CDP3M), and confirmed disability progression at six months (CDP6M) were analyzed in the NMA model to estimate the relative treatment effects of peginterferon beta-1a 125 mcg once every two weeks compared with the aforementioned comparators of interest. Sets of Bayesian hierarchical models using non-informative priors were run in WinBUGS software, version 1.4.3.

A Poisson distribution was used to analyze the ARR and used "total number of relapses within a treatment group out of the total person-time follow-up for that treatment group calculated from study follow-up."[60] Subsequently, Poisson regression was used to examine the fit.

AE comparisons were calculated descriptively and not analyzed statistically or through NMA due to the lack of study power to ascertain statistical significance and the unacceptably high heterogeneity

between the AE definitions, measurements, and trial durations. Two-year data unadjusted for placebo results were used to assess the annualized AE risks using weighted averages across trials.

Fixed effects and random effects models were used to estimate the treatment effect sizes, with the random effects model constituting the primary analysis due to the heterogeneity in patient and trial characteristics. The residual deviance and deviance information criteria (DIC) were used to evaluate model fit, with lower DIC values indicating a better fit. To assess heterogeneity across trials, Tau^2 (T^2) was used to indicate the level of between-study variability; a value of ≥ 1 is indicative of high variability. The authors also provided model fit statistics (fixed effect and random effect) with and without the INCOMIN trial data, a trial that had no blinding of outcome assessors. Upon performing the NMA with and without the INCOMIN trial data, the authors ascertained that DIC was similar enough in both models and decided to exclude it from all subsequent NMA analyses.

To ascertain consistency within the evidence networks between the direct and indirect results, conventional pairwise meta-analyses and a back-calculation method were used. The null hypothesis of consistency between the direct and indirect evidence would be rejected if there was a statistically significance difference of $P < 0.05$ between the direct and indirect evidence.

Baseline comparability was fully assessed for each analysis, with no studies being excluded. Sensitivity analyses were performed to ascertain the robustness of the base-case analyses after omitting studies with the following characteristics:

- Study duration:
  - ARR: excluding studies of less than one year and greater than two years' duration
  - CDP3M and CDP6M: Listed as a sensitivity analysis, but it was unclear what studies were removed in performing the analysis
- Blinding status:
  - ARR, CDP3M, and CDP6M: excluding studies in which blinding status was unclear or studies with partial or assessor blinding only
- Sample size:
  - ARR and CDP6M: excluding studies with fewer than 50 patients per treatment group.

No information was presented in the main publication or appendices regarding the burn-in period, the number of iterations performed, or when the results converged.

***Tramacere*[36]**

Relapses and discontinuations due to AEs over 12 months in the NMA were analyzed using a frequentist random effects model. It was assumed that heterogeneity was equal across all of the comparisons and was statistically assessed using τ^2 (the assessment was based on its magnitude) estimated from the models. The NMA was performed in Stata 13. Direct comparisons were analyzed using conventional pairwise, random effects meta-analysis. The presence of heterogeneity was assessed using the I^2 and τ^2 statistic.

Inconsistency was assessed both locally and globally. The loop-specific approach was used to assess local inconsistency, whereby inconsistency was evaluated separately in each closed loop of the network. Within each loop, the authors assumed common heterogeneity. The "design-by-treatment" model was used as the global approach to assess inconsistency in the entire NMA using a Chi^2 test (in this model, different sources of inconsistency are accounted for). To ascertain the differences between the sources of variability (i.e., inconsistency and heterogeneity), the authors also assessed inconsistency using I^2.

Subgroup analyses were performed for the efficacy outcomes at the 12-, 24-, and 36-month follow-up. Effect modifiers such as diagnostic criteria, previous treatment, relapse definition, and pre-trial relapse rates were used as potential sources of either inconsistency or heterogeneity or both. The following sensitivity analyses were also performed: exclusion of trials with fewer than 50 patients, restricting inclusion to studies with low risk of bias, and exclusion of studies without clearly reported reasons for missing data.

Results

Tolley[60]

Trial Characteristics

Of the 16 trials included in the NMA, methods for randomization and allocation concealment were reported in only 11. Detection bias was avoided by appropriate blinding in 15 of the trials; outcomes were analyzed on an intention-to-treat basis in 15 trials, and baseline characteristics were balanced between treatment groups in all trials. While the majority of trials reported a low risk of bias in specific category assessment (randomization, baseline characteristics, blinding, withdrawal or discontinuation, outcome selection/reporting/other, and statistical analysis), there were 10 trials that did not report information for at least one category; the majority of these (n = 6) did not report information for multiple categories. The Calabrese 2011 study was the only study in which there was a high risk of bias in one of the specific categories assessed, that being their statistical analysis; however, the sample size was small. Publication bias was not performed due to the relatively small number of studies that examined similar interventions and comparators.

Heterogeneity between trials was observed in the definition of relapse. This was particularly evident in the duration of symptoms, whereby the cut-off time in some trials was "at least 24 hours," while it was "at least 48 hours" in other trials. New or worsening of old neurological symptoms lasting at least 24 hours was the definition of relapse used in nine trials, while five trials defined relapse as the appearance of more than one new or worsening neurological symptom lasting for at least 48 hours. Two of the trials did not specify any duration with regard to the definition of relapse.

Annualized Relapse Rate

There was no statistically significant difference in ARR when peginterferon beta-1a 125 mcg was compared with any of the other DMT regimens. It should be noted that there was significant heterogeneity in the study-level relapse rate (CADTH-calculated) (Table 19). While some studies had similar rates to that found in the ADVANCE trial (ARR of 0.4), there were many outliers (range 0.11 to 1.32). Detailed results for ARR are presented in Table 20.

Confirmed Disability Progression at Three Months

There were no statistically significant differences in CDP3M between peginterferon beta-1a 125 mcg and any of the other DMT regimens examined in this NMA. Credible intervals were large for the reported hazard ratios. Detailed results for CDP3M are presented in Table 20.

Confirmed Disability Progression at Six Months

There were no statistically significant differences in CDP6M between peginterferon beta-1a 125 mcg and any of the other DMT regimens (save interferon beta-1a 22 mcg three times a week, as there were no comparisons available in any of the included trials for this efficacy outcome). The only exception was the comparison with interferon beta-1a 30 mcg once a week, where peginterferon beta-1a 125 mcg demonstrated a statistically significant reduction in risk of CDP6M. As with the CDP3M results, the 95%

credible intervals were large surrounding the hazard ratio point estimates. Detailed results for CDP3M are presented in Table 20.

TABLE 20: RESULTS OF THE NETWORK META-ANALYSIS BY TOLLEY ET AL.

Treatment[a]	Outcomes					
	ARR		CDP3M		CDP6M	
	RR	95% CrI	HR	95% CrI	HR	95% CrI
PegIFN beta-1a versus:						
IFN beta-1a 30 mcg QW	0.88	0.65 to 1.2	0.74	0.43 to 1.26	0.54	0.28 to 0.99
IFN beta-1a 22 mcg TIW	0.92	0.64 to 1.3	0.75	0.42 to 1.3	–	–
IFN beta-1a 44 mcg TIW	0.98	0.72 to 1.36	0.83	0.48 to 1.43	0.55	0.28 to 1.09
IFN beta-1b 250 mcg EOD	0.95	0.7 to 1.31	0.71	0.42 to 1.17	0.8	0.23 to 3.31
GA 20 mg OD	1	0.75 to 1.37	0.71	0.42 to 1.16	0.62	0.31 to 1.19
IFN beta-1a 30 mcg QW versus:						
PegIFN beta-1a 125 mcg every 2 weeks	1.14	0.84 to 1.54	1.36	0.8 to 2.34	1.87	1.01 to 3.56
IFN beta-1a 22 mcg TIW	1.05	0.83 to 1.3	1.02	0.67 to 1.54	–	–
IFN beta-1a 44 mcg TIW	1.12	0.98 to 1.3	1.13	0.82 to 1.59	1.03	0.67 to 1.58
IFN beta-1b 250 mcg EOD	1.08	0.91 to 1.31	0.96	0.65 to 1.44	1.5	0.47 to 5.86
GA 20 mg OD	1.15	0.99 to 1.33	0.96	0.65 to 1.41	1.16	0.75 to 1.77
IFN beta-1a 22 mcg TIW versus:						
PegIFN beta-1a 125 mcg every 2 weeks	1.09	0.77 to 1.56	1.34	0.77 to 2.38	–	–
IFN beta-1a 30 mcg QW	0.96	0.77 to 1.2	0.98	0.65 to 1.49	–	–
IFN beta-1a 44 mcg TIW	1.07	0.88 to 1.32	1.12	0.77 to 1.61	–	–
IFN beta-1b 250 mcg EOD	1.04	0.82 to 1.33	0.95	0.61 to 1.45	–	–
GA 20 mg OD	1.09	0.89 to 1.37	0.94	0.62 to 1.44	–	–
IFN beta-1a 44 mcg TIW versus:						
PegIFN beta-1a 125 mcg every 2 weeks	1.02	0.74 to 1.38	1.2	0.7 to 2.07	1.81	0.92 to 3.63
IFN beta-1a 30 mcg QW	0.89	0.77 to 1.02	0.88	0.63 to 1.22	0.97	0.64 to 1.5
IFN beta-1a 22 mcg TIW	0.93	0.76 to 1.13	0.9	0.62 to 1.29	–	–
IFN beta-1b 250 mcg EOD	0.97	0.81 to 1.16	0.85	0.57 to 1.27	1.46	0.45 to 5.7
GA 20 mg OD	1.02	0.89 to 1.18	0.85	0.57 to 1.25	1.12	0.76 to 1.64
IFN beta-1b 250 mcg EOD versus:						
PegIFN beta-1a 125 mcg every 2 weeks	1.05	0.77 to 1.44	1.41	0.85 to 2.39	1.25	0.3 to 4.38
IFN beta-1a 30 mcg QW	0.92	0.76 to 1.1	1.04	0.7 to 1.53	0.66	0.17 to 2.13
IFN beta-1a 22 mcg TIW	0.96	0.75 to 1.22	1.06	0.69 to 1.63	-	-
IFN beta-1a 44 mcg TIW	1.04	0.86 to 1.23	1.18	0.79 to 1.75	0.69	0.18 to 2.23
GA 20 mg OD	1.05	0.92 to 1.23	1	0.8 to 1.25	0.77	0.21 to 2.39
GA 20 mg OD versus:						
PegIFN beta-1a 125 mcg every 2 weeks	1	0.73 to 1.34	1.42	0.86 to 2.38	1.62	0.84 to 3.18
IFN beta-1a 30 mcg QW	0.87	0.75 to 1.01	1.04	0.71 to 1.53	0.86	0.57 to 1.33
IFN beta-1a 22 mcg TIW	0.91	0.73 to 1.13	1.06	0.7 to 1.63	–	–

Treatment[a]	Outcomes					
	ARR		CDP3M		CDP6M	
	RR	95% CrI	HR	95% CrI	HR	95% CrI
IFN beta-1a 44 mcg TIW	0.98	0.85 to 1.13	1.18	0.8 to 1.74	0.9	0.61 to 1.31
IFN beta-1b 250 mcg EOD	0.95	0.82 to 1.08	1	0.8 to 1.25	1.3	0.42 to 4.85
DICs[b] of Random Effects and Fixed Effects Models						
	ARR		CDP3M		CDP6M	
	Random	Fixed	Random	Fixed	Random	Fixed
DIC	293.962	292.070	123.140	123.410	96.177	97.311
Residual deviance						
Mean (SD)	38.57 (7.32)	39.39 (6.66)	–	–	–	–
Median (95% CrI)	38.03 (26.05 to 54.29)	38.71 (28.40 to 54.17)	–	–	–	–

ARR = annualized relapse rate; CDP3M = confirmed disability progression at 3 months; CDP6M = confirmed disability progression at 6 months; CrI = credible interval; DIC = deviance information criteria; EOD = every other day; GA = glatiramer acetate; HR = hazard ratio; IFN = interferon; OD = once daily; PegIFN = peginterferon beta-1a; QW = once weekly; RR = rate ratio; SD = standard deviation; TIW = three times a week.

[a] Placebo results are not included.

[b] Lower DIC indicates better model fit.

Source: Tolley, 2015.[60]

Sensitivity Analyses

Results from the sensitivity analyses based on blinding, sample size, and study duration were not statistically different from the results of the main analyses, nor were there substantial changes in the direction or magnitude of the point estimates for peginterferon beta-1a 125 mcg versus the other treatments. The results of the main analyses were also not impacted by the risk of bias assessment.

Harms

While not examined within the NMA, comparisons of the safety of peginterferon beta-1a 125 mcg revealed no additional AE burden, with harms consistent with the other injectable formulations that were assessed. The annualized AE risk associated with peginterferon beta-1a 125 mcg was generally lower than with the other injectable formulations. The annualized risk of injection-site reactions was similar between peginterferon beta-1a and IFN beta-1a 44 mcg three times a week, but higher than other IFNs and glatiramer acetate; however, the majority of these injection-site reactions were mild or moderate (similar to other IFNs and glatiramer acetate). Of note, 3% of patients using peginterferon beta-1a 125 mcg reported severe injection-site reactions during the two years of the ADVANCE trial.

Tramacere[36]

Trial Characteristics

Of the 39 included studies, 15 studies (40%) were active-comparator trials and 24 studies (60%) were placebo-controlled. For the assessment of overall risk of bias, the authors noted that three, 16, and 20 studies were deemed to be of low risk of bias, moderate risk of bias, and high risk of bias, respectively. Allocation methods were reported in 34 studies, while the authors noted that the other five trials were lacking in the information necessary to assess sequence generation. According to the authors, adequate allocation concealment was evident in 21 studies; one study used an unconcealed procedure, and the other 17 studies did not provide adequate information on allocation concealment. In addition, both investigators and patients were blinded in 12 studies; no blinding was reported in 15 studies, and sufficient information on blinding was not reported in 12 other studies. A low risk of detection bias was

evident in 19 studies, high risk was evident in seven studies, and sufficient information on detection bias was not provided in 13 studies, according to the authors. The criteria for low risk of incomplete outcome data were determined to be met in 20 studies; 14 studies were at high risk, and the remaining five studies did not provide sufficient information for this assessment. Patients lost to follow-up in the 39 included studies ranged between 0% and 43%, with a median of 11.9% and a mean of 13.5%. Only three trials did not report primary benefit outcomes (CONFIRM, DEFINE, and TEMSO).

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

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

Efficacy at 12 Months

No statistically significant differences were observed for the proportion of patients experiencing relapses over 12 months between those taking peginterferon beta-1a or any of the other first-line injectables (IFN beta-1a [Avonex, Rebif], IFN beta-1b [Betaseron], IFN beta, or glatiramer acetate) when examined using NMA (Table 9). In addition, pairwise analysis also confirmed that there were no statistically significant differences between peginterferon beta-1a and these agents (other than peginterferon beta-1a). Alemtuzumab, mitoxantrone, and natalizumab all demonstrated significantly lower proportions of patients experiencing relapses over 12 months when compared with each of the other active treatments examined in the NMA. Fingolimod also demonstrated significantly lower proportions of patients experiencing new relapses over 12 months when compared with all other treatments, except alemtuzumab.

There was no evidence of local inconsistency or heterogeneity for relapses over 12 months. In addition, there was no evidence for global inconsistency when examining the network as a whole, with $P = 0.99$, 0.97, and 0.08 for relapses over 12 months, relapses over 24 months, and disability worsening over 24 months, respectively.

No differences were observed between the results of the NMA analyses and the results from the pre-specified subgroup and sensitivity analyses.

No data were available to compare peginterferon beta-1a with other agents on disability progression at 12 months.

Harms

No statistically significant differences were observed for discontinuations due to AEs over 12 months between peginterferon beta-1a or any of the other first-line injectables (IFN beta-1a [Avonex, Rebif], IFN beta-1b [Betaseron], IFN beta, or glatiramer acetate) when examined using NMA (Table 9). Pairwise analysis confirmed there were no statistically significant differences between peginterferon beta-1a and the other injectables. Fingolimod was the only newer agent that, when compared with glatiramer acetate, teriflunomide, and IFN beta-1a (Avonex), demonstrated a significantly higher proportion of patients withdrawing due to AEs.

When examined using the pairwise meta-analysis, there were no statistically significant differences in the proportion of patients experiencing SAEs; however, the authors noted that SAEs were poorly reported, there was a very low number of events, and the results were heterogeneous.

TABLE 21: RESULTS OF THE NETWORK META-ANALYSIS BY TRAMACERE ET AL.

Treatment	Outcomes			
	Risk of Relapse Over 12 Months		Discontinuation Due to AEs Over 12 Months	
	RR	95% CI	RR	95% CI
PegIFN beta-1a versus:				
Avonex (IFN beta-1a)	0.96	0.72 to 1.28	0.64	0.22 to 1.85
Betaseron (IFN beta-1b)	0.91	0.48 to 1.72	–	–
Glatiramer acetate	0.90	0.68 to 1.19	0.77	0.27 to 2.21
Rebif (IFN beta-1a)	0.98	0.74 to 1.30	1.72	0.68 to 4.40
IFN beta	–	–	2.45	0 to NA

AE = adverse event; CI = confidence interval; IFN = interferon; NA = not available; PegIFN = peginterferon beta-1a; RR = risk ratio.
Note: Only treatments of first-line injectables were included in this table. Other treatment comparisons were discussed briefly in the narrative.

Critical Appraisal

The recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons were used to guide the critical appraisal of both NMAs.[36,60]

Tolley[60]

Strengths

The authors had clear objectives and rationale for performing their IDC. Their eligibility criteria, information sources, search strategy, data extraction, and quality assessment of individual studies were clearly outlined and appropriate, as was the study-selection process (for the most part — see Limitations). In particular, they assessed the risk of bias associated with the study-randomization process, baseline characteristics, blinding, withdrawals, outcome selection, reporting, and statistical analysis for each of the included trials. Outcome measures were described, as were inconsistencies associated with definitions between the different trials. Baseline characteristics of the individual trials were provided, along with the raw data of the efficacy outcome measures. It was also evident that all appropriate injectable comparators and their respectively approved dosing regimens were included.

Methods surrounding the NMA were provided, along with detailed network diagrams for each of the pre-specified outcome measures of interest. NMA results for both fixed effects and random effects models were performed to ascertain potential differences; model fit using the residual deviance and DIC for both the fixed effects and random effects models was ascertained. Accordingly, the random effects model was used for the primary analysis in order to account for between-trial heterogeneity. In addition, the authors used non-informative priors for the Bayesian NMA. Quality assessment of the included trials revealed one trial (INCOMIN) to be an outlier, and model fit statistics were used to determine that the INCOMIN trial could be excluded from subsequent analysis.

Numerous sensitivity analyses were performed, including those for blinding, sample size, and study duration. None of the results of the main analysis differed significantly from those obtained in the

sensitivity analyses (data not shown). All of the results from the primary and subsequent sensitivity analyses were presented in a clear fashion.

Limitations

Several limitations were observed regarding this NMA. Two of the main limitations, as noted by the authors, included the difference in the definitions of "relapse" and the assumption that the treatment effects were similar across trials despite the varying definitions. A more robust approach might have been to test the different definitions of relapse through sensitivity analyses. In addition, the individual study relapse rates (CADTH-calculated) were heterogeneous, ranging from 0.11 to 1.32 (0.4 in ADVANCE). Since these were not previously calculated by the authors, the report by Tolley et al. did not discuss the potential reasons why these relapse rates were so different across studies. It is possible that the heterogeneity was due to differences in relapse definition, how the studies dealt with missing data, or differences in the study population. Regardless of the source of heterogeneity, this aspect of the analysis increases the uncertainty surrounding the ARR NMA results.

The clinical expert involved in this review noted the lack of magnetic resonance imaging (MRI) outcomes in the NMA. As an objective outcome, MRI data could have provided further support for the results for relapse rate. No reason for excluding MRI outcomes was provided in the NMA report. It should be noted that the CADTH Therapeutic Review on MS drugs also did not perform an NMA on MRI outcomes for the following reason: ". . . data were sparsely reported and, in the case of MRI, eight out of 14 studies reporting MRI outcomes were subsets of randomized populations with unclear selection criteria for MRI scans." According to the clinical expert consulted for this review, another outcome not included in this NMA that would have been helpful in understanding the comparative efficacy of peginterferon beta-1a versus other treatments is the percentage of relapse-free patients at 12 months. In addition, health-related quality-of-life outcomes provide the patient perspective and help to inform whether treatments are effective. The authors did not include any of these outcomes in their analyses.

Another sensitivity analysis that could have been performed is removal, or separation of, studies involving treatment-experienced patients. Treatment experience is another potential source of between-study heterogeneity that could have been a confounding factor in the NMA.

While most steps in the process of selecting relevant articles were performed in duplicate, there was no description of duplicate selection during the initial screening of titles and abstracts; therefore, there remains the possibility that some studies may have been missed.

AE results were compared based on naive comparisons between trials rather than formal indirect comparisons. These results should therefore be interpreted with caution for many reasons, including potential differences across trials in AE definitions and study populations. The rationale for not analyzing AE data using NMA — i.e., that studies are not powered to detect significant differences in harms outcomes — is of questionable validity. Indeed, meta-analytic techniques offer a method for increasing power by pooling studies that individually may be underpowered. As well, it is unlikely that all studies included in the NMAs of sustained disability progression were powered for this outcome. Another potential limitation is that the authors chose to report only those AEs that occurred in at least 5% of patients in the ADVANCE trial; therefore, some important AEs (especially with regard to AEs associated with glatiramer acetate) may have been missed.

Tramacere[36]

Strengths

The authors provided clear objectives and rationale for performing their IDC. Their eligibility criteria, information sources, search strategy, study-selection process, data extraction, and assessment of study quality were clearly outlined and appropriate. In particular, they assessed the risk of bias associated with allocation concealment, blinding, incomplete outcome data, selective reporting, potential bias associated with sponsorship, methods of AE monitoring, and SAE definitions and reporting. In addition, outcome measures were provided. High-level descriptions of the baseline characteristics in the included studies were provided, along with reasons why certain evidence was downgraded; however, detailed baseline characteristics were not provided (see Limitations). A list of excluded studies was also provided, along with reasons for exclusion.

Methods for performing the NMA were provided, along with detailed network diagrams for each of the pre-specified outcome measures of interest; however, the actual studies examining discontinuations due to AEs over 12 months were not reported (see Limitations). Data analyses were based on random effects NMA (for indirect and mixed comparisons) and pairwise comparisons (for direct comparisons), and there were appropriate assessments of both heterogeneity and inconsistency (both local and global [e.g., involving the entire network]). The assumption of transitivity was evaluated and validated through an assessment of differences in EDSS scores, age, predefined effect modifiers, and duration of disease. Numerous pre-specified subgroup and sensitivity analyses were performed.

Limitations

Several limitations were observed regarding this NMA. The authors noted that evidence for 15 treatments for RRMS came from a small number of trials relative to the number of available treatments (only 39 RCTs were identified). Furthermore, evidence was primarily taken from only 16 of the studies (n = 16,162) and most of them were placebo-controlled (60%).

Evidence was frequently downgraded by the authors based on GRADE criteria from high quality to moderate or low quality for most comparisons. Only three of the 39 studies were judged to be at low risk of bias for outcome data being complete, outcome assessor blinding, and allocation concealment. With regard to inconsistency and imprecision, evidence for 40% of comparisons was downgraded for preventing relapses over 12 months.

As with the Tolley IDC,[60] MRI outcomes were not included in the NMA. As an objective outcome, according to the clinical expert consulted for this submission, MRI data could have provided further support for the results for the relapses over 12 months. No reason for excluding MRI outcomes was provided in the NMA report.

Significant limitations were noted in individual trials with respect to reporting of SAEs. The authors noted that SAE data were often sparsely or poorly reported, and heterogeneous.

4. Conclusion

The manufacturer provided one IDC by Tolley et al.[60] that compared the efficacy and safety of peginterferon beta-1a 125 mcg once every two weeks with other approved injectable IFNs and glatiramer acetate. Another IDC by Tramacere et al.[36] was identified in a monthly alert in September 2015. While the objectives for each of the IDCs were different, the results were similar with regard to the first-line injectable treatments. In patients with RRMS, no statistically significant differences were reported on ARR or sustained disability progression at three and six months between peginterferon

beta-1a 125 mcg once every two weeks and IFN beta-1a 30 mcg once weekly, IFN beta-1a 22 mcg three times a week, IFN beta-1a 44 mcg three times a week, IFN beta-1a 30 mcg once weekly, IFN beta-1b 250 mcg every other day, and glatiramer acetate 20 mg once daily.[60] However, these results require caution in their interpretation due to the heterogeneity across studies in the definition and baseline relapse rate across studies, and the relatively wide confidence intervals of the effect estimates. Only a naive comparison, rather than formal indirect comparison, was performed for AEs in the manufacturer's analysis; peginterferon beta-1a 125 mcg once every two weeks appeared to have a safety profile comparable to the included injectable IFNs and glatiramer acetate.[60] In the Tramacere review, neither the risk of relapse nor the risk of discontinuation due to AEs was statistically significantly different between peginterferon beta-1a and the other first-line injectable treatments.[36]

REFERENCES

1. PrPlegridy™ (peginterferon beta-1a) liquid for injection: 125 µg [product monograph]. Mississauga (ON): Biogen Canada Inc.; 2015 Aug 10.
2. Clinical study report: 105MS301. A multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of pegylated interferon beta-1a (BIIB017) in subjects with relapsing multiple sclerosis [**CONFIDENTIAL** internal manufacturer's report]. Cambridge (MA): Biogen Idec Inc.; 2014 Jun 27.
3. Arnold DL, Calabresi PA, Kieseier BC, Sheikh SI, Deykin A, Zhu Y, et al. Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. BMC Neurol [Internet]. 2014 [cited 2015 Aug 25];14:240. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4311432
4. Multiple sclerosis: management of multiple sclerosis in primary and secondary care [Internet]. London (UK): National Institute for Clinical Excellence; 2003. [cited 2015 Aug 20]. (NICE clinical guideline 8). Available from: http://www.nice.org.uk/guidance/cg8
5. Canadian Institute for Health Information. The burden of neurological diseases, disorders and injuries in Canada [Internet]. Ottawa (ON): The Institute; 2007. [cited 2015 Aug 20]. Available from: https://secure.cihi.ca/free_products/BND_e.pdf
6. Multiple Sclerosis Society of Canada [Internet]. Toronto (ON): The Society. About MS; 2014 [cited 2015 Aug 20]. Available from: http://mssociety.ca/en/information/default.htm
7. Freedman MS, Kaplan JM, Markovic-Plese S. Insights into the mechanisms of the therapeutic efficacy of alemtuzumab in multiple sclerosis. J Clin Cell Immunol [Internet]. 2013 Jul 8 [cited 2015 Aug 20];4(4). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3869402
8. Tsang BK, Macdonell R. Multiple sclerosis- diagnosis, management and prognosis. Aust Fam Physician [Internet]. 2011 Dec [cited 2015 Aug 20];40(12):948-55. Available from: http://www.racgp.org.au/download/documents/AFP/2011/December/201112tsang.pdf
9. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol [Internet]. 2011 Feb [cited 2015 Aug 20];69(2):292-302. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3084507
10. Freedman MS, Selchen D, Arnold DL, Prat A, Banwell B, Yeung M, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. Can J Neurol Sci. 2013 May;40(3):307-23.
11. CADTH therapeutic review. Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis [Internet]. Ottawa: CADTH; 2013 Oct; updated 2014 Mar. [cited 2015 Sep 21]. (CADTH therapeutic review vol. 1, no. 2b). Available from: https://www.cadth.ca/sites/default/files/pdf/TR0004_RRMS_ScienceReport_e.pdf
12. PrGilenya™ fingolimod (as fingolimod hydrochloride): oral capsules, 0.5 mg fingolimod (as fingolimod hydrochloride) [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2014 Feb 12.
13. PrTysabri® (natalizumab) concentrate for solution for intravenous infusion: 300 mg/15 mL [product monograph]. Mississauga (ON): Biogen Idec Canada Inc.; 2014 Nov 12.

14. PrLemtrada™ (alemtuzumab): 12 mg/1.2mL concentrate for solution for intravenous infusion [product monograph]. Mississauga (ON): Genzyme Canada Inc.; 2013 Dec 12.
15. PrTecfidera™ (dimethyl fumarate) delayed-release capsules,120 mg and 240 mg [product monograph]. Mississauga (ON): Biogen Idec Canada Inc.; 2014 Jan 23.
16. PrCopaxone® (glatiramer acetate) injection: 20 mg / 1 mL, pre-filled syringes for subcutaneous injection [product monograph]. Petach, Tikva (IL): Teva Pharmaceutical Industries Ltd.; 2011 Jul 7.
17. PrRebif® (interferon beta-1a): 8.8 µg/0.2 mL, 22 µg/0.5 mL and 44 µg/0.5 mL. Solution for injection in pre-filled syringes. Multidose 22 µg x 3 (66 µg/1.5 mL). Multidose 44 µg x 3 (132 µg/1.5 mL). Solution for Injection in pre-filled cartridges. PrRebif® RebiDose® 8.8 µg/0.2 mL, 22 µg/0.5 mL and 44 µg/0.5 mL. Solution for Injection in pre-filled pens [product monograph]. Mississauga (ON): EMD Serono, A Division of EMD Inc., Canada; 2013 May 2.
18. PrAvonex® (interferon beta-1a) liquid for injection [product monograph]. Mississauga (ON): Biogen Idec Canada Inc.; 2013 Jul 19.
19. PrExtavia (interferon beta1-b) lyophilized powder for subcutaneous injection: 0.3 mg/vial [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2014 Nov 12.
20. PrBetaseron® (interferon beta-1b) lyophilized powder for subcutaneous injection: 0.3 mg/vial [product monograph]. Toronto: Bayer Inc.; 2014 Nov 12.
21. PrAubagio™ (teriflunomide) tablets: 14 mg [product monograph]. Mississauga (ON): Genzyme Canada, a division of Sanofi-Aventis, Canada Inc.; 2013 Nov 12.
22. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014 Jul;13(7):657-65.
23. Kieseier BC, Arnold DL, Balcer LJ, Boyko AA, Pelletier J, Liu S, et al. Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. Mult Scler. 2015 Jul;21(8):1025-35.
24. Newsome SD, Guo S, Altincatal A, Proskorovsky I, Kinter E, Phillips G, et al. Impact of peginterferon beta-1a and disease factors on quality of life in multiple sclerosis. Mult Scler Relat Disord. 2015 Jul;4(4):350-7.
25. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Plegridy (peginterferon beta-1a) prefilled syringe and Plegridy Pen (peginterferon beta-1a) prefilled pen. Company: Biogen Idec, Inc. Application no.: 125499. Approval date: 8/15/2014. Rockville (MD): The Center; 2014 Sep 17 [cited 2015 Jul 15]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125499Orig1s000TOC.cfm.
26. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Plegridy (peginterferon beta-1a) prefilled syringe and Plegridy Pen (peginterferon beta-1a) prefilled pen. Company: Biogen Idec, Inc. Application no.: 125499. Approval date: 8/15/2014. Rockville (MD): The Center; 2014 Sep 17 [cited 2015 Jul 15]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125499Orig1s000TOC.cfm.
27. CDR submission: Plegridy™ (peginterferon beta-1a); 63, 94 and 125 µg/pre-filled syringe or pen. Company: Biogen Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Biogen Canada Inc.; 2015 Jun.
28. Lyseng-Williamson KA, Hoy SM. Peginterferon beta-1a in relapsing-remitting multiple sclerosis: a guide to its use in the EU. Drugs Ther Perspect. 2015;31(6):190-5.

29. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC Neurology [Internet]. 2014 [cited 2015 Aug 21];14:58. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3986942

30. Parmenter BA, Weinstock-Guttman B, Garg N, Munschauer F, Benedict RH. Screening for cognitive impairment in multiple sclerosis using the Symbol Digit Modalities Test. Mult Scler. 2007 Jan;13(1):52-7.

31. Alemtuzumab and the value of neurological research. Lancet Neurol. 2014 Mar;13(3):233.

32. Daniels GH, Vladic A, Brinar V, Zavalishin I, Valente W, Oyuela P, et al. Alemtuzumab-related thyroid dysfunction in a phase 2 trial of patients with relapsing-remitting multiple sclerosis. J Clin Endocrinol Metab [Internet]. 2014 Jan [cited 2015 Aug 20];99(1):80-9. Available from: http://press.endocrine.org/doi/pdf/10.1210/jc.2013-2201

33. Ruiz-Peña JL, Piñero P, Sellers G, Argente J, Casado A, Foronda J, et al. Magnetic resonance spectroscopy of normal appearing white matter in early relapsing-remitting multiple sclerosis: correlations between disability and spectroscopy. BMC Neurology [Internet]. 2004 Jun 10 [cited 2015 Aug 21];4:8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC446197

34. Costelloe L, O'Rourke K, Kearney H, McGuigan C, Gribbin L, Duggan M, et al. The patient knows best: significant change in the physical component of the Multiple Sclerosis Impact Scale (MSIS-29 physical). J Neurol Neurosurg Psychiatry [Internet]. 2007 Aug [cited 2015 Sep 10];78(8):841-4. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2117755

35. Manufacturer's comments on CDR clinical and pharmacoeconomic reviewers' reports on peginterferon beta-1a (Plegridy) [**CONFIDENTIAL** manufacturer's report]. Mississauga (ON): Biogen Canada Inc.; 2015 Oct 6.

36. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev. 2015 Sep 18;9:CD011381.

37. Potter VT, Krishnamurthy P, Barber LD, Lim Z, Kenyon M, Ireland RM, et al. Long-term outcomes of alemtuzumab-based reduced-intensity conditioned hematopoietic stem cell transplantation for myelodysplastic syndrome and acute myelogenous leukemia secondary to myelodysplastic syndrome. Biol Blood Marrow Transplant. 2014 Jan;20(1):111-7.

38. Alemtuzumab. Gynakologische Praxis. 2006;30(1):171.

39. Barkhof F. MR imaging in monitoring the treatment of MS: making good use of resources. Advances in MRI Contrast. 1996;4(2):46-53.

40. Derwenskus J, Lublin FD. Future treatment approaches to multiple sclerosis. Handb Clin Neurol. 2014;122:563-77.

41. Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. Med Care. 2005 Jul;43(7):736-49.

42. Kohn CG, Sidovar MF, Kaur K, Zhu Y, Coleman CI. Estimating a minimal clinically important difference for the EuroQol 5-Dimension health status index in persons with multiple sclerosis. Health Qual Life Outcomes [Internet]. 2014 [cited 2015 Aug 21];12:66. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4018196

43. Ontaneda D, LaRocca N, Coetzee T, Rudick R, NMSS MSFC Task Force. Revisiting the Multiple Sclerosis Functional Composite: proceedings from the National Multiple Sclerosis Society (NMSS) Task Force on Clinical Disability Measures. Mult Scler. 2012 Aug;18(8):1074-80.

44. Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, Jak AJ, et al. Use of the Multiple Sclerosis Functional Composite as an outcome measure in a phase 3 clinical trial. Arch Neurol. 2001 Jun;58(6):961-7.

45. Polman CH, Rudick RA. The Multiple Sclerosis Functional Composite: a clinically meaningful measure of disability. Neurology. 2010 Apr 27;74 Suppl 3:S8-15.

46. Learmonth YC, Hubbard EA, McAuley E, Motl RW. Psychometric properties of quality of life and health-related quality of life assessments in people with multiple sclerosis. Qual Life Res. 2014 Sep;23(7):2015-23.

47. Busija L, Pausenberger E, Haines TP, Haymes S, Buchbinder R, Osborne RH. Adult measures of general health and health-related quality of life: Medical Outcomes Study Short Form 36-Item (SF-36) and Short Form 12-Item (SF-12) Health Surveys, Nottingham Health Profile (NHP), Sickness Impact Profile (SIP), Medical Outcomes Study Short Form 6D (SF-6D), Health Utilities Index Mark 3 (HUI3), Quality of Well-Being Scale (QWB), and Assessment of Quality of Life (AQoL). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S383-412.

48. Nortvedt MW, Riise T, Maeland JG. Multiple sclerosis and lifestyle factors: the Hordaland Health Study. Neurol Sci. 2005 Dec;26(5):334-9.

49. Klawiter EC. Current and new directions in MRI in multiple sclerosis. Continuum (Minneap Minn) [Internet]. 2013 Aug [cited 2015 Aug 20];19(4 Multiple Sclerosis):1058-73. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4234130/pdf/20130800.0-0017.pdf

50. Rovira A, Auger C, Alonso J. Magnetic resonance monitoring of lesion evolution in multiple sclerosis. Ther Adv Neurol Disord [Internet]. 2013 Sep [cited 2015 Aug 20];6(5):298-310. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3755529/pdf/10.1177_1756285613484079.pdf

51. Schaffler N, Kopke S, Winkler L, Schippling S, Inglese M, Fischer K, et al. Accuracy of diagnostic tests in multiple sclerosis--a systematic review. Acta Neurol Scand. 2011 Sep;124(3):151-64.

52. Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. Lancet Neurol. 2013 Jul;12(7):669-76.

53. Sormani MP, Stubinski B, Cornelisse P, Rocak S, Li D, De Stefano N. Magnetic resonance active lesions as individual-level surrogate for relapses in multiple sclerosis. Mult Scler. 2011 May;17(5):541-9.

54. Sormani MP, Bonzano L, Roccatagliata L, De Stefano N. Magnetic resonance imaging as surrogate for clinical endpoints in multiple sclerosis: data on novel oral drugs. Mult Scler. 2011 May;17(5):630-3.

55. Kappos L, Moeri D, Radue EW, Schoetzau A, Schweikert K, Barkhof F, et al. Predictive value of gadolinium-enhanced magnetic resonance imaging for relapse rate and changes in disability or impairment in multiple sclerosis: a meta-analysis. Gadolinium MRI Meta-analysis Group. Lancet. 1999 Mar 20;353(9157):964-9.

56. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain. 2001 May;124(Pt 5):962-73.

57. McGuigan C, Hutchinson M. The Multiple Sclerosis Impact Scale (MSIS-29) is a reliable and sensitive measure. J Neurol Neurosurg Psychiatry [Internet]. 2004 Feb [cited 2015 Sep 10];75(2):266-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1738881

58. Riazi A, Hobart JC, Lamping DL, Fitzpatrick R, Thompson AJ. Multiple Sclerosis Impact Scale (MSIS-29): reliability and validity in hospital based samples. J Neurol Neurosurg Psychiatry [Internet]. 2002 Dec [cited 2015 Sep 10];73(6):701-4. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1757371

59. Clinical study report: 105MS302. A dose-frequency blinded, multicenter, extension study to determine the long-term safety and efficacy of pegylated interferon beta-1a (BIIB017) in subjects with relapsing multiple sclerosis [**CONFIDENTIAL** internal manufacturer's report]. Cambridge (MA): Biogen Idec Inc.; 2013 Apr 23.

60. Tolley K, Hutchinson M, You X, Wang P, Sperling B, Taneja A, et al. A network meta-analysis of efficacy and evaluation of safety of subcutaneous pegylated interferon beta-1a versus other injectable therapies for the treatment of relapsing-remitting multiple sclerosis. PLoS One [Internet]. 2015 [cited 2015 Jul 29];10(6):e0127960. Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0127960