CADTH

CADTH Common Drug Review

Clinical Review Report

Ozanimod (Zeposia)

(Celgene Inc., a Bristol Myers Squibb company)

Indication: Treatment of Adult Patients With Relapsing-Remitting Multiple Sclerosis

Service Line:	Common Drug Review
Version:	Final (with redactions)
Publication Date:	August 2021
Report Length:	178 Pages

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

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Abbreviations

9-HPT	9-Hole Peg Test
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARR	annual relapse ratio
AST	aspartate aminotransferase
CDP	confirmed disability progression
CDP12	confirmed disability progression at 12 months
CDP24	confirmed disability progression at 24 months
CI	confidence interval
CMSWG	Canadian Multiple Sclerosis Working Group
CNS	central nervous system
CrI	credible interval
DIC	deviance information criterion
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
GdE	gadolinium-enhanced
HR	hazard ratio
HRQoL	health-related quality of life
IM	intramuscular
ITC	indirect treatment comparison
ITT	intention-to-treat
LCLA	Low-Contrast Letter Acuity Test
LOCF	last observation carried forward
MAIC	matching adjusted indirect comparison
MID	minimal important difference
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite

MSQOL-54	Multiple Sclerosis Quality of Life-54 items
NEDA	no evidence of disease activity
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OLE	open-label extension
PASAT	Paced Auditory Serial Addition Test
PPMS	primary progressive multiple sclerosis
PRMS	progressive relapsing multiple sclerosis
RCT	randomized controlled trial
RR	rate ratio
RMS	relapsing forms of multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
S1P	sphingosine 1-phosphate
SAE	serious adverse event
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SPMS	secondary progressive multiple sclerosis
T25W	Timed 25-Foot Walk

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Ozanimod (Zeposia) capsule 0.23 mg, 0.46 mg, 0.92 mg (as ozanimod hydrochloride), oral
Indication	The treatment of patients with relapsing-remitting multiple sclerosis to decrease the frequency of clinical exacerbations
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard review
Notice of Compliance date	October 2, 2020
Sponsor	Celgene Inc., a Bristol Myers Squibb company

Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory, demyelinating disease of the central nervous system (CNS).[1] It is more prevalent in females than in males and has a mean age of onset from 28 to 31 years.[2] The Public Health Agency of Canada reports that more than 77,000 Canadians live with MS and about 60% of newly diagnosed adults are between the ages of 20 and 49 years.[3] Symptoms of MS are varied and include painful monocular vision loss, double vision, motor weakness, gait disturbance and balance problems, pain, spasticity, sensory symptoms in the limbs or face, and bladder and bowel symptoms.[1,4] Relapsing-remitting multiple sclerosis (RRMS) is characterized by episodes of symptom exacerbation, or relapses, that are followed by partial or complete remission. During these episodes, symptoms generally develop over hours or days and then go into remission over weeks or months.[5] Most patients who initially present with RRMS go on to develop secondary progressive multiple sclerosis (SPMS), which is a progressive phase of the disease.[1,4]

There is currently no curative treatment for MS. The principal goal of treatment for RRMS is to delay or prevent the accumulation of disability by reducing the frequency of relapses and MRI lesions.[6] It is recommended that all patients with MS should begin treatment with a disease-modifying therapy (DMT) as soon as possible following diagnosis to reduce the risk of disability worsening and improve long-term outcomes.[6,7] Several DMTs for RRMS available in Canada allow for a personalized approach to treatment. As direct comparative evidence is limited for first-line DMTs, treatments are selected based on the individual's level of disease activity, disease severity, and comorbidities, as well as the drug safety profile.[6,8] Treatment optimization by switching DMTs is typically carried out in the event of a lack of efficacy or poor tolerability.

The current drug under review, ozanimod, is a sphingosine 1-phosphate (S1P) receptor modulator. It is available as 0.23 mg, 0.46 mg, and 0.92 mg capsules of ozanimod hydrochloride for the treatment of patients with RRMS to decrease the frequency of clinical exacerbations.[9] The Health Canada–recommended initial dose-escalation regimen of ozanimod is 0.23 mg once daily on days 1 to 4 then 0.46 mg once daily on days 5 to 7. The maintenance dosage is 0.92 mg once daily taken orally starting on day 8.[9] The sponsor has requested reimbursement of ozanimod as per the Health Canada–approved indication.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of ozanimod capsules (0.23 mg, 0.46 mg, and 0.92 mg) for the treatment of patients with RRMS.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from a clinical expert consulted by CADTH for the purpose of this review.

Patient Input

One patient group responded to the call from CADTH to provide input on the topic: The Multiple Sclerosis Society of Canada, an organization that provides programs and services for people with MS and their families and advocates for those living with MS. The society collected condition-related patient input from an online survey posted on the main page of its national website (www.mssociety.ca) and Facebook page between August 4, 2020, and September 4, 2020, in both English and French. Most respondents appeared to be from Canada. However, "country of origin" was not a survey question. A total of 69 people responded to the survey: 75% were female; more than 91% were MS patients and the remainder were caregivers; 71% had RRMS, 4% had SPMS, 7.2% had primary progressive multiple sclerosis (PPMS), and 6% were unsure of the type of MS they had. The ages of respondents ranged from 31 years to 60 years.

According to the input received from the patient group, the most common symptoms of MS include fatigue, difficulty walking, visual impairment, cognitive difficulties, depression, weakness, bladder problems, and pain. Other symptoms may include trouble with balance, sexual dysfunction, spasticity, tremors, and difficulty speaking and swallowing.

Patients noted that, depending on the type and severity of the symptoms, an individual's quality of life can be greatly affected. Living with MS creates employment issues such as the inability to maintain a stable job or remain in the workplace due to relapses, symptoms, medication side effects, and disability progression.

There is a growing number of high-efficacy DMTs, with varied administrations, dosing schedules, and decreased monitoring requirements — factors that are consistently identified as priorities for patients when selecting a DMT. Patients place a high value on the ability to choose the administration, dosing schedule, side-effect profile, and level of medication monitoring that best fits their lifestyle and personal preference.

Patients reported that common side effects associated with current therapies include injection-site reactions, flushing, hair-thinning, skin rash or hives, joint and/or musculoskeletal pain, gastrointestinal symptoms, increased risk of infections, and flu-like symptoms.

Ozanimod offers patients an oral regimen, eliminating the need to take time away from work, school, or other commitments.

Clinician Input

According to the clinical expert consulted by CADTH for this review, the ideal goal for patients with RRMS is a cure. In the absence of a cure, the clinical expert identified the following current goals of treatment with DMTs: delay disease progression, decrease the

burden of disability/symptoms, decrease the number and severity of relapses, preserve mobility and cognition, and facilitate independence and employment.

The clinical expert indicated that personalized medicine — choosing the right DMT for the right patient — is the best overall approach. The clinical expert did not identify a specific group of patients with the greatest unmet need for a treatment such as ozanimod, but noted that ozanimod would be an option for all persons with RRMS who require a DMT.

The clinical expert stated that ozanimod should not be used in combination with any other DMT. In the expert's opinion, ozanimod would be an ideal first-line treatment, as well as an option when switching treatments due to lack of efficacy with a different DMT, following personalized treatment and/or medicine.

According to the clinical expert, response to treatment should be assessed yearly in patients with MS. To determine whether a patient is responding to treatment in clinical practice, the clinical expert recommended patients be monitored clinically and radiologically.

When making a decision to discontinue treatment, factors such as safety (for example, in those over the age of 65) and significant disability (an Expanded Disability Status Scale [EDSS] score of 8.0) should be considered.

Last, the clinical expert stated that any health care setting (community setting, hospital or outpatient clinic, or specialty clinic) would be appropriate for treatment with ozanimod. The expert indicated that it would be ideal to have a specialist diagnose, treat, and monitor patients who might receive ozanimod, but acknowledged that it may be difficult to access such specialists in some areas of the country.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The 2 pivotal trials for ozanimod, RADIANCE Part B (N = 1,320) and SUNBEAM (N = 1,346), were the only studies that met the criteria for inclusion in the CADTH systematic review. The RADIANCE Part B and SUNBEAM studies followed a randomized, double-blind, double-dummy, active comparator-controlled, parallel-group, multi-centre design. The main difference between the 2 phase III studies was the duration of treatment, which was 24 months for RADIANCE Part B, and up to approximately 22 months (mean duration of 13.6 months) for SUNBEAM, with treatment continued until all patients received a minimum of 12 months of treatment. Patients included in the 2 studies were adults (18 to 55 years of age) with a diagnosis of relapsing forms of MS (RMS), an EDSS score of between 0 and 5.0 (inclusive), and documentation of recent (1 to 2 years) disease activity based on relapses and/or imaging features. Patients were randomized 1:1:1 to receive either ozanimod 1 mg once daily, ozanimod 0.5 mg once daily, or interferon beta-1a 30 mcg, administered as an intramuscular (IM) injection weekly in a double-dummy manner. The primary objective of both studies was to assess whether the clinical efficacy of ozanimod is superior to interferon beta-1a in reducing the rate of confirmed clinical relapses based on the annualized relapse rate (ARR) in patients with RMS. The key secondary objectives were to assess whether the efficacy of ozanimod is superior to interferon beta-1a in terms of various disability outcomes based on the EDSS, MRI outcomes, Multiple Sclerosis

Functional Composite (MSFC), and Low-Contrast Letter Acuity (LCLA) tests. In addition, health-related quality of life (HRQoL) as measured by the Multiple Sclerosis Quality of Life-54 items (MSQOL-54), mobility (Timed 25-Foot Walk [T25FW]), 9-Hole Peg Test [9-HPT]), cognitive function (Symbol Digital Modalities Test [SDMT]) in SUNBEAM, and Paced Auditory Serial Addition Test (PASAT) in RADIANCE Part B, as well as a composite outcome for no evidence of disease activity (NEDA), were reported in the 2 trials. Ozanimod 0.5 mg is not an approved maintenance dose in Canada and therefore this review focused on the ozanimod 1 mg dose.

The majority of patients were female (63% to 69%) and White (98% to 100%), with a mean age of 35.5 years (range of 18 to 55 years) and a mean body mass index of 24.19 kg/m^2. The majority of enrolled patients were from the Eastern European region (86% to 94%), with only 1 patient enrolled from Canada. Most patients had RRMS at study entry (98.1%) and the remainder had SPMS (0.17%) or progressive relapsing multiple sclerosis (PRMS) (1.7%). The mean number of years since MS diagnosis ranged from 3.60 to 3.97. Approximately 98% of patients had at least 1 relapse in the past year, including approximately 27% of patients with at least 2 relapses. Patients had a range of disability, with a mean EDSS score of 2.6, and 17.2% of patients had an EDSS score of at least 3.5. Approximately 70% of the patients were DMT-naive in spite of a mean duration since MS symptom onset of 6.96 years in the SUNBEAM study and 6.50 years in RADIANCE Part B study.

Efficacy Results

A summary of key efficacy results from the 2 pivotal trials, RADIANCE Part B and SUNBEAM, is provided in Table 2.

The primary outcome in RADIANCE Part B was the ARR at the end of month 24, and in SUNBEAM it was the ARR during the treatment period. The ARR was based on confirmed clinical relapses. In RADIANCE Part B, the adjusted ARRs in patients in the ozanimod 1 mg and interferon beta-1a treatment groups were 0.172 (95% confidence interval [CI], 0.142 to 0.208) and 0.276 (95% CI, 0.234 to 0.324), respectively. This corresponded to a reduction in the ARR of 37.662% (95% CI, 23.222 to 49.386; P < 0.0001), in favour of ozanimod 1.0 mg. Similarly, in SUNBEAM, the adjusted ARRs in patients in the ozanimod 1 mg treatment group and interferon beta-1a treatment group were 0.181 (95% CI, 0.140 to 0.236) and 0.350 (95% CI, 0.279 to 0.440), respectively. This corresponded to a reduction in the ARR of 48.211% (95% CI, 33.702 to 59.545; P < 0.0001) in favour of ozanimod 1.0 mg. This reduction was also considered clinically relevant by the clinical expert consulted by CADTH. These results from both RADIANCE Part B and SUNBEAM were supported by multiple pre-specified sensitivity analyses, including confirmed and unconfirmed relapses assuming a negative binomial distribution. In both RADIANCE Part B and SUNBEAM the rate ratios (RRs) and 95% CIs for the ARR were generally consistent across the subgroups (age, relapses in prior 12 months, baseline gadolinium-enhanced (GdE) lesions, baseline EDSS, and prior use of a DMT). The use of the ARR as the primary end point is aligned with guidance from the European Medicines Association (EMA)[10] and is a clinically relevant outcome to clinicians, as indicated by the clinical expert consulted for this review.

The number of new or enlarging hyperintense T2-weighted brain MRI lesions and the number of GdE brain MRI lesions were included in the pivotal trials as key secondary outcomes, which were also included in the statistical testing hierarchy. Ozanimod 1 mg demonstrated superiority to interferon beta-1a in terms of the number of new or enlarging hyperintense T2-weighted brain MRI lesions, with reductions in new or enlarging

hyperintense T2 lesions in favour of ozanimod 1.0 mg of 42.351% (95% CI, 28.580 to 53.467; P < 0.0001) and 48.330% (95% CI, 37.469 to 57.304; P < 0.0001) in RADIANCE Part B and SUNBEAM, respectively. Similarly, ozanimod 1 mg was superior to interferon beta-1a in terms of the number of GdE brain MRI lesions, with a 52.944% (95% CI, 27.530 to 69.445; P = 0.0006) and 62.973% (95% CI, 46.406 to 74.419; P < 0.0001) reduction in number of GdE brain MRI lesions in RADIANCE Part B and SUNBEAM, respectively. Although ozanimod 1 mg achieved statistical significance in the reduction of lesion numbers over interferon beta-1a group, [redacted].

After 1 year on study treatment, the proportions of patients meeting the criteria for NEDA in SUNBEAM were 26.8 (95% CI, 22.3 to 31.2) and 22.5 (95% CI, 18.3 to 26.8) for the ozanimod 1 mg and interferon beta-1a treatment groups, respectively. After 2 years on study treatment, the proportions of patients meeting the criteria for NEDA in RADIANCE Part B were 24.2 (95% CI, 19.5 to 28.8) and 17.0 (95% CI, 13.0 to 21.0) for the ozanimod 1 mg and interferon beta-1a treatment groups, respectively. This outcome was not controlled for multiplicity, limiting the ability to draw conclusions based on this outcome.

The MSQOL-54 is a well-validated HRQoL outcome for patients with MS, with minimal important differences (MIDs) of 2.5 points and 1.5 points from total scores of 100 for the mental and physical summary scores, respectively. In RADIANCE Part B, the between-group difference for the physical health composite summary score was 1.345 (95% CI, −0.252 to 2.943; P = 0.0988), [redacted]. In SUNBEAM, the between-group difference for the physical health composite summary score was 1.642 (95% CI, 0.104 to 3.180; nominal P = 0.0364), [redacted]. However, the MSQOL-54 as was not included in the statistical testing hierarchy. In addition, in both studies [redacted]

There was no difference between treatment groups for the assessment of MSFC, T25FW, and 9-HPT in either study. The clinical expert consulted for this review suggested that treatments such as ozanimod are designed to reduce relapses and inflammatory activity, but a change in mobility is the result physiotherapy and other paramedical services that patients are able to focus on when active disease is less of a barrier. As a result, significant changes in mobility may not be recognized in the short term, and patients should be followed for more than 2 years to assess these outcomes.

In the RADIANCE Part B and SUNBEAM studies, cognitive function was assessed using different measures (SDMT in SUNBEAM and PASAT in RADIANCE Part B), but neither of these measures were included in the statistical testing hierarchy. Further, input from the clinical expert consulted for this review indicated that the duration of the studies may not be adequate to observe any potential changes in cognitive function.

Time to onset of disability progression, as defined by a sustained worsening of 1.0 points or more in EDSS scores confirmed after 3 months and again after 6 months, was a key

secondary end point in both SUNBEAM and RADIANCE Part B studies. Neither study demonstrated a benefit from ozanimod compared to interferon beta-1a with regard to disease progression.

Harms Results

In the RADIANCE Part B study, the majority of patients reported at least 1 treatment-emergent adverse event (AE), with 324 patients (74.7%) in the ozanimod 1 mg group and 365 patients (83.0%) in the interferon beta-1a group experiencing at least 1 treatment-emergent AE. In the SUNBEAM study, 268 patients (59.8) in the ozanimod 1 mg group and 336 patients (75.5) in the interferon beta-1a group experienced at least 1 treatment-emergent AE. The most commonly reported AEs overall were influenza-like illness (3.8% to 51.0%), nasopharyngitis (6.7% to 15.7%), headache (5.6% to 12.0%), upper respiratory tract infection (4.0% to 8.4%), increased alanine aminotransferase (ALT) (1.8% to 6.0%), and pyrexia (1.1% to 6.4%). In both studies, influenza-like illness, upper respiratory tract infection, and pyrexia were reported in greater proportions of patients in the interferon beta-1a group (influenza-like illness, 48.9% to 51.0%; upper respiratory tract infection, 4.4% to 8.4%; pyrexia, 6.3% to 6.4%) compared with the ozanimod 1 mg group (influenza-like illness, 3.8% to 6.2%; upper respiratory tract infection, 4.0% to 7.8%; pyrexia, 1.1% to 2.5%). The overall higher incidence of AEs in the interferon beta-1a treatment group compared with the ozanimod treatment groups can be attributed to the predominance of influenza-like illness and pyrexia events.

Serious adverse events (SAEs) were reported by 2.5% to 6.5% of patients in the treatment groups of both studies, but the frequency of individual SAEs was low. In the RADIANCE Part B study, SAEs occurring in more than 1 patient in any treatment group were appendicitis (ozanimod 1 mg: 2 patients [0.5%]; interferon beta-1a: 2 patients [0.5%]) and ovarian cysts (ozanimod 1 mg: 2 patients [0.5%]; interferon beta-1a: 0 patients). In the SUNBEAM study, no SAE was reported in more than 1 patient in either treatment group.

The proportions of patients who stopped treatment due to AEs were also low, ranging from 2.9% and 4.1% of patients across the 2 pivotal trials, and were similar between treatment groups in each study.

No deaths were reported during the SUNBEAM study. In the RADIANCE Part B study, 1 death due to chronic kidney failure in the ozanimod 1 mg group occurred 157 days after treatment discontinuation.

Adverse events of special interest were rare, and the only events that occurred in more than 1 patient in RADIANCE Part B were increased ALT (6 patients [1.4%] in the ozanimod 1 mg group, and 8 patients [1.8%] in the interferon beta-1a group), increased aspartate aminotransferase (AST) (5 patients [1.1%] in the interferon beta-1a group), increased transaminases (2 patients [0.5%] in the ozanimod 1 mg group), increased blood pressure (3 patients [0.7%] in the ozanimod 1 mg group), and macular edema (2 patients [0.5%] in the interferon beta-1a group). In SUNBEAM, events that occurred in more than 1 patient were increased ALT and increased blood pressure, which were reported in 3 patients (0.7%) and 4 patients (0.9%), respectively, in the ozanimod 1 mg group.

Table 2: Summary of Key Results from RADIANCE Part B and SUNBEAM

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	IFN beta-1a 30 mg (N = 441)	Ozanimod 1 mg (N = 447)	IFN beta-1a 30 mcg (N = 448)
Annualized relapse rate during the treatment period[a]				
Total number of relapses	143	236	97	184
Adjusted annualized relapse rate (95% CI)	0.172 (0.142 to 0.208)	0.276 (0.234 to 0.324)	0.181 (0.140 to 0.236)	0.350 (0.279 to 0.440)
Rate ratio (ozanimod/IFN beta-1a) (95% CI)	0.623 (0.506 to 0.768)	Reference	0.518 (0.405 to 0.663)	Reference
Reduction (95% CI)	37.662% (23.222 to 49.386)	Reference	48.211% (33.702 to 59.545)	Reference
P value	< 0.0001		< 0.0001	
Number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months in RADIANCE Part B and over 12 months in SUNBEAM[b]				
Number of patients contributing to the analysis	327	336	388	382
Rate atrio (ozanimod/IFN beta-1a) (95% CI)[c]	0.576 (0.465 to 0.714)	Reference	0.517 (0.427 to 0.625)	Reference
Percent reduction (95% CI)[c]	42.351 (28.580 to 53.467)	Reference	48.330 (37.469 to 57.304)	Reference
P value[c]	< 0.0001		< 0.0001	
Number of GdE brain MRI lesions at month 24 in RADIANCE Part B and at month 12 in SUNBEAM				
Number of patients contributing to the analysis	327	336	388	382
Adjusted mean (95% CI)[d]	0.176 (0.116 to 0.266)	0.373 (0.256 to 0.543)	0.160 (0.106 to 0.242)	0.433 (0.295 to 0.635)
Rate ratio (ozanimod/IFN beta-1a) (95% CI)[d]	0.471 (0.306 to 0.725)	Reference	0.370 (0.256 to 0.536)	Reference
Percent reduction (95% CI)[d]	52.944 (27.530 to 69.445)	Reference	62.973 (46.406 to 74.419)	Reference
P value[d]	0.0006		< 0.0001	
Change from baseline to month 24 in RADIANCE Part B and to month 12 in SUNBEAM in the physical health composite summary of the MSQOL-54				
n	433	441	443	445
Mean (SD)	0.209 (12.321)	−1.526 (12.319)	1.925 (11.870)	0.046 (12.578)
Difference in means (95% CI)[e]	1.345 (−0.252 to 2.943)	Reference	1.642 (0.104 to 3.180)	Reference
P value[e]	0.0988		0.0364[f]	
[redacted]				
n	[redacted]			
Mean (SD)	[redacted]			

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	IFN beta-1a 30 mg (N = 441)	Ozanimod 1 mg (N = 447)	IFN beta-1a 30 mcg (N = 448)
Difference in means (95% CI)[e]	[redacted]		[redacted]	
P value[e]	[redacted]		[redacted]	
Harms, n (%) (safety population)				
Adverse events	324 (74.7)	365 (83.0)	268 (59.8)	336 (75.5)
Serious adverse events	28 (6.5)	28 (6.4)	13 (2.9)	11 (2.5)
WDAEs (from study treatment)	13 (3.0)	18 (4.1)	13 (2.9)	16 (3.6)
Deaths	1 (0.2)	0	0	0
Notable harms				
Infections and infestations				
Herpes zoster	1 (0.2)	0	0	1 (0.2)
Varicella-zoster virus infection	1 (0.2)	0	0	0
Corynebacterium Infection	0	0	1 (0.2)	0
Abscess limb	0	0	0	1 (0.2)
Hepatitis C	0	0	0	1 (0.2)
Bradycardia	0	0	0	0
Liver-function tests				
Increased alanine aminotransferase	6 (1.4)	8 (1.8)	3 (0.7)	1 (0.2)
Increased aspartate aminotransferase	0	5 (1.1)	0	0
Increased transaminases	2 (0.5)	0	0	1 (0.2)
Liver-function test abnormal	0	1 (0.2)	1 (0.2)	1 (0.2)
Effects in pregnancy				
Vanishing twin syndrome	1 (0.2)	0	0	0
Placental polyp	1 (0.2)	0	0	0
Spontaneous abortion	0	0	1 (0.2)	0
Increased blood pressure	3 (0.7)	1 (0.2)	4 (0.9)	1 (0.2)
Decreased pulmonary function	1 (0.2)	0	0	0
Eye disorder				
Macular edema	1 (0.2)	2 (0.5)	0	1 (0.2)
Macular hole	0	1 (0.2)	0	0
Maculopathy	0	0	0	1 (0.2)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	IFN beta-1a 30 mg (N = 441)	Ozanimod 1 mg (N = 447)	IFN beta-1a 30 mcg (N = 448)
Neoplasms (benign, malignant and unspecified, including cysts and polyps)				
Basal cell carcinoma	1 (0.2)	0	1 (0.2)	0
Breast cancer	1 (0.2)	0	0	0
Invasive breast carcinoma	1 (0.2)	0	0	0
Chronic lymphocytic leukemia	0	1 (0.2)	0	0

CI = confidence interval; GdE = gadolinium-enhanced; IFN = interferon; MSQOL-54 = Multiple Sclerosis Quality of Life-54 items; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] Based on the Poisson regression model, adjusted for region (Eastern Europe versus rest of the world), age at baseline, and the baseline number of GdE lesions, and including the natural log transformation of time on study as an offset term.

[b] Based on number of new or enlarging T2 lesions over 24 months in RADIANCE Part B and over 12 months in SUNBEAM at a patient level.

[c] Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe versus rest of the world), age at baseline, and baseline number of GdE lesions. The natural log transformation of the number of available MRI scans over 24 months in RADIANCE Part B and over 12 months in SUNBEAM is used as an offset term.

[d] Based on the negative binomial regression model, adjusted for region (Eastern Europe versus rest of the world), age at baseline, and the baseline number of GdE lesions. The natural log transformation of the number of available MRI scans at 24 months in RADIANCE Part B and at 12 months in SUNBEAM (1 scan per patient) was used as an offset term.

[e] Difference in means and P value for comparison between the ozanimod and IFN beta-1a 30 mcg treatment groups are based on an analysis of covariance model, adjusted for region (Eastern Europe versus rest of the world), Expanded Disability Status Scale category as recorded by an interactive voice response system, and the baseline summary score of interest. Missing data were imputed using a mixed-effects regression model (random slope and intercept).

[f] P value has not been adjusted for multiple testing.

Source: Clinical Study Reports for the RADIANCE Part B and SUNBEAM trials.[11,12]

Critical Appraisal

Overall, the RADIANCE Part B and SUNBEAM trials were well conducted and consistent with guidance from the EMA on clinical trials of treatments for MS. A double-blind, double-dummy study design was employed to maintain blinding in the studies; however, differential frequencies of AEs that are known risks of treatment with interferon beta-1a had potential for unblinding. In both trials, the rate of withdrawal was disproportionate, with more patients discontinuing in the interferon beta-1a groups (8.0% and 15.1%) compared with the ozanimod 1 mg groups (6.5% and 10.4%). This difference between the treatment groups suggests that the rate of withdrawal may have been influenced by unblinding or post-randomization events. [redacted] The imputation methodologies in 2 of the pre-specified sensitivity analyses allowed a patient who dropped out of the study early to have a lesion number value imputed as the average lesion number of the patients who had completed a longer study. In other words, patients who remained in the trial for longer periods likely had greater cumulative treatment effects compared with the patients who were earlier dropouts, which could also introduce a bias into the analysis. As the dropout rate was higher for the interferon beta-1a group, this would likely overestimate the effect in the interferon beta-1a group, which would likely bias results conservatively against ozanimod.

Both RADIANCE Part B and SUNBEAM included mainly Eastern European centres, almost exclusively White patients, few North American centres, and only 1 Canadian patient from 1

centre. The clinical expert consulted by CADTH for this review noted that standard care in Eastern Europe may differ from Canada's in that a greater proportion of patients with MS may be treatment-naive. However, the clinical expert did not expect any difference in how MS progresses between Eastern European and North American populations. The majority of study participants were female, which is consistent with populations for relapsing MS. Diagnosis of MS was based on 2010 revised McDonald criteria, which is consistent with Canadian clinical practice. The clinical expert consulted by CADTH suggested that the patients enrolled in the pivotal trials were reasonably reflective of patients encountered in routine Canadian practice. Patients were required to have an EDSS score of 0 to 5.0 to be eligible for the RADIANCE Part B and SUNBEAM studies. Although common in clinical trials for MS, this criterion excludes a number of patients with more severe disability who could be eligible to receive ozanimod in clinical practice. The efficacy and safety of ozanimod in such patients is uncertain. Approximately 30% of patients across all treatment groups in both studies had been previously treated with a DMT.

Indirect Comparisons

Description of Studies

Two indirect treatment comparisons (ITCs) were identified, reviewed, and critically appraised; 1 was submitted and commissioned by the sponsor,[13] and 1 (Swallow et al.[14]) was funded by the sponsor. The sponsor-submitted ITC[13] conducted a systematic review and used a Bayesian network meta-analysis (NMA) to evaluate the relative clinical efficacy and safety of ozanimod 1 mg compared to cladribine, dimethyl fumarate, fingolimod, teriflunomide, alemtuzumab, natalizumab, ocrelizumab, glatiramer acetate, interferon beta-1a, interferon beta-1b, and peginterferon beta-1a in adult patients with RRMS. While Swallow et al.[14] included no systematic review, a matching adjusted indirect comparison (MAIC) was used to compare ozanimod to fingolimod in patients with RRMS, using individual patient data from the RADIANCE Part B and SUNBEAM trials to match and adjust patients to those included in the comparator trials.

Efficacy Results

The sponsor-submitted ITC[13] reported that ozanimod was favoured in reducing the ARR compared to many first-line therapies, including interferons, glatiramer acetate, and teriflunomide. When compared with therapies reserved for more active or severe disease (i.e., ocrelizumab, alemtuzumab, and natalizumab), ozanimod was found to be less efficacious in reducing the ARR. In sensitivity analyses, results were largely insensitive to the exclusion of studies, with statistically significant heterogeneity for the ARR or short study duration.

For confirmed disability progression (CDP) at 12 weeks (CDP12), there was no difference between ozanimod and all treatments included in the network, with the exception of alemtuzumab and ocrelizumab, which were superior to ozanimod. For CDP at 24 weeks (CDP24), the NMA found that Betaseron (interferon beta-1b), cladribine, alemtuzumab, natalizumab, and ocrelizumab were favoured when compared with ozanimod. Notably, no difference in CDP24 was found between ozanimod and fingolimod, which are in the same class of S1P receptor modulators. A series of CDP scenario analyses was conducted to estimate the effect of different data assumptions on the model results. Imputation scenarios for missing CDP24 data produced results similar to those of the base-case analysis.

The MAIC by Swallow et al.[14] reported that that ozanimod and fingolimod were comparable in terms of reducing ARRs and the proportion of patients with CDP.

Harms Results

For the analysis of treatment discontinuation, the sponsor-submitted ITC[13] reported that ozanimod was favoured when compared with many first-line injectable therapies, including most interferons. There was no difference for discontinuation between ozanimod and other oral first-line therapies, including teriflunomide and dimethyl fumarate, or between ozanimod and fingolimod, cladribine, ocrelizumab, and natalizumab. Only alemtuzumab was superior to ozanimod for treatment discontinuation. For SAEs, ozanimod was no better or worse than any other treatment. However, the analysis found ozanimod was associated with similar or lower odds of AEs compared with interferon beta-1a, glatiramer acetate, peginterferon beta-1a, dimethyl fumarate, and alemtuzumab.

The MAIC by Swallow et al.[14] reported that ozanimod was associated with statistically significantly lower risks of adverse outcomes over 1 year and 2 years of follow-up compared with fingolimod.

Critical Appraisal

The sponsor-submitted ITC[13] did not report on certain items that would have improved the certainty of the indirect evidence. In addition, it could have used more sensitivity and subgroup analysis to satisfy the assumptions of transitivity and homogeneity, and a meta-regression could have adjusted for effect modifiers that could have influenced the results. Given that the sponsor-submitted NMA did not adjust for the ARR in the placebo arm, the value of the comparison between ozanimod and other therapies for RRMS is uncertain, as are the long-term efficacy and tolerability of the various treatments for RRMS.

There are concerns regarding the overlap between the ozanimod and fingolimod trial populations, as well as the availability of data to allow for matching. The small effective sample size of many analyses further suggests that substantial differences exist between the patient populations in the ozanimod and fingolimod trials, in which the effective sample size was only 31% of RADIANCE Part B and SUNBEAM patients after matching. Definitions for the outcomes included in the analyses were not provided. Data were pooled and results were combined in a manner that was not clearly specified and likely does not align with recommendations by the National Institute for Health and Care Excellence (NICE) Decision Support Unit. Given these issues, there is substantial uncertainty in the MAIC results, and firm conclusions cannot be drawn from them. In addition, this MAIC has the same limitations as the sponsor-submitted ITC, as the network for the NMA contains the same studies that were included in the MAIC. The identified sources of heterogeneity between the studies included in the MAIC would also be of concern with respect to introducing bias in the NMA as NMAs are generally less robust to sources of heterogeneity compared to MAICs.

Other Relevant Evidence

Description of Studies

The DAYBREAK study is a multi-site, open-label extension (OLE) study of 1 mg ozanimod hydrochloride oral capsules administered to patients with RMS. The DAYBREAK study was conducted at 227 sites in 27 countries in North America, Europe, South Africa, and New Zealand. Study participants who had completed 1 of the parent trials (RPC01-1001, RADIANCE Part A Extension, RADIANCE Part B, or SUNBEAM) were eligible to enroll in DAYBREAK. The DAYBREAK study is ongoing, and the results presented are based on an interim analysis.

Efficacy Results

Open-label treatment with ozanimod led to sustained reductions in ARRs. Patients who continued on ozanimod 1 mg had ARRs of 0.169 (95% CI, 0.133 to 0.214), 0.129 (95% CI, 0.097 to 0.171), and 0.124 (95% CI, 0.088 to 0.174) at the end of year 1, year 2, and year 3, respectively.

The mean (standard deviation [SD]) numbers of new or enlarging T2 lesions at 24 months from parent study baseline were 10.4 (17.69), 6.4 (11.10), and 5.6 (11.88) for interferon beta-1a, ozanimod 0.5 mg, and ozanimod 1.0 mg, respectively. At 24 months from the OLE baseline, mean (SD) values for new T2 lesions were 2.3 (3.51), 2.6 (6.56), and 2.5 (5.39) for interferon beta-1a → ozanimod 1 mg, ozanimod 0.5 mg → ozanimod 1 mg, and ozanimod 1.0 mg → ozanimod 1 mg, respectively.

The mean (SD) GdE MRI lesion counts at 24 months from the parent study baseline were 0.9 (2.46), 0.4 (1.31), and 0.3 (1.21) for interferon beta-1a, ozanimod 0.5 mg, and ozanimod 1.0 mg, respectively compared to 0.1 (0.45), 0.3 (0.84), and 0.1 (0.42) at 24 months from the OLE baseline for interferon beta-1a → ozanimod 1 mg, ozanimod 0.5 mg → ozanimod 1 mg, and ozanimod 1.0 mg → ozanimod 1 mg, respectively.

The mean (SD) percent changes in brain volume at 24 months from the parent baseline were −1.085 (1.008), −0.763 (0.781), and −0.858 (0.930) for interferon beta-1a, ozanimod 0.5 mg, and ozanimod 1.0 mg, respectively, and −0.224 (0.917), −0.218 (0.937), and −0.178 (0.968) at 24 months from the OLE baseline for interferon beta-1a → ozanimod 1 mg, ozanimod 0.5 mg → ozanimod 1 mg, and ozanimod 1.0 mg → ozanimod 1 mg, respectively.

Overall, patients who were initially randomized to interferon beta-1a or ozanimod 0.5 mg in the parent studies and switched to ozanimod 1 mg in the OLE showed improvements in MS activity in terms of ARR and lesion count similar to those seen in patients initially randomized to ozanimod 1 mg. However, due to the lack of a randomized comparison group, and the open-label design, the study results should be interpreted with caution.

Harms Results

Of the 2,494 patients in the OLE safety population, 1,704 (68.3%) experienced an AE. The most common AEs (≥ 5%) were nasopharyngitis (11.7%), headache (8.9%), lymphopenia (8.3%), upper respiratory tract infection (6.8%), and decreased lymphocyte count (6.6%).

A total of 144 patients (5.8%) had at least 1 SAE. The most common SAEs observed in more than 2 patients were pyelonephritis acute (5 patients), appendicitis (4 patients), pneumonia (3 patients) and uterine leiomyoma (5 patients); other SAEs were reported in 1 to 2 patients each.

Thirty (1.2%) patients had AEs that caused them to discontinue ozanimod 1 mg, and 29 (1.2%) withdrew from the study due to AEs. The most common reasons for discontinuation were neoplasms (n = 7, 0.3%) and infections and infestations (n = 5, 0.2%).

There were 3 deaths, 2 of which took place during the study (1 craniocerebral injury and 1 pulmonary embolism). The third occurred after the patient had permanently discontinued the drug without a specified cause of death.

Adverse events of special interest occurred in 34 patients (1.4%). Infections and infestations, neoplasms, and eye disorders were the most common, occurring in 11 (0.4%), 8 (0.3%), and 5 (0.2%) patients, respectively.

Critical Appraisal

The overall design of the OLE study imposed several limitations. The lack of a randomized comparison group to provide context and control for potential confounders may have influenced the perception of improvement by patients and clinicians. Specific limitations of the DAYBREAK study include the lack of a group that would have been maintained on interferon beta-1a, while another would have switched to ozanimod, making it difficult to extract high-quality information on the benefits of switching from interferon beta-1a to ozanimod. As part of the eligibility criteria for the OLE study, patients had to complete 1 of the parent studies, potentially allowing for selection bias. [redacted] There was also the potential for survival bias as any patients who discontinued the parent studies due to AEs were excluded. This could result in the enrolment of more patients who were better able to tolerate ozanimod and possibly fewer reports of AEs.

Because the patients who took part in the DAYBREAK OLE were originally from the parent studies and the eligibility criteria remained the same, it is reasonable to expect that the same limitations on generalizability apply to the OLE study. In DAYBREAK, ozanimod appears to have been used according to the product monograph outline, and as it is anticipated to be used in clinical practice. [redacted]
The median times to first confirmed relapse and onset of disability progression could not be estimated for the phase III intention-to-treat (ITT) populations due to low rates of disease progression and the limited time for data collection. Despite the lack of enrolled Canadians, the results from the DAYBREAK study may be generalizable to the Canadian population and should still be interpreted with caution.

Conclusions

RADIANCE Part B and SUNBEAM demonstrated the superiority of ozanimod 1 mg to interferon beta-1a in adult patients with RRMS in terms of relapse and imaging outcomes. This includes a reduction in ARRs and the number of new or enlarging hyperintense T2-weighted brain MRI lesions and the number of GdE brain MRI lesions. Outcomes related to HRQoL were noted as important to patients, but the effect of ozanimod on HRQoL was uncertain due to a lack of control for multiplicity. No difference between ozanimod 1 mg and interferon beta-1a was demonstrated in either study for disability progression, mobility, or cognitive function, which could be due to the short duration of the trials.

No direct comparative evidence for ozanimod 1 mg with DMTs other than interferon beta-1a was identified. One sponsor-submitted ITC comparing ozanimod 1 mg to other DMTs suggested that ozanimod was more effective in reducing the ARR compared to many first-line therapies, including interferons, glatiramer acetate, and teriflunomide.

[redacted] The value of the ITC results is uncertain due to heterogeneity between studies.

There were no concerns regarding the safety of ozanimod in the pivotal trials, other than the potential cardiac effects known to be associated with S1P modulators. Serious AEs were reported by 2.5% to 6.5% of patients in the treatment groups of both studies, but the frequency of individual SAEs was low. There is no evidence concerning the long-term risk of malignancies, cardiovascular morbidity, and withdrawal effects following ozanimod withdrawal.

Introduction

Disease Background

Multiple sclerosis is a chronic, immune-mediated, inflammatory, demyelinating disease of the CNS.[1] It is more prevalent in females than in males and has a mean age of onset of 28 to 31 years.[2] The Public Health Agency of Canada reports that more than 77,000 Canadians live with MS and about 60% of newly diagnosed adults are between the age of 20 and 49 years.[3] While the etiology of MS remains unknown, it is commonly accepted that autoreactive lymphocytes are involved.[2] The disease is characterized by focal demyelinated plaques in the CNS, which can be accompanied by inflammation and gliosis.[2] Symptoms of MS are varied and include painful monocular vision loss, double vision, motor weakness, gait disturbance and balance problems, pain, spasticity, sensory symptoms in the limbs or face, and bladder and bowel symptoms.[1,4]

The McDonald criteria, which were most recently updated in 2017, are used to diagnose MS.[15] Clinical evidence can be sufficient to meet the diagnostic criteria, although MRI evidence can be used in conjunction with clinical evidence to make a diagnosis.[15,16] More specifically, the criteria for diagnosis are based on the occurrence of one or more attacks (relapse, exacerbation, and/or clinically isolated syndrome) and objective clinical evidence of 1 or more lesions.[15,16] Depending on the number of attacks or lesions present, additional data may be required to make the diagnosis. This may include the dissemination in time, demonstrated by evidence of an additional lesion, and/or dissemination in space, demonstrated by evidence of lesions in at least 2 regions of the CNS.[15]

Approximately 85% of patients with MS experience RRMS at disease onset.[1,4] This phenotype is characterized by episodes of symptom exacerbation, or relapses, followed by partial or complete remission. During these episodes, symptoms generally develop over hours or days and then go into remission over weeks or months.[5] Most patients who initially present with RRMS go on to develop SPMS, which is a progressive phase of the disease.[1,4] According to the MS Society of Canada, about 50% of patients with RRMS develop SPMS within 10 years of their diagnosis of RRMS.[17]

Major financial burdens are common for MS patients, their families, and the health care system.[18]

Standards of Therapy

There is currently no curative treatment for MS. The principal goal of treatment for RRMS is to delay or prevent the accumulation of disability by reducing the frequency of relapses and MRI lesions.[6] The clinical expert consulted by CADTH noted that, ideally, the goals of treatment with DMTs are a delay in disease progression, a decrease in the burden of disability/symptoms, a decrease in the number and severity of relapses, preserved mobility and cognition, and improved independence and employment. The expert also noted that all of these factors would then contribute to a better HRQoL as well as a decrease in burdens on caregivers. It is recommended that all patients with RMS begin treatment with a DMT as soon as possible following diagnosis to reduce the risk of disability worsening and improve long-term outcomes.[6,7] The clinical expert noted that all persons with active disease should be offered a DMT and that what may differ is which DMT is chosen in terms of safety, taking into account, for example, pregnancy in a younger female patient, type 2 diabetes in an older patient, or hypertension. The clinical expert also indicated that it is important to

weigh the benefit of any DMT against potential harm; the lower the harm, the more ideal the DMT.

Several DMTs for MS are currently available in Canada, allowing for a personalized approach to treatment. According to Canadian Multiple Sclerosis Working Group (CMSWG) recommendations for treatment optimization in MS, a total of 5 injectable agents (glatiramer acetate, interferon beta-1b, and 3 formulation of interferon beta-1a) and 2 oral agents (teriflunomide and dimethyl fumarate) are used as starting treatments for RMS.[6] Additionally, natalizumab, alemtuzumab, and ocrelizumab (all intravenous infusion agents), as well as fingolimod and cladribine (oral agents), are regarded as higher-efficacy therapies that tend to be used as second-line interventions and are reserved for patients with more advanced disease due to toxicities and cost.[8] Moreover, alemtuzumab and fingolimod may be more likely to be considered as third-line therapies due to safety concerns and reimbursement criteria, respectively, according to the clinical expert consulted for this review. Because direct comparative evidence is limited for the first-line DMTs, treatments are selected based on the individual's level of disease activity, disease severity, and comorbidities, as well as the drug's safety profile,[6,8] according to the clinical expert consulted for this review. Although not the most common or conservative approach, the selection of higher-efficacy therapies may also offer an initial therapy for patients with high disease activity or aggressive or rapidly evolving MS at onset.[6] Otherwise, the choice of drug in many cases is guided by patient tolerance for various side effects, such as alopecia for teriflunomide, flushing for dimethyl fumarate, flu-like symptoms for interferon, and injection-site reactions for glatiramer.

Treatment optimization by switching DMTs is typically carried out due to lack of efficacy or poor tolerability. To address a tolerability issue, a patient may switch between first-line therapies or to a therapy that is expected to address and limit the specific tolerability issue. The clinical expert cited the example of a patient who may be switched to a therapy with a similar mechanism of action that has a different route of administration if the latter was the cause of a tolerability issue. To address lack of efficacy, one might switch to a "second-line" drug, or a higher-efficacy therapy when there is suboptimal response to a first-line drug.[6] However, as pointed out by the clinical expert, the main approach would be to switch to a DMT that has a different mechanism of action than the therapy that lacked efficacy. The CMSWG stated that there is a lack of consensus on how to define adequate treatment response, and consequently relapses and/or active MRI lesions are used as a proxy measure of response to treatment.

Clinical criteria to identify patients who should discontinue treatment have not been established because of limited data on the long-term safety of chronic immunosuppression.[6] The CMSWG noted that treatment discontinuation may be considered for patients who have been clinically stable for more than 5 years, but with the caveat that stability in patients under the age of 60 is unlikely to indicate treatment success. Patient-specific safety issues would also be a reason to consider treatment discontinuation.[6]

Aside from DMTs, patients with MS may receive medications or non-pharmacological interventions to manage MS-related complications and symptoms. These include medications for bladder or bowel dysfunction, depression, fatigue, pain, paroxysmal attacks, seizures, and spasticity.[19] However, some MS symptoms and treatments can exacerbate other symptoms, and potential underlying causes should also be addressed. Several non-pharmacological approaches, such as behavioural modification techniques, physical therapy, mobility aids, feeding tubes, and non-invasive ventilation, are available to

manage complications and symptoms.[19] For patients with MS and mild to moderate disability, the Canadian Physical Activity Guidelines recommend at least 30 minutes of moderate-intensity aerobic activity and strength-training exercises for major muscle groups, both twice a week.[20]

Drug

Ozanimod is an S1P receptor modulator. The binding of ozanimod and its metabolites to S1P receptors on lymphocytes prevents lymphocyte egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which ozanimod and its active metabolites exert their therapeutic effects in MS is unknown but may involve reduction of lymphocyte migration into the CNS.[9]

Ozanimod is indicated for the treatment of patients with RRMS to decrease the frequency of clinical exacerbations.[9] Ozanimod is administered orally and is available as 0.23 mg, 0.46 mg, and 0.92 mg capsules of ozanimod hydrochloride.[9] Treatment is initiated in all patients with an initiation pack that lasts for 7 days. The Health Canada–recommended initial dose-escalation regimen of ozanimod is 0.23 mg once daily on days 1 to 4 followed by 0.46 mg once daily on days 5 to 7. The maintenance dosage is 0.92 mg once daily taken orally starting on day 8.[9]

The sponsor has requested reimbursement of ozanimod as per the Health Canada–approved indication.

Table 3: Key Characteristics of DMTs for RRMS

	Mechanism of action	Indication[a]	Route of administration	Recommended dosage	Serious side effects or safety issues
Ozanimod (Zeposia)[9]	An S1P receptor modulator; the mechanism by which ozanimod and its active metabolites exert their therapeutic effects in MS is unknown but may involve reduction of lymphocyte migration into the central nervous system	RRMS to decrease the frequency of clinical exacerbations	Oral capsule	Initial dosing: days 1 to 4 (0.23 mg once daily), days 5 to 7 (0.46 mg once daily) Maintenance dosage is 0.92 mg once daily taken orally starting on day 8	May result in transient reductions in heart rate and atrioventricular delays Elevations of aminotransferases may occur May increase the susceptibility to infections Causes a reduction in circulating lymphocyte counts to approximately 43% to 47% of baseline values
Teriflunomide (Aubagio)[21]	Not completely understood; may reduce numbers of activated lymphocytes available for migration into the CNS	RRMS[b]	Oral tablet	14 mg once daily	Hepatotoxicity and risk of teratogenicity Contraindicated in: patients hypersensitive to this drug or to leflunomide; patients currently treated with leflunomide; severe hepatic impairment; pregnant women or women of child-bearing age who are not using contraception; immunodeficiency states such as AIDS; serious active infection; impaired bone marrow function or with significant anemia, leucopenia, neutropenia, or thrombocytopenia
Dimethyl fumarate (Tecfidera)[22]	Not completely understood; activates the Nrf2 pathway, which is involved in cellular response to oxidative stress	RRMS[b]	Oral capsule	240 mg twice daily (total of 480 mg daily)	PML, reduced lymphocyte counts Contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container
Interferon beta-1a (Avonex; Rebif)[23,24]	Its effects in MS not completely understood; it exerts its biological effects by	RMS (RRMS, SPMS with relapses); and patients with a single	IM injection (Avonex) SC injection (Rebif)	IM: 30 mcg per week (increase up to 60 mcg per week if needed)	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts),

	Mechanism of action	Indication[a]	Route of administration	Recommended dosage	Serious side effects or safety issues
	binding to specific receptors on the surface of human cells and inducing the expression of numerous IFN-induced gene products	demyelinating event, accompanied by abnormal MRI scans, with lesions typical of MS		SC: 22 mcg or 44 mcg 3 times per week	injection-site reactions, depression or suicide Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease (Rebif only), pregnant women (Rebif only)
Interferon beta-1b (Betaseron; Extavia)[25,26]	Its effects in MS not completely understood; it exerts its biological effects by binding to specific receptors on the surface of human cells, and inducing the expression of numerous IFN-induced gene products	RRMS; SPMS; single demyelinating event accompanied by at least 2 clinically silent lesions typical of MS	SC injection	0.25 mg every other day	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection-site reactions, depression/suicidal ideation Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, pregnant women, and patients with current severe depression and/or suicidal ideation (Extavia only)
Pegylated IFN beta-1a (Plegridy)[27]	Its effects in MS not completely understood. It exerts its biological effects by binding to type 1 IFN receptors on the surface of human cells	RRMS	SC injection	125 mcg every 2 weeks	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection-site reactions, depression or suicidal ideation Contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon or any other component of the formulation or the container, pregnant patients, patients with current severe depression and/or suicidal ideation
Glatiramer acetate (Copaxone)[28]	Likely modifies the immune processes responsible for pathogenesis of MS	RRMS; single demyelinating event, accompanied by	SC injection	20 mg/day	Contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol

	Mechanism of action	Indication[a]	Route of administration	Recommended dosage	Serious side effects or safety issues
		abnormal MRI scans and considered to be at risk of developing cclinically definite MS			
Ocrelizumab (Ocrevus)[29]	Reduction in CD 20 molecules	RRMS PPMS	IV infusion	600 mg Q6M	Infusion reactions, infections (herpes, respiratory tract) Contraindicated in patients with active/severe infection or with PML
Cladribine (Mavenclad)[30]	Inhibits lymphocyte proliferation	monotherapy for the treatment of adult patients with RRMS	Oral	3.5 mg/kg over 2 years	Lymphopenia, infections (herpes zoster, TB or latent TB reactivation, PML), malignancies, teratogenic
Fingolimod (Gilenya)[31]	An S1P receptor modulator; its effects in MS are not fully known; its active metabolite binds to receptors on lymphocytes, blocks lymphocytes from leaving lymph nodes, reduces the number of lymphocytes in peripheral blood, and reduces lymphocyte migration into CNS	RRMS[b]; generally recommended in MS patients who have had inadequate response to, or are unable to tolerate, 1 or more therapies for MS	Oral capsule	0.5 mg/day	PML, skin cancer, infections (Varicella-VZV vaccination recommended), heart block Contraindicated in patients who are hypersensitive to fingolimod, who are at increased risk for opportunistic infection, have hepatic insufficiency, active severe infections, known active malignancies, major cardiovascular issues, severe arrhythmias, and pregnancy
Natalizumab (Tysabri)[32]	Binds to the alpha-4 subunit of human integrin: blocks interaction of alpha-4 beta-1 integrin with VCAM-1; and blocks the interaction of alpha-4 beta-7 integrin with MadCAM-1	RRMS[b]; generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, other therapies for MS	IV infusion	300 mg every 4 weeks	PML, herpes Contraindicated in patients who have or have had PML, at risk for PML; hypersensitive to this drug or to any ingredient in the formulation or any component of the drug; immunocompromized, including those immunocompromized due to immunosuppressant or antineoplastic therapies, or immunodeficiencies

	Mechanism of action	Indication[a]	Route of administration	Recommended dosage	Serious side effects or safety issues
Alemtuzumab (Lemtrada)[33]	Not fully understood; binds to CD52; may involve immunomodulation through the depletion and repopulation of lymphocytes	RRMS with highly active disease despite an adequate course of treatment with at least 2 other DMTs	IV infusion	Initial treatment cycle: 12 mg per day for 5 consecutive days Second treatment cycle: 12 mg per day for 3 consecutive days administered 12 months after the initial treatment course	Autoimmune and immune-mediated conditions, infections, infusion reactions, stroke, malignancies Contraindicated in patients who are hypersensitive to alemtuzumab or to any ingredient in the formulation or component of the container; are infected with HIV; have active or latent TB, active severe infections, or active malignancies; are on antineoplastic or immunosuppressive therapies; have a history of PML

CNS = central nervous system; DMT = disease-modifying therapy; IFN = interferon; IM = intramuscular; IV = intravenous; MadCAM-1 = mucosal addressin cell adhesion molecule-1; MS = multiple sclerosis; Nfr2 = nuclear factor (erythroid-derived)-like-2; PML = progressive multifocal leukoencephalopathy; PPMS = primary progressive multiple sclerosis; RMS = relapsing forms of MS; RRMS = relapsing-remitting MS; S1P = sphingosine 1-phosphate; SC = subcutaneous; SPMS = secondary progressive MS; TB = tuberculosis; VCAM-1 = vascular cell adhesion molecule-1; VSV = varicella-zoster virus.

[a] Health Canada–approved indication.

[b] Indicated as monotherapy.

Source: Product monographs for: cladribine,[30] ocrelizumab,[29] Plegridy,[27] alemtuzumab,[33] dimethyl fumarate,[22] fingolimod,[31] glatiramer acetate,[28] Avonex,[23] Rebif,[24] Betaseron,[25] Extavia,[26] natalizumab,[32] and teriflunomide.[21]

Stakeholder Engagement

Patient Group Input

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

Patient Groups and Information Gathered

One patient group submission, authored by the MS Society of Canada, was received for this review. The MS Society of Canada provides information, support and advocacy to people affected by MS. The society works toward an MS-free world by funding research that aims to find the cause and cure for the disease. Since its inception in 1948, the MS Society of Canada has contributed $200 million toward MS research. A disclosure of any conflicts of interest is available on the CADTH website.

The MS Society of Canada collected condition-related patient input from an online survey posted on the main page of its national website (www.mssociety.ca) and Facebook page. The survey was posted from August 4, 2020, to September 4, 2020, in both English and French. Most respondents appeared to be from Canada, although "country of origin" was not a survey question. A total of 69 people responded to the survey: 75% were female; more than 91% were MS patients, and the remainder were caregivers; 71% had RRMS, 4% had SPMS, 7.2% had PPMS, and 6% were unsure of the type of MS they had. The ages of respondents ranged from 31 to 60 years.

Disease Experience

Depending on the type and severity of the symptoms, an individual's quality of life can be greatly affected. Living with MS creates employment issues such as the inability to maintain a stable job or remain in the workplace due to relapses, symptoms, medication side effects, and disability progression. MS can also create a barrier to education, physical activity, family commitments, interpersonal relationships, and social and recreational life. The lives of caregivers are also greatly affected by MS, as they play an instrumental role in the overall care and management plan of the people living with the disease.

Experience with Treatment

There is a growing number of high-efficacy DMTs, with varied administrations, dosing schedules, and decreased monitoring requirements, factors that are consistently identified as priorities for patients when selecting a DMT. Patients place a high value on the ability to choose the administration, dosing schedule, side-effect profile, and level of medication monitoring that best fits their lifestyle and personal preferences. Without a choice, adherence becomes an issue, resulting in decreased clinical benefits and health outcomes. Common side effects associated with current therapies include injection-site reactions, flushing, hair-thinning, skin rash or hives, joint and/or musculoskeletal pain, gastrointestinal symptoms, increased risk of infections, and flu-like symptoms.

The MS Society of Canada did not receive feedback from patients with current or previous experience with ozanimod. The survey included a question about risks versus perceived benefits of ozanimod. Of those who answered this question, 28 (45%) said they would not take the risk, 27 (44%) did not know if they were willing to trade the risks for perceived benefits, and 7 (11%) said they would be willing to take the risk.

Improved Outcomes

According to the patient group input, ozanimod is anticipated to offer patients an oral regimen, eliminating the need to take time away from work, school, or other commitments. It is expected to fill a significant gap in MS treatment for patients who are recommended to be treated with an S1P receptor modulator as there is no requirement for first-dose monitoring. Patients are looking for a treatment that would result in fewer relapses requiring hospitalization and decreased work absenteeism, and allow them to remain active within their social networks.

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. They provide guidance on the development of the review protocol, assist in the critical appraisal of clinical evidence, interpret the clinical relevance of the results, and provide guidance on the potential place in therapy. The following input was provided by a clinical specialist with expertise in the diagnosis and management of MS.

Unmet Needs

The clinical expert indicated that the ideal goal for patients with RMS is a cure. The expert relayed that currently, not all patients respond to the same mechanism of action of a DMT; some may not respond to the "first-line therapy" and require a higher-efficacy DMT that may come with a higher risk. The clinical expert also noted the need to take into account lifestyle factors, such as whether the patient lives in a remote area that does not have access to an infusion site or MRI to monitor risk of progressive multifocal leukoencephalopathy, and whether the patient is of child-bearing age. Also, some DMTs may be contraindicated due to comorbidities or severe side effects that interfere with compliance. The clinical expert indicated that overall personalized medicine — choosing the right DMT for the right patient — is the best approach. The clinical expert did not identify a specific group of patients with the greatest unmet need for a treatment such as ozanimod, but noted that ozanimod would be an option for all persons with RMS who require a DMT.

Place in Therapy

Regarding where ozanimod would fit into the current treatment paradigm, the clinical expert stated that ozanimod should not be used in combination with any other DMT. The clinical expert also indicated that ozanimod would be an ideal option for both first-line treatment, as well as an option if a patient needed to switch treatments if a different DMT was not efficacious, following a personalized treatment approach. The clinical expert added that it would not be appropriate to recommend that patients try other treatments before initiating treatment with ozanimod, as ozanimod is both safe and effective, and if started early could contribute to improving the disease and, as a result, the patient's HRQoL.

Patient Population

As previously noted, the clinical expert stated that ozanimod would be suitable for any person with RRMS who requires a DMT, and that patients should be identified using clinician judgment while considering the involvement of an MS expert (from a specialty practice, with an MS fellowship, or within an MS clinic). The expert did not identify patients

who would be least suitable for treatment with ozanimod. The clinical expert also stated that it is not possible to identify patients who would be most likely to exhibit a response to treatment with ozanimod; however, the clinical expert noted that growing evidence suggests that starting a DMT earlier in all persons with MS will help improve disease-related outcomes.

Assessing Response to Treatment

According to the clinical expert, response to treatment should be assessed yearly in patients with MS. To determine whether a patient is responding to treatment in clinical practice, the clinical expert recommended clinical and radiological monitoring. The clinical expert also noted that there are no clear markers that indicate a medication is not working for a person with MS, and that switching criteria are detailed in the 2020 treatment optimization recommendations.[6] The clinical expert described a clinically meaningful response as the relative stabilization of MS. Although the ultimate goal is to stop all disease activity, the expert stated that this is not a realistic goal and again referred to 2020 treatment optimization recommendations.[6]

Discontinuing Treatment

The clinical expert indicated that factors such as safety (for example, in those over the age of 65) and significant disability (an EDSS score of 8.0) should be considered when making a decision to discontinue treatment.

Prescribing Conditions

The clinical expert stated that a community setting, hospital, or outpatient or specialty clinic would be appropriate for treatment with ozanimod. The expert added that it would be ideal to have a specialist diagnose, treat, and monitor patients who might receive ozanimod; but acknowledged that this may be unrealistic in some areas of the country.

Clinical Evidence

The clinical evidence included in the review of ozanimod is presented in 3 sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies selected according to an a priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of ozanimod capsules (0.23 mg, 0.46 mg, and 0.92 mg) for the treatment of patients with RRMS.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adults with RRMS Subgroups • Prior treatment experience • Disease severity • Disease activity (e.g., highly active or not) • Age
Intervention	Ozanimod administered orally once daily • Treatment initiation period: days 1 to 4 (0.23 mg once daily), days 5 to 7 (0.46 mg once daily). • Maintenance period: 0.92 mg once daily taken orally starting on day 8
Comparators	DMTs including: • ocrelizumab • interferon beta-1a (Avonex, Rebif) • interferon beta-1b (Betaseron, Extavia) • peginterferon beta-1a (Plegridy) • glatiramer acetate (Copaxone, Glatect) • teriflunomide (Aubagio) • dimethyl fumarate (Tecfidera) • natalizumab (Tysabri) • cladribine (Mavenclad) • fingolimod (Gilenya) • alemtuzumab (Lemtrada)

Outcomes	**Efficacy outcomes** • Relapse (e.g., relapse rate and relapse-free rate) • Imaging outcomes (e.g., MRI brain lesions, MRI brain volume) • Health-related quality of life[a] • Mobility[a] • Cognitive function[a] • Symptoms of MS (e.g., fatigue, cognition, and visual disturbance)[a] • Ability to work or attend school[a] • Use of rescue medication • Disability progression or improvement[a] **Harms outcomes** • Adverse events • Serious adverse events • Withdrawal due to adverse events • Mortality • Notable harms: infection, bradyarrhythmia and atrioventricular conduction delays, liver Injury, effects in pregnancy, increased blood pressure, decline in pulmonary function, and macular edema
Study design	Published and unpublished phase III and IV randomized controlled trials

DMT = disease-modifying therapy; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis.

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

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[34]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was ozanimod. Clinical trial registries searched included the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on September 24, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on January 20, 2021.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[35] Health Technology Assessment (HTA) Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. Appendix 2 provides more information on the grey literature search strategy.

Two CADTH 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 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings from the Literature

Two studies were identified from the literature for inclusion in the systematic review (

Figure 1). The included studies are summarized in Table 5. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

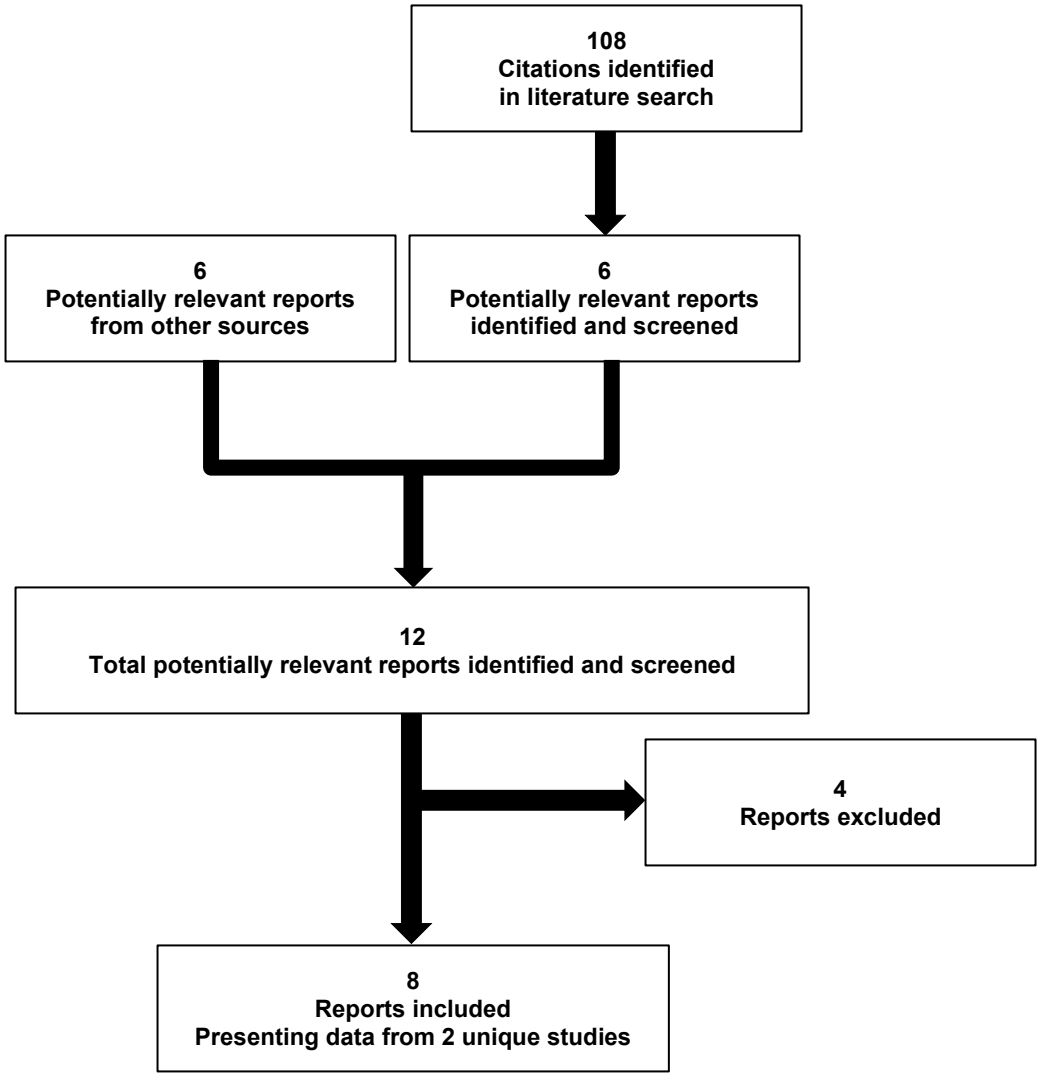


Table 5: Details of Included Studies

		RADIANCE Part B	SUNBEAM
Designs and Populations	**Study design**	Multi-centre, parallel-group, double-blind, double-dummy, active-controlled RCT	
	Locations	150 sites across 21 countries (US, Canada, Europe, and South Africa)	152 sites across 20 countries (US, Europe, and New Zealand)
	Randomized (N)	1,320 patients • Ozanimod 1 mg (n = 434) • Ozanimod 0.5 mg (n = 443) • Interferon beta-1a (n = 443)	1,346 patients • Ozanimod 1 mg (n = 447) • Ozanimod 0.5 mg (n = 451) • Interferon beta-1a (n = 448)
	Inclusion criteria	• MS, as diagnosed by the revised 2010 McDonald criteria • Exhibited a relapsing clinical course consistent with RMS and a history of brain MRI lesions consistent with MS • Aged 18 and 55 years of age, inclusive • EDSS score between 0 and 5.0 at baseline • Met one of the following disease activity criteria: ○ At least 1 documented relapse within the last 12 months prior to screening ○ At least 1 documented relapse occurred within the last 24 months prior to screening and evidence of at least 1 GdE lesion on brain MRI within the last 12 months prior to randomization • No history of relapse from 30 days prior to screening until randomization; during this period, patients must have been clinically stable, without systemic corticosteroid treatment or ACTH	
	Exclusion criteria	• Primary progressive MS at screening • Disease duration of more than 15 years in patients with an EDSS score of 2.0 or lower • Contraindications to MRI or gadolinium contrast, such as known allergy to gadolinium contrast dyes, renal insufficiency, claustrophobia, body size incompatible with the scanner, pacemaker, cochlear implants, intracranial vascular clips • Incompatibility with beta interferon use including prior cessation of interferon beta-1a therapy due to poor tolerability, liver-function abnormalities or other toxicities, or poor tolerability or toxicity that was likely to recur with interferon beta-1a therapy • Specific cardiac conditions were excluded, including history or presence of: ○ Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea ○ Prolonged QTcF interval (longer than 450 ms for males; longer than 470 ms for females), or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome, concurrent therapy with QT-prolonging drugs) ○ Patients with other pre-existing stable cardiac conditions who were not cleared for the study by an appropriate cardiac evaluation by a cardiologist ○ Other clinically significant conduction abnormalities or any other significant cardiac condition that could jeopardize a patient's health or put them at significant safety risk during the course of the study in the opinion of treating investigator • Resting heart rate of less than 55 beats per minute at screening • History of uveitis • History of cancer, including solid tumours and hematological malignancies • Prior use of any investigational agent within 6 months prior to enrolment • Treatment with other immunosuppressant agents such as azathioprine, cyclosporine, methotrexate, or mycophenolate within 6 months prior to randomization • Systemic corticosteroid therapy or ACTH use within 30 days prior to screening • Treatment with other disease-modifying therapies (e.g., dimethyl fumarate, teriflunomide, daclizumab, laquinimod) within 3 months prior to randomization • Diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1C of at least 7% in the RADIANCE Part B study and hemoglobin A1C of at least 9% in the SUNBEAM study, or diabetic patients with significant comorbid conditions such as retinopathy or nephropathy	

		RADIANCE Part B	SUNBEAM
Drugs	**Intervention**	• 1 mg ozanimod hydrochloride oral capsule daily plus interferon beta-1a-matching placebo injections • 0.5 mg ozanimod hydrochloride oral capsule daily plus interferon beta-1a-matching placebo injections[a]	
	Comparator(s)	Interferon beta-1a 30 mcg IM weekly plus ozanimod-matching placebo capsule orally	
Duration	**Phase**		
	Screening	Up to 30 days	Up to 30 days
	Double-blind	24 months	At least 12 months
	Follow-up	4 weeks	4 weeks
Outcomes	**Primary end point**	ARR at the end of month 24	ARR during the treatment period
	Secondary and exploratory end points	**Key secondary efficacy end points (rank-ordered)** • Number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months • Number of GdE brain MRI lesions at month 24 • Time to onset of disability progression as defined by a sustained worsening of 1.0 points or more on the EDSS, confirmed after 3 months and after 6 months **Other secondary efficacy end points** • Proportion of patients who were GdE lesion-free at month 24 • Proportion of patients who were new or enlarging T2 lesion-free at month 24 • Percent change in normalized brain volume (atrophy) on brain MRI scans from baseline to month 24 • Change in MSFC score from baseline to month 24 (including the LCLA measurement of visual function as a component) • Change in MSQOL-54 score from baseline to month 24 **Exploratory** • Number and volume of GdE T1 lesions • Volume of T2 lesions • Number of new or enlarging T2 lesions • Volume of non-enhanced T1 lesions • Number of new non-enhanced T1 lesions • Measures of brain atrophy	**Key secondary efficacy end points (rank-ordered)** • Number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 months • Number of GdE brain MRI lesions at month 12 • Time to onset of disability progression as defined by a sustained worsening of 1.0 points or more on the EDSS, confirmed after 3 months and after 6 months **Other secondary efficacy end points** • Proportion of patients who were GdE lesion-free at month 12 • Proportion of patients who were new or enlarging T2 lesion-free at month 12 • Percent change in normalized brain volume (atrophy) on brain MRI scans from • Baseline to month 12 • Change in MSFC score from baseline to month 12 (including the LCLA measurement of visual function as a component) • Change in MSQOL-54 score from baseline to month 12 **Exploratory** • Number and volume of GdE T1 lesions • Volume of T2 lesions • Number of new or enlarging T2 lesions • Volume of non-enhanced T1 lesions • Number of new non-enhanced T1 lesions • Measures of brain atrophy
Notes	**Publications**	Cohen et al. (2019) [36]	Comi et al. (2019) [37]

ACTH = adrenocorticotrophic hormone; ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhanced; IM = intramuscular; LCLA = Low-Contrast Letter Acuity test; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSQOL-54 = Multiple Sclerosis Quality of Life-54 items; QTcF = corrected QT interval using Fridericia's formula; RCT = randomized controlled trial; RMS = relapsing forms of multiple sclerosis.

Note: Four additional reports were included (CADTH Common Drug Review submission,[38] FDA clinical and statistical reviews,[39,40] and European Medicines Agency assessment report[41]).

[a] Not a Health Canada–approved dosage.

Source: Cohen et al. (2019),[36] Comi et al. (2019),[37] Clinical Study Reports for the RADIANCE Part B and SUNBEAM studies.[11,12]

Description of Studies

The RADIANCE Part B (N = 1,320) and SUNBEAM (N = 1,346) studies were multi-centre, randomized, double-blind, double-dummy, active-controlled, parallel-group phase III randomized controlled trials (RCTs) to evaluate the efficacy and safety of ozanimod in the treatment of adult patients with RMS. These studies consisted of 3 periods: a 30-day screening period for study protocol eligibility, a blinded active-treatment period of at least 12 months (SUNBEAM) or 24 months (RADIANCE Part B), and a 28-day safety follow-up period. The main difference between the 2 phase III studies was the duration of treatment, which was 24 months for RADIANCE Part B, and up to approximately 22 months (mean duration of 13.6 months) for SUNBEAM, in which treatment was continued until all patients received a minimum of 12 months of treatment. Additionally, MRI assessments were conducted at months 6 and 12 in the SUNBEAM study, whereas in RADIANCE Part B the MRI assessments were conducted at months 12 and 24. Figure 2 provides a schematic of the design of the RADIANCE Part B and SUNBEAM studies. RADIANCE Part B and SUNBEAM randomized 1,320 and 1,346 patients with RMS, respectively. RADIANCE Part B included patients from a single site in Canada while SUNBEAM did not include patients from sites in Canada.

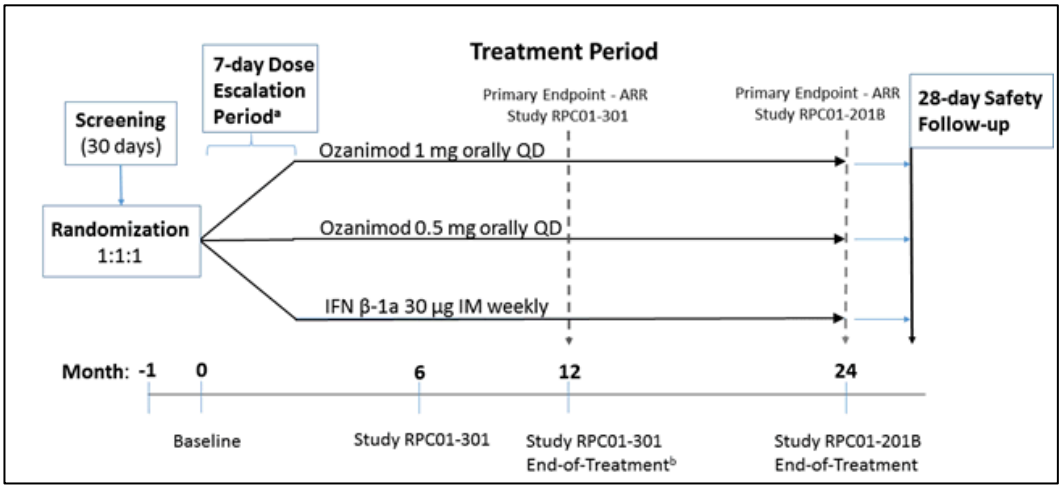
Eligible patients were randomized 1:1:1 to receive either ozanimod 1 mg once daily (referred to as the ozanimod 1 mg group), ozanimod 0.5 mg once daily (the ozanimod 0.5 mg group), or interferon beta-1a 30 mcg IM weekly (the interferon beta-1a group) in a double-dummy manner. Randomization was based on a stratified blocked algorithm and was performed centrally using an interactive voice response system. Patients were stratified by EDSS score (≤ 3.5 or > 3.5) and country.

A “dual assessor” approach (treating investigator and independent blinded evaluator) was used to evaluate efficacy and safety to prevent potential unblinding as a result of observed efficacy, AEs, or laboratory changes. The independent blinded evaluator assessed scores on the EDSS, MSFC, and LCLA. Central blinded evaluation of MRIs was performed. The blinded evaluator was not involved with any other aspect of patient care or management, and remained blinded to all other data that could potentially reveal the treatment assignment. The treating investigator and independent blinded evaluator were not permitted to switch roles.

Patients completing the RADIANCE Part B and SUNBEAM studies had the option of entering the long-term OLE (the DAYBREAK study), in which all patients received ozanimod 1.0 mg following the dose-escalation regimen described for the parent studies.

Data will not be presented for ozanimod 0.5 mg, which is not aligned with the Health Canada–approved dose.

Figure 2: Study Design for RADIANCE Part B and SUNBEAM Studies



ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IFN = interferon; IM = intramuscular; QD = once daily; Study RPC01-201B = RADIANCE Part B study; Study RPC01-301 = SUNBEAM study.

Note: Brain MRIs were performed at screening, month 6, and month 12 in SUNBEAM, and at screening, month 12, and month 24 in RADIANCE Part B. The EDSS assessments were performed every 3 months in each study.

[a] Participants randomized to ozanimod received 0.25 mg on days 1 to 4, 0.5 mg on days 5 to 7, and 0.5 or 1.0 mg on day 8 and thereafter.

[b] The end of treatment occurred when the last active patient received 12 months of treatment with study drug.

Source: CADTH Common Drug Review submission.[38]

Populations

Inclusion and Exclusion Criteria

Patients aged 18 to 55 years were eligible for the RADIANCE Part B and SUNBEAM if they had an active RMS as defined by a relapsing clinical course consistent with RMS and a history of brain MRI lesions consistent with MS, including a documented relapse during the 12 months prior to screening or, if their last documented relapse was 12 to 24 months prior to screening, evidence of at least 1 GdE lesion on brain MRI within the 12 months prior to randomization. Patients had to have an EDSS score of between 0 and 5.0 at baseline. The MS diagnosis was to be made using the 2010 revised McDonald criteria.[16]

Patients who were naive to MS treatment or had received previous MS therapies were eligible, except for those who had received alemtuzumab, anti-CD4 antibodies, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, or a bone marrow transplant. Documentation of immunocompetence to varicella zoster or vaccination 30 days before baseline was required. Patients with certain pre-existing cardiovascular conditions were eligible to participate in the studies if the event occurred more than 6 months prior to screening (e.g., myocardial infarction, unstable angina, transient ischemic attack, decompensated heart failure requiring hospitalization, class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea).

Key exclusion criteria included evidence of a relapse within 30 days prior to screening, treatment with a systemic corticosteroid or adrenocorticotrophic hormone within 30 days prior to screening, disease duration of more than 15 years (unless the EDSS score was greater than 2.0), a history of uveitis, an absolute lymphocyte count less than 800/µL, a forced expiratory volume in 1 second or forced vital capacity of less than 70% of predicted

values, a resting heart rate below 55 beats per minute at screening, and incompatibility with interferon beta-1a use (e.g., intolerable side effects).

Baseline Characteristics

The demographic characteristics of patients were generally well balanced across treatment groups within each study as well as across the studies. The majority of patients were female (63% to 69%) and White (98% to 100%), with a mean age of 35.5 years (range 18 to 55 years) and mean body mass index of 24.19 kg/m^2. The majority of patients were enrolled from the Eastern European region (86% to 94%), with only 1 patient enrolled from Canada in the RADIANCE Part B study. Most patients (98.1%) had RRMS at study entry and the remainder had SPMS (0.17%) or PRMS (1.7%). The mean number of years since MS diagnosis ranged from 3.60 to 3.97 years. Approximately 98% of patients had at least 1 relapse in the past year, including approximately 27% of patients with 2 or more relapses. Patients had a range of disability, with a mean EDSS score of 2.6, and 17.2% of patients had an EDSS score of at least 3.5 (Table 6).

Approximately 70% of the patients were DMT-naive, with a mean duration since MS symptom onset of 6.96 years in the SUNBEAM study and 6.50 years in RADIANCE Part B, and the presence of a significant level of inflammatory activity as per inclusion criteria. Active disease was further evidenced by the presence of GdE lesions at baseline in 45.0% of patients with at least 1 GdE lesion, including 28.1% of patients with at least 2 GdE lesions. A total of 22.8% of patients met the definition for having highly active MS at baseline as defined as (1) at least 2 relapses in the prior 12 months and at least 1 baseline GdE lesion, and/or (2) having received at least 1 year of DMT in the prior 2 years, having the most recent relapse in the previous 12 months while on that DMT, and having 9 or more baseline hyperintense T2-weighted brain MRI lesions or at least 1 baseline GdE brain MRI lesion.

The prior use of MS-related treatments was generally well balanced across treatment groups within each study as well as across the studies, with some variability in the type of MS medication used (Table 7). More than 90% of patients had been previously treated with prior corticosteroids. Approximately 30% of patients across all treatment groups in both studies had been previously treated with a DMT, with the 2 most common DMTs being interferon (19.2%) and glatiramer acetate (12.0%).

Table 6: Summary of Baseline Characteristics

Baseline characteristics	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Demographics				
Sex n (%)				
Female	291 (67.2)	304 (68.9)	283 (63.3)	300 (67.0)
Age (years)				
Mean (SD)	36.0 (8.89)	35.1 (9.07)	34.8 (9.24)	35.9 (9.11)
Median (range)	36.0 (18 to 55)	35.0 (18 to 55)	33.0 (18 to 55)	36.0 (18 to 55)
Race, n (%)				
White	428 (98.8)	432 (98.0)	446 (99.8)	447 (99.8)
Black	5 (1.2)	7 (1.6)	0	0

Baseline characteristics	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Asian	0	1 (0.2)	1 (0.2)	0
Other	0	1 (0.2)	0	1 (0.2)
Weight (kg), mean (SD)	70.94 (17.014)	70.14 (16.374)	69.70 (15.482)	69.95 (16.199)
BMI (kg/m^2), mean (SD)	24.55 (4.958)	24.28 (5.304)	24.06 (4.596)	24.20 (4.595)
Region				
North America	16 (3.7)	16 (3.6)	12 (2.7)	11 (2.5)
Canada	0	1 (0.2)	0	0
US	16 (3.7)	15 (3.4)	12 (2.7)	11 (2.5)
Western Europe	36 (8.3)	40 (9.1)	17 (3.8)	16 (3.6)
Eastern Europe	374 (86.4)	379 (85.9)	415 (92.8)	419 (93.5)
South Africa	7 (1.6)	6 (1.4)	0	0
New Zealand	0	0	3 (0.7)	2 (0.4)
Multiple sclerosis disease history				
Age at symptom onset (years)				
Mean (SD)	29.2 (8.67)	28.9 (8.60)	28.4 (8.42)	29.5 (8.92)
Median (range)	28.0 (7 to 52)	28.0 (7 to 52)	27.0 (13 to 52)	28.0 (10 to 53)
Age at diagnosis (years)				
Mean (SD)	32.1 (8.95)	31.6 (8.82)	31.6 (8.81)	32.7 (9.01)
Median (range)	32.0 (13 to 55)	30.0 (15 to 55)	30.0 (14 to 55)	32.0 (13 to 55)
Years since diagnosis				
Mean (SD)	3.97 (5.171)	3.63 (4.613)	3.60 (4.193)	3.71 (4.361)
Median (range)	2.06 (0.1 to 31.3)	1.63 (0.1 to 28.1)	1.95 (0.1 to 23.2)	1.91 (0.1 to 27.7)
Type of MS				
RRMS	425 (98.2)	432 (98.0)	438 (98.0)	441 (98.4)
SPMS	0	1 (0.2)	0	2 (0.4)
PRMS	8 (1.8)	8 (1.8)	9 (2.0)	5 (1.1)
EDSS score at baseline				
Mean (SD)	2.55 (1.145)	2.49 (1.158)	2.61 (1.160)	2.62 (1.138)
Median (range)	2.50 (0.0 to 5.5)	2.50 (0.0 to 5.0)	2.50 (0.0 to 5.0)	2.50 (0.0 to 5.0)
EDSS ≤ 3.5	366 (84.5)	377 (85.5)	360 (80.5)	370 (82.6)
EDSS > 3.5	67 (15.5)	64 (14.5)	87 (19.5)	78 (17.4)
Number of relapses within the last 12 months prior to screening				
Mean (SD)	1.3 (0.56)	1.3 (0.58)	1.3 (0.57)	1.3 (0.55)
Median (range)	1.0 (0 to 3)	1.0 (0 to 4)	1.0 (0 to 3)	1.0 (0 to 4)
Number of relapses within the last 12 months category n (%)				
0	8 (1.8)	7 (1.6)	10 (2.2)	7 (1.6)
1	317 (73.2)	306 (69.4)	323 (72.3)	330 (73.7)
2 to 3	108 (24.9)	124 (28.1)	114 (25.5)	10 (24.6)
≥ 4	0	4 (0.9)	0	1 (0.2)

Baseline characteristics	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Number of relapses within the last 24 months prior to screening				
Mean (SD)	1.7 (0.82)	1.8 (0.86)	1.8 (0.86)	1.7 (0.84)
Median (range)	1.0 (1 to 5)	2.0 (1 to 5)	2.0 (1 to 5)	2.0 (1 to 6)
Months since most recent pre-study relapse				
Mean (SD)	5.91 (3.241)	6.04 (3.321)	6.06 (3.566)	6.18 (3.829)
Median (range)	4.94 (1.6 to 23.7)	5.14 (1.3 to 22.7)	5.23 (1.5 to 24.1)	5.29 (1.2 to 44.6)
Baseline MRI				
Gadolinium-enhanced lesion count				
Mean (SD)	1.6 (3.78)	1.8 (3.54)	1.8 (3.41)	1.7 (3.22)
Median (range)	0 (0 to 53)	0 (0 to 22)	0 (0 to 19)	0 (0 to 20)
Gadolinium-enhanced lesion count category n (%)				
0	255 (58.9)	244 (55.3)	233 (52.1)	231 (51.6)
1 to 4	130 (30.0)	136 (30.8)	159 (35.6)	163 (36.4)
5 to 8	33 (7.6)	28 (6.3)	27 (6.0)	30 (6.7)
≥ 9	15 (3.5)	32 (7.3)	28 (6.3)	23 (5.1)
Gadolinium-enhanced lesion volume (cm^3)				
Mean (SD)	0.212 (0.533)	0.250 (0.615)	0.203 (0.542)	0.178 (0.463)
Median (range)	0 (0.00 to 6.80)	0 (0.00 to 5.16)	0 (0.000 to 5.096)	0 (0.000 to 5.562)
T2 lesion count				
Mean (SD)	47.9 (32.37)	48.7 (32.62)	54.5 (39.48)	53.7 (37.80)
Median (range)	42.0 (1 to 222)	41.0 (1 to 202)	45.0 (0 to 219)	45.0 (1 to 197)
T2 lesion volume (cm^3)				
Mean (SD)	11.638 (13.404)	11.500 (13.293)	12.492 (15.310)	13.571 (15.246)
Median (range)	7.368 (0.03 to 102.54)	6.588 (0.02 to 99.71)	7.147 (0.000 to 131.626)	8.246 (0.057 to 107.30)
Non-enhanced T1 lesion count				
Mean (SD)	33.4 (31.62)	33.3 (32.39)	35.9 (37.66)	38.1 (37.19)
Median (range)	23.0 (0 to 190)	23.0 (1 to 181)	23.0 (0 to 183)	27.0 (0 to 194)
Non-enhanced T1 lesion volume (cm^3)				
Mean (SD)	3.941 (6.179)	3.532 (5.366)	3.671 (6.127)	4.116 (6.077)
Median (range)	1.465 (0.00 to 50.99)	1.342 (0.00 to 37.36)	1.299 (0.000 to 45.179)	1.823 (0.000 to 44.970)
Normalized brain volume (cm^3)				
Mean (SD)	1,441.949 (79.228)	1,449.581 (77.156)	1,455.980 (77.941)	1,443.355 (78.731)
Median (range)	1,445.978 (1,190.49 to 1,660.72)	1,455.662 (1,208.19 to 1,667.70)	1,458.301 (1,190.843 to 1,662.986)	1,445.526 (1,222.696 to 1,635.156)

BMI = body mass index; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; PRMS = progressive relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SPMS = secondary progressive multiple sclerosis.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

Table 7: Multiple Sclerosis Treatment History

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Number of patients with any prior treatment for MS	402 (92.8)	407 (92.3)	422 (94.4)	427 (95.3)
Number of patients previously treated with a disease-modifying treatment	123 (28.4)	126 (28.6)	128 (28.6)	151 (33.7)
Glatiramer acetate	46 (10.6)	43 (9.8)	49 (11.0)	56 (12.5)
Interferon (U = unspecified)	2 (0.5)	0	0	0
Interferon beta-1a	39 (9.0)	47 (10.7)	45 (10.1)	53 (11.8)
Interferon beta-1b	48 (11.1)	46 (10.4)	33 (7.4)	38 (8.5)
Daclizumab	2(0.5)	4 (0.9)	4 (0.9)	4 (0.9)
Dimethyl fumarate	1 (0.2)	1 (0.2)	3 (0.7)	2 (0.4)
Peginterferon beta-1a	4 (0.9)	4 (0.9)	8 (1.8)	9 (2.0)
Teriflunomide	1 (0.2)	2 (0.5)	11 (2.5)	10 (2.2)
Mitoxantrone hydrochloride	0	0	2 (0.4)	0
Number of patients previously treated with corticosteroids	394 (91.0)	393 (89.1)	416 (93.1)	421 (94.0)
Number of patients with other MS medications prior to study treatment	27 (6.2)	20 (4.5)	11 (2.5)	16 (3.6)

MS = multiple sclerosis.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM.[11,12]

Interventions

Three ozanimod dose strengths were prepared for clinical investigation: 0.25 mg ozanimod hydrochloride (equivalent to 0.23 mg ozanimod), 0.5 mg ozanimod hydrochloride (equivalent to 0.46 mg ozanimod), and 1 mg ozanimod hydrochloride (equivalent to 0.92 mg ozanimod). This review refers to 0.46 mg ozanimod and 0.92 mg ozanimod as the ozanimod 0.5 mg, and ozanimod 1 mg treatment groups, respectively. Data were not presented for the ozanimod 0.5 mg treatment group because such as a dose is not Health Canada–approved.

Patients were randomized to receive either ozanimod 1 mg once daily, or interferon beta-1a 30 mcg IM weekly. During the active blinded-treatment period, patients randomized to ozanimod 1 mg received weekly matching placebo IM injections and patients randomized to interferon beta-1a 30 mcg also received daily matching placebo oral capsules. Patients randomized to ozanimod 1 mg received an initial dose-escalation regimen of ozanimod 0.25 mg on days 1 to 4, ozanimod 0.5 mg on days 5 to 7 and ozanimod 1 mg on day 8 and thereafter. Patients randomized to interferon beta-1a 30 mcg received ozanimod-matching placebo titration kits. Patients received the first dose of the study drug in the clinic and were monitored for potential cardiac events for 6 hours before discharge.

Ozanimod hydrochloride was blended with microcrystalline cellulose, silicon dioxide, croscarmellose sodium, and magnesium stearate in Swedish Orange opaque hard-gelatin

capsules. For the matching placebo, the same size-4 Swedish Orange opaque hard-gelatin capsules contained the same blended excipients. All 3 doses of ozanimod and placebo capsules were identical in appearance. To maintain blinding with the ozanimod capsules, matching placebo capsules were packaged in 30 cm^3 white high-density polyethylene bottles (35 capsules per bottle for treatment medication capsules, and 12 capsules per bottle in the dose-escalation kits), closed with a 28 mm child-resistant induction-sealed screw cap. The cap on the treatment bottles was white and the cap on the dose-escalation bottles was blue.

Interferon beta-1a matching placebo for injection contained 0.9% sodium chloride. The pre-filled placebo syringes were labelled and kits identical to the investigational packaging of Avonex (interferon beta-1a) were assembled to provide blinded syringes for injection. Interferon beta-1a and matching placebo injections were supplied in kits containing 14 pre-filled syringes, which were dispensed to patients at each visit and contained a sufficient supply of interferon beta-1a (or matching placebo) for each dosing interval. Study treatment (interferon beta-1a or matching placebo) pre-filled syringes and needles were for single use only; any study treatment remaining was not to be used for another dose. Patients were instructed by a nurse or physician on how to self-administer injections. The first injection was self-administered under the supervision of a nurse or physician. On the days of interferon beta-1a or placebo IM injection administration, prophylactic treatment (acetaminophen or ibuprofen) of flu-like symptoms was recommended.

Concomitant treatment with medications with a known impact on the cardiac conduction system (e.g., beta-blockers, calcium-channel blockers, or class Ia or class III antiarrhythmics) were not permitted during the study. Systemic corticosteroids were not permitted during the study except for patients experiencing a protocol-defined relapse. As per protocol, methylprednisolone 1 g per day over a maximum of 5 consecutive days was permitted as rescue medication. Treatments were permitted for symptoms related to MS such as spasticity, incontinence, pain, and fatigue.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 8. These end points are further summarized below. A detailed discussion and critical appraisal of the outcome measures are provided in Appendix 4.

Table 8: Summary of Outcomes of Interest Identified in RADIANCE Part B and SUNBEAM

Outcome category	RADIANCE Part B	SUNBEAM
Primary end point	ARR at the end of month 24	ARR during the treatment period
Key secondary efficacy end points	The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months	The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 months
	The number of GdE brain MRI lesions at month 24	The number of GdE brain MRI lesions at month 12
	Time to onset of disability progression as defined by a sustained worsening in EDSS score of 1.0 points or more, confirmed after 3 months and after 6 months	Time to onset of disability progression as defined by a sustained worsening in EDSS score of 1.0 points or more, confirmed after 3 months and after 6 months
Other secondary efficacy end points	Proportion of patients who are GdE lesion-free at month 24	Proportion of patients who are GdE lesion-free at Month 12

Outcome category	RADIANCE Part B	SUNBEAM
	Proportion of patients who are new or enlarging T2 lesion-free at month 24	Proportion of patients who are new or enlarging T2 lesion-free at month 12
	Percent change in normalized brain volume (atrophy) on MRI scans from baseline to month 24	Percent change in normalized brain volume (atrophy) on MRI scans from baseline to month 12
	Change in MSFC score from baseline to month 24 (LCLA measurement of visual function as a component)	Change in MSFC score from baseline to month 12 (including the LCLA measurement of visual function as a component)
	Change in MSQOL-54 score from baseline to month 24	Change in MSQOL-54 score from baseline to month 12
Exploratory	Proportion of patients with NEDA through month 24	Proportion of patients with NEDA through month 12

ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhanced; LCLA = Low-Contrast Letter Acuity Test; MSFC = Multiple Sclerosis Functional Composite; NEDA = no evidence of disease activity.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

Relapse

Annualized Relapse Rate

The primary outcome in the RADIANCE Part B study was the confirmed ARR at the end of month 24, and in the SUNBEAM study it was the ARR during the treatment period. A relapse was defined as the occurrence of new or worsening neurological symptoms attributable to MS that persisted for at least 24 hours, was not attributable to confounding clinical factors (e.g., fever, infection, injury, and adverse reactions to concomitant medications), and was immediately preceded by a relatively stable or improving neurological state for at least 30 days. A clinical relapse was confirmed by the treating investigator when it was accompanied by objective neurologic worsening, as measured by a change in EDSS of at least half a point, 2 points on 1 of the appropriate functional system scores, or 1 point on 2 or more of the appropriate functional system scores, as assessed by the independent EDSS evaluator blinded to treatment and previous EDSS assessments. When a patient experienced new or worsening symptoms that could indicate a possible relapse, the patient was to telephone the treating investigator within 48 hours of symptoms onset. The treating investigator (or designee) was to conduct a telephone questionnaire and, if necessary, arrange an unscheduled relapse assessment visit. A description of the measurement properties is not applicable for the ARR, although internal validity is reinforced by the concept of blinding of the outcome assessors in both studies. An MID for the ARR has not been identified.

Imaging Outcomes

Total Number of GdE Lesions, Number of New or Enlarging Hyperintense T2-Weighted Lesions, Lesion Volume (T2-Weighted Images), and Brain Volume (i.e., Brain Volume Loss)

Magnetic resonance imaging provides sensitive and quantitative measures of MS disease activity. Although no single MRI assessment is accepted as predictive of clinical disease, key MRI end points included in MS studies assess aspects of disease such as active inflammation (GdE T1 brain MRI lesions) as well as accumulation of disease burden (e.g., hyperintense T2-weighted brain MRI lesions) that are related to clinical disease activity and disability.[16,42] Hyperintense T2-weighted brain MRI lesions in MS reflect processes as diverse as edema, inflammation, demyelination, axonal loss, and gliosis, and are reflective

of the “burden of disease” overall. An increase in hyperintense T2-weighted brain MRI lesions is associated with more brain atrophy.[43] In MS, gadolinium enhancement is a product of the leakage of gadolinium into the perivascular space as a result of local breakdown of the blood brain barrier due to inflammation. Changes in brain volume are a cumulative measure of disease activity. Similar to the ARR, a description of the measurement properties is not applicable to these clinical outcomes, although internal validity is reinforced by the concept that all scans in both studies were read by the same central MRI reading centre, and readers were blinded to treatment and clinical safety and efficacy outcomes. An MID has not been identified for these outcomes.

The numbers of new or enlarging T2-weighted lesions over 12 months and over 24 months were key secondary end points in SUNBEAM and RADIANCE Part B studies, respectively. The numbers of GdE lesions at month 12 in the SUNBEAM study and at month 24 in RADIANCE Part B were key secondary end points.

The proportion of patients who were GdE lesion-free at month 12 in SUNBEAM and at month 24 in RADIANCE Part B, the proportion of patients who were free of new or enlarging T2 lesions at month 12 in SUNBEAM and at month 24 in RADIANCE Part B, and the percent change in normalized brain volume (atrophy) on brain MRI scans from baseline to month 12 in SUNBEAM and to month 24 in RADIANCE Part B were other secondary end points in both studies.

Health-Related Quality of Life

Health-related quality of life was evaluated using the MSQOL-54 in both included studies.

Multiple Sclerosis Quality of Life-54 Items

The MSQOL-54 is a self-reported, generic, and disease-specific quality-of-life instrument consisting of Likert scales and multiple-choice items.[44,45] It contains 12 subscales, 2 summary scores, and 2 additional single-item measures. The subscales include physical function, role limitations physical, role limitations–emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function, while the additional single-item measures are satisfaction with sexual function and change in health.[44] The MSQOL-54 has no single overall score, although the 2 summary scores, physical health and mental health, can be derived from a weighted combination of scale scores, which range from 0 to 100, with a higher score indicating improved quality of life.[46] Minimal important differences of 2.5 points and 1.5 points each from total scores of 100 have been estimated for the mental and physical summary scores, respectively. The MSQOL-54 has also demonstrated internal consistency, reliability, and validity. Change in MSQOL-54 score from baseline to month 12 in the SUNBEAM study and to month 24 in RADIANCE Part B were other secondary end points.

Mobility

The MSFC, T25FW, and 9-HPT instruments were used to inform mobility-related outcomes in SUNBEAM and RADIANCE Part B.

Multiple Sclerosis Functional Composite

This instrument has 3 components and assesses different clinical dimensions: arm (9-HPT, the time needed to insert and remove 9 pegs), leg (T25FW, the time needed to walk 25 feet), and cognition (PASAT, the total number of correct additions). For 9-HPT and T25FW, a higher test result means the patient worsened from baseline. For PASAT, a higher test

result means that the patient improved from baseline. To ensure that all measures are in the same direction, a transformation is necessary.[47] The raw scores for each item are transformed into z scores to achieve a common metric in SD units (i.e., a mean of 0 and an SD of 1). A z score represents the number of SDs by which a patient's test result is higher ($z > 0$) or lower ($z < 0$) than the average test result ($z = 0$) of the reference population. The mean and SD from test results at the baseline visit for all patients in each study were used as the reference population values to create z scores for each component of the composite. The z score is calculated by subtracting the mean of the reference population from the test result and then dividing the result by the SD of the reference population. In creating the composite outcome measure, it was decided that a higher test result would indicate improvement from baseline.[48] The z scores for each component are averaged to generate a single MSFC score.[49] However, the MSFC has been criticized on the basis that z scores are difficult to interpret intuitively and that calculation of z scores depend on a reference population. The weighting of the different MSFC components has also been criticized.[50-52] The EDSS and MSFC exhibit a moderate to strong correlation ($r = -0.41$ to -0.83) and the correlation between MRI outcomes and MSFC is also moderate ($r < 0.5$). The MSFC has demonstrated excellent test-retest reliability. An MID for the MSFC was not identified.

The PASAT was used as a cognitive component in the RADIANCE Part B study but was replaced with the SDMT in the SUNBEAM study.

Timed 25-Foot Walk Test

The T25FW is a component of the MSFC that measures gait velocity.[53] A standardized protocol is used to reduce variability between raters and across administration sites, and involves the patient safely walking a clearly marked, straight, 25-foot course as quickly as possible. Using a stopwatch, the time is measured from the initiation of the walk from a static start position to completion. The task is administered again with the patient walking back over the same distance. The T25FW score is the average of the 2 completed trials, reported in seconds. Patients may use assistive devices (e.g., canes, crutches, walkers) when completing the T25FW.[52] A higher test result represents a worse outcome. The T25FW test has a strong correlation (convergent validity) with the EDSS ($r = 0.84$). Strong reliability over various time periods has been demonstrated, with an intraclass correlation coefficient (ICC) of between 0.94 and 0.99, although this can vary depending on the patient's EDSS score. A 20% change in T25FW scores is considered clinically meaningful.

9-Hole Peg Test

The 9-HPT is a component of the MSFC that assesses a patient's manual dexterity by having them pick up and place 9 pegs into 9 holes on a board, then remove the pegs as quickly as possible.[54] The test is performed twice with each hand and the score is recorded as the mean time in seconds required to complete the task for each hand. A higher test result represents a worse outcome. The 9-HPT has a moderate correlation with EDSS ($r = 0.51$). The test-retest reliability ranges from 0.902 to 0.972, indicating almost perfect agreement. A 20% change in 9-HPT scores is considered clinically meaningful.

Cognitive Function

The PASAT was used as a cognitive component in the RADIANCE Part B study but was replaced with the SDMT in the SUNBEAM study.

Paced Auditory Serial Addition Test

The PASAT is a neuropsychological measure of cognitive function, auditory processing ability, and verbal communication.[54] It was developed to monitor the recovery of patients who had sustained mild head injuries, later adapted for use in patients with MS by Rao et al. in 1989, and is now widely used in MS studies.[49,55] During the test, a number is presented every 3 seconds to a total of 60 numbers. Each new digit must be added to the last and the sum is spoken aloud by the patient. The total number of correct additions is then recorded. The PASAT has been criticized for its association with psychological stress and agitation, high reports of patient dropouts, the necessity for the patient to have a minimum level of mathematical ability, and the potential for practice effects.[56]

The PASAT has weak correlation with EDSS (r = 0.31), and strongly correlation with SDMT (validity coefficients ranged from 0.54 to 0.62). It has good internal consistency for individual trials (correlations ranging from 0.76 to 0.95) and high test-retest reliability (range = 0.90 to 0.97). A change in SD of 0.5 in patients with MS is considered clinically meaningful.

Symbol Digital Modalities Test

The SDMT is a commonly used neuropsychological screening tool for cognitive impairment that takes little time to administer and score.[57] Similar to PASAT, the SDMT measures processing speed along with visual working memory rather than auditory processing, all of which tend to decline with MS progression.[30] The SDMT and PASAT are alike in terms of practice effect and reliability when performed at weekly intervals in patients with MS; however, the SDMT demonstrates superior sensitivity when discriminating between healthy controls and patients with MS. It has been suggested that the SDMT would be an acceptable complementary test when examining cognitive impairment in patients with MS. The patient is given a test sheet that includes a row of single digits, 1 to 9, corresponding to 9 unique symbols, at the top, and an array of symbols paired with empty spaces below.[57,58] The patient must choose the correct matching number as rapidly as possible in 90 seconds.[56] At the end of the test, the total number of correct responses, from 0 to 110, is recorded. Higher scores indicate a better outcome. The test shows moderate to weak correlations with other outcomes measures: PASAT (r = 0.54), 9-HPT (r = −0.47), T25FW (r = −0.42), EDSS (r = −0.34), and LCLA (r = 0.34). Studies have suggested a decrease in 3 to 5 points as being a notable difference in patients who experienced relapses,[58] while a 10% change in magnitude was considered an MID in the SDMT.[58]

Visual Disturbance

Low-Contrast Letter Acuity

The LCLA has been added as fourth component to the MSFC in both studies to include an evaluation for visual disfunction. The LCLA, which is performed with the MSFC assessments, is conducted using the Sloan Letter Charts, which display grey letters that progressively decrease in size against a white background.[59] Sitting 2 m away, and with any usual corrective lenses, patients read aloud from the charts and the number of correct letters is recorded to a maximum score of 60 or 70 letters, depending on the chart.[59,60] Charts with 100%, 2.5%, and 1.25% contrast are typically used in MS clinical trials.[60] This test is subject to both floor and ceiling effects with low and high contrast levels, respectively, and patients can have scores of 0 or near 0 for low-contrast or perfect or near-perfect scores that do not change over time. The Low-Contrast Sloan Letter Charts have been reported as both sensitive and reliable for measuring contrast letter acuity in patients

with MS compared to healthy individuals.[59,60] There are still differing opinions on what constitutes a clinically meaningful change, with the most commonly reported range being from greater than 5 to 7 letters.[60]

Disability Progression or Improvement

Expanded Disability Status Scale

The EDSS is an ordinal scale used to measure disability in MS and addresses disability in 8 functional system domains.[61] These are pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. The scores range from 0 to 10 (in increments of 0.5) and incorporate functional system grades as well as the degree of functional disability and ambulation.[62] A score from 0 to 4.5 represents normal ambulation, while a score of at least 5 represents a progressive loss of ambulatory ability.

The distribution of EDSS scores among MS patients is typically bimodal, accumulating at 2 to 3 points and 6 to 7 points, indicating that patients do not stay equally long at each step of the scale. The EDSS has been subjected to many criticisms, including the fact that it has moderate intra-rater reliability (kappa values between 0.32 to 0.76 and between 0.23 to 0.58 for the individual functional system have been reported),[62] it is a poor assessment of upper limb and cognitive function, and it lacks linearity between score difference and the clinical severity.[63-66] The EDSS was also found to correlate poorly with neuropsychological impairment and brain changes measured by MRI.[62] Other limitations include its heavy reliance on the evaluation of motor function and the ability to walk; as such, a patient who might not be able to walk but maintains full dexterity is classified toward the severe end of the scale. In published literature, the MID was estimated to be a 1.0-point change when the EDSS score was between 0.0 and 5.5, but decreased to a 0.5-point change when the EDSS score was between 5.5 and 8.5.[67]

Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and again after 6 months, was a key secondary end point in both the SUNBEAM and RADIANCE Part B studies. Sustained disability progression was defined as at least a 1.0-point increase on the EDSS score from baseline, confirmed after a 3-month and a 6-month period. Confirmation of MS disease progression must not have occurred at the time of a relapse. If the patient was scheduled to be evaluated to confirm disability at the time of a relapse, the disability event was assessed at a later visit, which may have been the next scheduled visit, or at an unscheduled visit conducted after the relapse resolved. The date of the initial visit at which the minimum increase in the EDSS was met was to be the date of onset of the progression (tentative progression). In both studies, the same blinded evaluator was to perform all EDSS assessments for an individual patient.

Composite Outcomes: NEDA (Relapses and Imaging)

No Evidence of Disease Activity

The proportion of subjects with NEDA, defined as no relapses, no disability progression, no new or enlarging T2 lesions, and no new GdE lesions, through month 24 in RADIANCE Part B and through month 12 in SUNBEAM, was an exploratory end point. Evidence of an MID was not identified.

Harms Outcomes

Safety was be evaluated in both studies by the incidence and type of AEs, SAEs, and AEs leading to discontinuation of study treatment. In addition, AEs of interest including bradycardia and heart-conduction abnormalities, pulmonary functioning, macular edema, liver-function tests, and cutaneous malignancy were evaluated in both studies.

Statistical Analysis

Power Calculation

Both SUNBEAM and RADIANCE Part B were independently powered to address the primary end point. Assuming extra-Poisson variation (sigma squared = 1.3),[68] a total sample size of 1,059 patients (353 per arm)[69] provides 80% power to detect a 43% reduction in the ARR (the ARR following treatment with interferon beta-1a was assumed to be approximately 0.3[70]) with alpha = 0.025. Each study required approximately 1,200 patients (400 patients per arm) to provide sufficient power to meet the primary ARR end point and account for an assumed dropout rate of approximately 12%.

Statistical Test or Model

In both SUNBEAM and RADIANCE Part B, the primary and key secondary end points were the ARR, new or enlarging hyperintense T2-weighted brain MRI lesions, GdE T1 brain MRI lesions, and CDP, respectively. In each study, both doses of ozanimod (1 mg and 0.5 mg) were compared to interferon beta-1a to assess the efficacy using the primary end point (ARR) and 2 key secondary end points (new or enlarging hyperintense T2-weighted brain MRI lesions and GdE T1 brain MRI lesions).

Primary End Point

For both studies, the primary analysis of the ARR was performed using a Poisson regression model. The model compared treatment groups, adjusted for region, age at baseline, and the baseline number of GdE lesions, and used the natural logarithmic transformation of time on study as an offset term. The ARRs and their associated 95% CIs, the RRs and their associated 95% CIs, and P values were reported. Statistical testing included 2 treatment comparisons: the ozanimod 1 mg group versus the interferon beta-1a group, and the ozanimod 0.5 mg group versus the interferon beta-1a group. To account for multiple comparisons, each of the 2 treatment comparisons was tested at the alpha = 0.025 level.

Key Secondary End Points

The cumulative total of new or enlarging T2-weighted lesions over 12 months in SUNBEAM and over 24 months in RADIANCE Part B was analyzed using a negative binomial regression model adjusted for region, age at baseline, and baseline number of GdE lesions, and included the natural log transformation of the number of available MRI scans as an offset term.

Analyses of the number of GdE lesions (at month 12 in SUNBEAM and month 24 in RADIANCE Part B) were performed using a negative binomial regression model adjusted for region, age at baseline, and baseline number of GdE lesions, and included the natural logarithmic transformation of the number of available MRI scans as an offset term.

The primary analysis of time to disability progression was analyzed using a Cox proportional hazards model with factors for treatment group, adjusted for region, age at baseline, and baseline EDSS score. Handling of ties was according to Efron. Patients who completed the studies without an observed disability progression or patients who discontinued from the studies prematurely without an observed disability progression were censored at the time they either completed or prematurely discontinued the study. The hazard ratio (HR), associated 95% CI, and P values were reported. Each of these analyses was performed on disability progressions confirmed after 3 months and again on disability progressions confirmed after 6 months. To increase the power of this end point, disability progression data from SUNBEAM and RADIANCE Part B were pooled.

To control for type I error, the 3 key secondary end points were tested in order in a sequential, closed hierarchical testing procedure that ranked the ozanimod 1 mg dose above the ozanimod 0.5 mg dose and the key secondary end points in the order shown in

Figure 3. If both doses were significant on the primary end point, the first comparison on the key secondary end points was between the ozanimod 1 mg group and the interferon beta-1a group at the 5% level of significance. If that comparison was successful, the same end point was tested for the ozanimod 0.5 mg group versus the interferon beta-1a group comparison at the 5% level of significance. This procedure (Figure 3A) continued down the rank-ordered list of key secondary end points until a comparison failed to reach statistical significance, after which all subsequent comparisons were considered exploratory. For the third key secondary end point of time to onset of sustained disability progression, the data from SUNBEAM and RADIANCE Part B were pooled for hypothesis testing. If only a single ozanimod dose group was significant on the primary end point, then the hierarchical testing procedure was employed on the rank-ordered list of key secondary end points for the surviving dose only, at the 2.5% level of significance for each key secondary end point (Figure 3B).

Other secondary and exploratory end point analyses did not include adjustments for multiple comparisons and multiple end points.

Other Secondary End Points

Other secondary end points — the proportion of patients who are GdE lesion–free at month 12 in SUNBEAM and at month 24 in RADIANCE Part B, and the proportion of patients who are T2 lesion–free at month 12 in SUNBEAM and at month 24 in RADIANCE Part B — were analyzed using a Cochran-Mantel-Haenszel test stratified by region and EDSS category at baseline. Patients who were missing the MRI data for month 12 and month 24 in the SUNBEAM and RADIANCE Part B studies, respectively, were to be considered non-responders (i.e., as not being lesion-free).

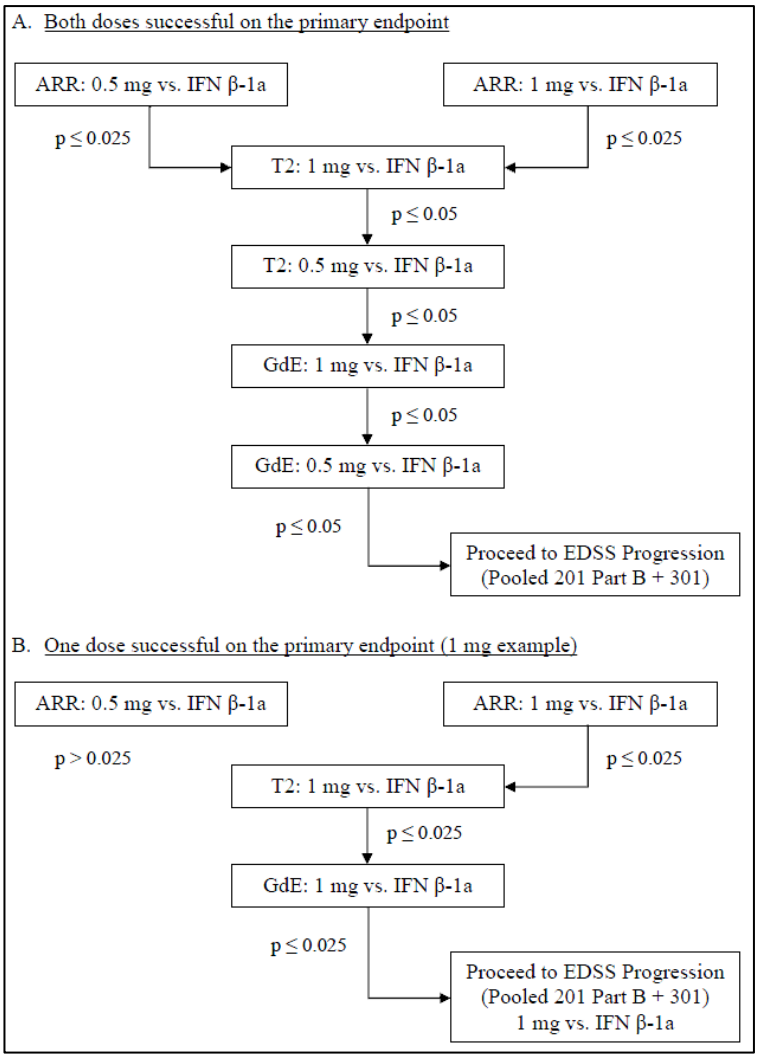
Comparisons of the change in brain volume and percent changes between the treatment groups were to be analyzed using an analysis of covariance (ANCOVA) model adjusted for region, EDSS category at baseline, and brain volume at baseline. Patients with missing data were to have their results imputed by the last observed carried forward (LOCF) method.

The change from baseline in the MSFC scores and the subscores were summarized in each treatment group using the LOCF to address missing data. The changes in MSFC scores at months 12 and 24 were analyzed and compared between treatment groups using an ANCOVA model adjusting for region, EDSS category at baseline, and baseline MSFC score.

Comparisons of the change in the MSQOL-54 from baseline to month 12 (SUNBEAM) and month 24 (RADIANCE Part B) for the 2 summary scores only between treatment groups were analyzed by an ANCOVA model adjusted for region, EDSS category at baseline, and baseline summary score of interest. Missing data were imputed using a single imputation mixed-effects regression model (random slope and intercept).

No statistical methods were reported for the analyses of the NEDA exploratory outcome.

Figure 3: Hierarchical Testing Procedures



ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhanced; INF = interferon.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

Data Imputation Methods

The SUNBEAM and RADIANCE Part B studies did not report whether missing data were imputed for the primary and key secondary end points.

Subgroup Analyses

Subgroup analysis was performed for the primary and secondary efficacy end points where applicable. The following were the predefined subgroups:

- baseline EDSS score (EDSS ≤ 3.5 versus EDSS > 3.5)
- baseline presence of GdE lesions (present versus absent)
- prior treatment status (treatment-naive versus previously treated)
- age at baseline (age ≤ 40 versus age > 40)
- sex (female versus male)
- race (white versus non-white)
- weight (< median versus ≥ median)
- number of relapses in the past 12 months (< 2 versus ≥ 2) for the ARR end point only
- regions (Eastern Europe and rest of world).

Any subgroup that did not have at least 5% of the overall sample size (approximately 60 patients) was not included in subgroup analyses.

Subgroups by prior treatment status, baseline EDSS score, baseline presence of GdE lesions, number of relapses in the past 12 months, and age at baseline were relevant to the CADTH systematic review protocol and were therefore included in this review.

Sensitivity Analyses

Two pre-specified sensitivity analyses of the ARR were performed. The first sensitivity analysis repeated the primary analysis counting both confirmed and unconfirmed relapses. The second sensitivity analysis used a negative binomial regression model, instead of the Poisson regression model, to compare relapse rates. The same covariates and offset term were used as specified in the primary analysis. This model was run twice — once repeating the primary analysis (confirmed relapses only) and once repeating the first sensitivity analysis (confirmed plus unconfirmed relapses).

Three pre-specified sensitivity analyses of T2-weighted brain MRI lesions were performed: the first analysis repeated the primary T2 analysis using the mean number of T2 lesions from patients from the same treatment group to impute missing T2 values. The second analysis repeated the primary T2 analysis using the LOCF method to impute missing T2 data values. Only data from post-baseline MRI scans were carried forward to the month 12 and month 24 time points for this analysis. The third analysis repeated the primary T2 analysis using only patients with complete T2 data at relevant MRI visits (observed cases analysis). All 3 sensitivity analyses included the natural log transformation of exposure time on study (instead of the number of available MRI scans) as the offset term.

Three pre-specified sensitivity analyses of GdE T1 brain MRI lesions were performed: the first analysis repeated the primary GdE analysis using the mean number of GdE lesions from patients from the same treatment group to impute missing GdE values. The second analysis repeated the primary GdE analysis using last LOCF method for imputing missing GdE data values. Only data from post-baseline MRI scans were carried forward to the month 24 time point for this analysis. The third analysis repeated the primary GdE analysis using only patients with complete GdE data at month 24 (observed cases analysis). All 3

sensitivity analyses included the natural log transformation of exposure time on study (instead of the number of available MRI scans) as the offset term.

Four pre-specified sensitivity analyses were performed on disability progressions confirmed after 3 months and disability progressions confirmed after 6 months and included the following:

- counting patients with a baseline EDSS = 0 as a progression only if the EDSS score increased by at least 1.5 points
- unconfirmed progressions in each analysis
- counting premature study discontinuations as confirmed progressions in each analysis
- unconfirmed progressions and counting premature discontinuations as progressions in each analysis.

Table 9: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Sensitivity analyses
RADIANCE Part B and SUNBEAM			
ARR	Poisson regression model	Region, age at baseline, and the baseline number of GdE lesions, and included the natural logarithmic transformation of time on study as an offset term	• Counting both confirmed and unconfirmed relapses • Negative binomial regression model with confirmed relapses only • Negative binomial regression model with confirmed and unconfirmed relapses
The number of new or enlarging hyperintense T2-weighted brain MRI lesions	Negative binomial regression model	Region, age at baseline, and baseline number of GdE lesions, and included the natural log transformation of the number of available MRI scans as an offset term	• Using the mean number of T2 lesions from patients from the same treatment group to impute missing T2 values • Using the LOCF method to impute missing T2 data values • Using only patients with complete T2 data at relevant MRI visits (observed cases analysis)
The number of GdE brain MRI lesions	Negative binomial regression model	Region, age at baseline, and baseline number of GdE lesions, and including the natural logarithmic transformation of the number of available MRI scans as an offset term	• Using the mean number of GdE lesions from patients from the same treatment group to impute missing GdE values • Using the LOCF method to impute missing GdE data values • Using only patients with complete GdE data at month 24 (observed cases analysis)

End point	Statistical model	Adjustment factors	Sensitivity analyses
Time to onset of disability progression as defined by a sustained worsening of 1.0 points or more on an EDSS, confirmed after 3 months and again after 6 months	Cox proportional hazards model	Region, age at baseline, and baseline EDSS score. Patients who completed the studies without an observed disability progression or patients who discontinued from the studies prematurely without an observed disability progression were censored at the time they either completed the study or prematurely discontinued the study	• Counting patients with a baseline EDSS = 0 as a progression only if the EDSS score increased by at least 1.5 points • Unconfirmed progressions in each analysis • Counting premature study discontinuations as confirmed progressions in each analysis • Unconfirmed progressions and counting premature discontinuations as progressions in each analysis
Proportion of patients who are GdE lesion-free	Cochran-Mantel-Haenszel test	Region and EDSS category at baseline	None
Proportion of patients who are new or enlarging T2 lesion-free	Cochran-Mantel-Haenszel test	Region and EDSS category at baseline	None
Percent change in normalized brain volume (atrophy) on MRI scans from baseline	ANCOVA model	Region, EDSS category at baseline, and brain volume at baseline	None
Change from baseline in MSFC score (LCLA measurement of visual function as a component)	ANCOVA model	Region, EDSS category at baseline, and the baseline MSFC score	None
Change from baseline in MSQOL-54 score	ANCOVA model	Region, EDSS category at baseline, and baseline summary score of interest	None

ANCOVA = analysis of covariance; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhanced; LCLA = Low-Contrast Letter Acuity Test; LOCF = last observation carried forward; MSQOL = Multiple Sclerosis Quality of Life-54 items.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

Analysis Populations

The ITT population included all randomized patients who received at least 1 dose of the study drug. Patients were grouped according to their randomized treatment, regardless of the actual treatment received. The ITT population was the primary population for all efficacy analyses.

The per-protocol population was a subset of the ITT population. Subjects not meeting specific eligibility criteria for diagnosis or prior disease activity and subjects with poor study-drug compliance were excluded from the population. The per-protocol population was used in addition to the ITT population for sensitivity analyses of the primary and the secondary efficacy end points.

The safety population included all randomized patients who received at least 1 dose of study drug. Patients were grouped according to the treatment they received. The safety population was the primary population for all safety analyses.

Results

Patient Disposition

A summary of the patient disposition in RADIANCE Part B and SUNBEAM is provided in Table 10. A total of 1,695 and 1,656 patients were screened, and 1,320 (77.9%) and 955 (81.3%) were randomized in the 2 studies, respectively. The most common reasons for screen failure in RADIANCE Part B were laboratory abnormality (8.14%) and other reasons (7.8%), while in SUNBEAM the most common reasons for screen failure were no documentation of positive varicella-zoster virus immunoglobin G antibody status, no documentation of complete varicella-zoster virus vaccination at least 30 days prior to randomization (5.6%), or no ability to provide written informed consent and to be compliant with the schedule of protocol assessments (2.8%).

In the RADIANCE Part B study, 3 patients (1 in the ozanimod 1 mg group and 2 in the interferon beta-1a group) were excluded from the ITT population, as they were randomized but did not receive any study drug. Five patients received the wrong study drug in error. In the SUNBEAM study, 5 patients received the wrong study drug in error.

A differential dropout rate (discontinuation from study) was reported for RADIANCE Part B, with 10.4% of patients in the ozanimod 1 mg treatment group discontinued compared to 15.1% of patients in the interferon beta-1a group. This difference was driven by the proportion of patients who discontinued due to voluntarily withdrawal (4.6% versus 7.2% for ozanimod 1 mg versus interferon beta-1a, respectively) and AEs (2.8% versus 4.1% for ozanimod 1 mg versus interferon beta-1a, respectively). Discontinuation rates in the SUNBEAM study were more balanced, with 6.5% and 8.0% of patients discontinuing in the ozanimod 1 mg and interferon beta-1a treatment groups, respectively. The most common reasons for discontinuation in SUNBEAM included voluntarily withdrawal (2.9% versus 2.2% for ozanimod 1 mg versus interferon beta-1a, respectively) and AEs (2.7% versus 3.6% for ozanimod 1 mg versus interferon beta-1a, respectively).

Table 10: Patient Disposition

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg	Interferon beta-1a 30 mcg	Ozanimod 1 mg	Interferon beta-1a 30 mcg
Screened, N	1,695		1,656	
Randomized, N (%)	434	443	447	448
Discontinued from study, n (%)	45 (10.4)	67 (15.1)	29 (6.5)	36 (8.0)
Reason for discontinuation, n (%)				
Adverse events	12 (2.8)	18 (4.1)	12 (2.7)	16 (3.6)
Lack of efficacy	1 (0.2)	2 (0.5)	0	3 (0.7)
Protocol violation	3 (0.7)	4 (0.9)	0	0
Lost to follow-up	0	1 (0.2)	2 (0.4)	1 (0.2)
Voluntarily withdrew	20 (4.6)	32 (7.2)	13 (2.9)	10 (2.2)

	RADIANCE Part B		SUNBEAM	
Physician decision	4 (0.9)	9 (2.0)	0	2 (0.4)
Other	5 (1.2)	1 (0.2)	2 (0.4)	4 (0.9)
Intention-to-treat population, N[a] (%)	433 (99.8)	441 (99.5)	447 (100)	448 (100)
Per-protocol population, N (%)	432 (99.5)	436 (98.4)	445 (99.6)	447 (99.8)
Safety population, N[b] (%)	434 (100)	440 (99.3)	448 (100.2)	445 (99.3)

[a] The intention-to-treat population included all randomized patients who received at least 1 dose of the study drug. All patients in the population were analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

[b] The safety population consisted of all patients who received at least 1 dose of randomized study drug. All patients in the safety population were analyzed according to the highest dose of ozanimod treatment actually received (up to 1 mg) and not according to the treatment they were randomized to receive, if different.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

Exposure to Study Treatments

A summary of exposure to study treatments is provided in Table 11. The extent of exposure was greater in the RADIANCE Part B study (mean duration of 22.2 months overall) than in the SUNBEAM study (mean duration of 13.6 months overall), corresponding to the duration of the studies (24 months and 12-plus months, respectively).

In RADIANCE Part B, exposure to study treatment was slightly larger, with patients in the ozanimod 1 mg group compared with the interferon beta-1a group (mean [SD] months of exposure of 22.592 [4.850] and 21.995 [5.625], respectively). Relative exposure was similar in SUNBEAM, in which patients in the ozanimod 1 mg group were exposed to treatment for a mean (SD) of 13.61 months (2.726), compared to 13.49 months (2.869) in the interferon beta-1a group.

In both RADIANCE Part B and SUNBEAM, no notable differences among treatment groups were reported in the median number of capsules administered, number of injections administered, or drug compliance rate. Overall, the median drug compliance rate for ozanimod or matching placebo was 100.0% for all treatment groups. The median drug compliance rate for interferon beta-1a or matching placebo was 100.0% for all treatment groups.

As previously described, use of rescue medication was permitted. Data specific to the use of rescue medication were not reported.

Table 11: Exposure to Study Treatments

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 434)	Interferon beta-1a 30 mcg (N = 440)	Ozanimod 1 mg (N = 448)	Interferon beta-1a 30 mcg (N = 445)
Overall study treatment duration of exposure (months)				
Mean (SD)	22.592 (4.850)	21.995 (5.625)	13.61 (2.726)	13.49 (2.869)
Median (range)	24.000 (0.10 to 24.53)	24.000 (0.03 to 24.46)	13.58 (0.1 to 22.1)	13.61 (0.2 to 21.0)
Compliance with study treatment				
Number of capsules administered				
Mean (SD)	690.7 (146.95)	671.8 (172.73)	418.0 (81.91)	413.7 (88.14)
Median (range)	731.0 (3 to 936)	731.0 (0 to 944)	416.0 (5 to 678)	418.0 (5 to 679)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 434)	Interferon beta-1a 30 mcg (N = 440)	Ozanimod 1 mg (N = 448)	Interferon beta-1a 30 mcg (N = 445)
Number of capsules expected				
Mean (SD)	689.2 (147.59)	672.0 (170.21)	417.1 (82.98)	413.3 (87.30)
Median (range)	732.0 (3 to 748)	732.0 (1 to 746)	416.0 (4 to 674)	417.0 (6 to 642)
Ozanimod or matching placebo compliance rate				
< 80%	0	1 (0.2)	1 (0.2)	1 (0.2)
81 to 100%	395 (91.0)	389 (88.4)	396 (88.4)	402 (90.3)
> 100%	39 (9.0)	48 (10.9)	50 (11.2)	41 (9.2)
Median, %	100.00	100.00	100.00	100.00
Number of injections administered				
Mean (SD)	98.6 (20.90)	95.7 (24.38)	59.4 (11.71)	58.8 (12.49)
Median (range)	104.0 (1 to 133)	104.0 (1 to 118)	59.0 (1 to 97)	59.0 (1 to 92)
Number of injections expected				
Mean (SD)	98.0 (21.23)	95.3 (24.61)	59.3 (12.02)	58.7 (12.58)
Median (range)	104.0 (1 to 106)	104.0 (1 to 106)	59.0 (1 to 96)	59.0 (1 to 91)
Interferon beta-1a or matching placebo compliance rate				
< 80%	1 (0.2)	2 (0.5)	4 (0.9)	1 (0.2)
81 to 100%	387 (89.2)	385 (87.5)	367 (81.9)	363 (81.6)
> 100%	46 (10.6)	52 (11.8)	77 (17.2)	81 (18.2)
Median %	100.00	100.00	100.00	100.00

SD = standard deviation.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

In RADIANCE Part B, the majority of patients took at least 1 concomitant medication. More patients in the interferon beta-1a group (399 patients, 90.7%) reported taking concomitant therapy than in the ozanimod 1 mg group (370 patients, 85.3%). Common drug classes were analgesics (ozanimod 1 mg: 201 patients, 46.3%; interferon beta-1a: 265 patients, 60.2%), anti-inflammatory and antirheumatic products (ozanimod 1 mg: 146 patients, 33.6%; interferon beta-1a: 193 patients, 43.9%), and corticosteroids for systemic use (ozanimod 1 mg: 108 patients, 24.9%; interferon beta-1a: 150 patients, 34.1%).

In SUNBEAM, the majority of patients took at least 1 concomitant medication. More patients in the interferon beta-1a group (403 patients, 90.6%) reported taking concomitant therapy than in the ozanimod 1 mg group (371 patients, 82.8%). Common drug classes were analgesics (ozanimod 1 mg: 199 patients, 44.4%; interferon beta-1a: 277 patients, 62.2%), anti-inflammatory and antirheumatic products (ozanimod 1 mg: 121 patients, 27.0%; interferon beta-1a: 165 patients, 37.1%), and corticosteroids for systemic use (ozanimod 1 mg: 85 patients, 19.0%; interferon beta-1a: 135 patients, 30.3%).

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. Appendix 3 provides detailed efficacy data.

Relapses

The primary outcome in the RADIANCE Part B study was the ARR at the end of month 24, and in the SUNBEAM study it was the ARR during the treatment period. Results pertaining to ARRs are presented in Table 12.

In RADIANCE Part B, the adjusted ARRs in patients in the ozanimod 1 mg and interferon beta-1a treatment groups were 0.172 (95% CI, 0.142 to 0.208) and 0.276 (95% CI, 0.234 to 0.324), respectively. This corresponded to a reduction in ARR of 37.662% (95% CI, 23.222 to 49.386; P < 0.0001) in favour of ozanimod 1.0 mg. Similarly, in SUNBEAM, the adjusted ARRs in patients in the ozanimod 1 mg and interferon beta-1a treatment groups were 0.181 (95% CI, 0.140 to 0.236) and 0.350 (95% CI, 0.279 to 0.440), respectively. This corresponded to a reduction in ARR of 48.211% (95% CI, 33.702 to 59.545; P < 0.0001), in favour of ozanimod 1.0 mg.

These results from both RADIANCE Part B and SUNBEAM were supported by multiple pre-specified sensitivity analyses, including confirmed and unconfirmed relapses, assuming a negative binomial distribution (Table 36).

In both RADIANCE Part B and SUNBEAM the RRs and 95% CIs for the ARRs were generally consistent across the subgroups (age, relapses in prior 12 months, baseline GdE lesions, baseline EDSS, and prior use of a DMT). The upper bound of the rate ratio of ozanimod 1 mg versus interferon beta-1a was lower than 1, except for the subgroup of patients with a baseline EDSS score greater than 3.5 in SUNBEAM, and patients older than 40 years of age in both studies (Table 37).

Table 12: Annualized Relapse Rate During the Treatment Period – ITT Population

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Annualized relapse rate during the treatment period[a]				
Number of patients contributing to the analysis	433	441	447	448
Total number of relapses	143	236	97	184
Adjusted annualized relapse rate (95% CI)	0.172 (0.142 to 0.208)	0.276 (0.234 to 0.324)	0.181 (0.140 to 0.236)	0.350 (0.279 to 0.440)
Rate ratio (ozanimod/interferon beta-1a) (95% CI)	0.623 (0.506 to 0.768)	Reference	0.518 (0.405 to 0.663)	Reference
Percent reduction (95% CI)	37.662 (23.222 to 49.386)	Reference	48.211 (33.702 to 59.545)	Reference
P value	< 0.0001		< 0.0001	

CI = confidence interval; ITT = intention-to-treat.

[a] Based on the Poisson regression model, adjusted for region (Eastern Europe versus rest of the world), age at baseline, and the baseline number of gadolinium-enhanced lesions, and including the natural log transformation of time on study as an offset term.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

Imaging Outcomes

The RADIANCE Part B study included the number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months, and the number of GdE brain MRI lesions at month 24 as key secondary outcomes, while the proportion of patients who were GdE lesion-free at month 24, proportion of patients who had new or enlarging T2 lesion–free at month 24, and percent change in normalized brain volume (atrophy) on MRI scans from baseline to month 24 were other secondary outcomes.

The SUNBEAM study included the number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 months, and the number of GdE brain MRI lesions at month 12 as key secondary outcomes, while the proportion of patients who were GdE lesion-free at month 12, proportion of patients who were free of new or enlarging T2 lesions at month 12, and percent change in normalized brain volume (atrophy) on MRI scans from baseline to month 12 were other secondary outcomes.

In RADIANCE Part B, the adjusted mean numbers of new or enlarging hyperintense T2 lesions over 24 months in patients in the ozanimod 1 mg and interferon beta-1a treatment groups were 3.665 (95% CI, 3.041 to 4.416) and 6.357 (95% CI, 5.273 to 7.665), respectively. This corresponded to a 42.351% (95% CI, 28.580 to 53.467; P < 0.0001) reduction in new or enlarging hyperintense T2 lesions, in favour of ozanimod 1.0 mg (Table 13). Similarly, in SUNBEAM, the adjusted mean numbers of new or enlarging hyperintense T2 lesions over 12 months in patients in the ozanimod 1 mg and interferon beta-1a treatment groups were 2.927 (95% CI, 2.403 to 3.564) and 5.679 (95% CI, 4.667 to 6.910), respectively. This corresponded to a 48.330% (95% CI, 37.469 to 57.304; P < 0.0001) reduction in new or enlarging hyperintense T2 lesions in favour of ozanimod 1.0 mg (Table 13).

The results for the number of new or enlarging hyperintense T2-weighted brain MRI lesions were supported by multiple pre-specified sensitivity analyses for the individual studies (at 12 months for SUNBEAM; at 24 months for RADIANCE Part B). These sensitivity analyses were consistent with the primary analyses and demonstrated similar results for the ozanimod treatment group compared to interferon beta-1a (Table 38).

In both RADIANCE Part B and SUNBEAM studies the RRs and 95% CIs for the number of new or enlarging hyperintense T2-weighted brain MRI lesions were generally consistent across the subgroups (age, relapses in prior 12 months, baseline GdE lesions, baseline EDSS, and prior DMT), for which the upper bound of the RR of ozanimod 1 mg versus interferon beta-1a was lower than 1, except for the subgroup of patients with a baseline EDSS score greater than 3.5 in the SUNBEAM study, and patients older than 40 years of age in RADIANCE Part B (Table 39).

In RADIANCE Part B, the proportions of patients free of new or enlarging T2 lesions at month 24 in the ozanimod 1 mg and interferon beta-1a treatment groups were 23.8 (95% CI, 19.8 to 27.8) and 18.4 (95% CI, 14.8 to 22.0), respectively. This corresponded to a difference in proportions of 5.4% (95% CI, 0.0 to 10.8; nominal P = 0.0466) in favour of ozanimod 1.0 mg (Table 42). In SUNBEAM, the proportions of patients free of new or enlarging T2 lesions at month 12 in patients in the ozanimod 1 mg and interferon beta-1a treatment groups were 27.96 (95% CI, 23.80 to 32.12) and 23.44 (95% CI, 19.51 to 27.36), respectively. This corresponded to a difference in proportions of 4.53% (95% CI, −1.19 to 10.24; P = 0.1180), indicating no difference between treatments (Table 42).

Table 13: Number of New or Enlarging Hyperintense T2-Weighted Brain MRI lesions – ITT Population

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months in the RADIANCE Part B study and over 12 months in the SUNBEAM study[a]				
Number of patients contributing to the analysis	327	336	388	382
Total number of lesions	1,875	3,691	1,798	2,818
Total number of available MRI scans	653	671	775	765
Adjusted mean (95% CI) per scan[b]	1.835 (1.523 to 2.211)	3.183 (2.640 to 3.838)	1.465 (1.203 to 1.784)	2.836 (2.331 to 3.451)
Adjusted mean (95% CI) over the treatment period[c]	3.665 (3.041 to 4.416)	6.357 (5.273 to 7.665)	2.927 (2.403 to 3.564)	5.679 (4.667 to 6.910)
Rate ratio (ozanimod/interferon beta-1a) (95% CI)[b]	0.576 (0.465 to 0.714)	Reference	0.517 (0.427 to 0.625)	Reference
Percent reduction (95% CI)[b]	42.351 (28.580 to 53.467)	Reference	48.330 (37.469 to 57.304)	Reference
P value[b]	< 0.0001		< 0.0001	

CI = confidence interval; ITT = intention-to-treat.

[a] Based on number of new or enlarging T2 lesions over 24 months in the RADIANCE Part B study and over 12 months in the SUNBEAM study at a patient level.

[b] Based on a negative binomial regression model using observed data, adjusted for region (Eastern Europe versus rest of the world), age at baseline, and baseline number of gadolinium-enhanced lesions. The natural log transformation of the number of available MRI scans over 24 months in the RADIANCE Part B study and over 12 months in the SUNBEAM study is used as an offset term.

[c] Adjusted mean (95% CI) over 24 months in the RADIANCE Part B study and over 12 months in the SUNBEAM study was calculated as the model-based adjusted mean (95% CI) per scan multiplied by the mean number of available MRI scans over 24 months in the RADIANCE Part B study and over 12 months in the SUNBEAM study.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

In RADIANCE Part B, the adjusted mean numbers of GdE brain MRI lesions over 24 months in patients in the ozanimod 1 mg and interferon beta-1a treatment groups were 0.176 (95% CI, 0.116 to 0.266) and 0.373 (95% CI, 0.256 to 0.543), respectively. This corresponded to a 52.944% (95% CI, 27.530 to 69.445; P = 0.0006) reduction in the number of GdE brain MRI lesions in favour of ozanimod 1.0 mg (Table 14). Similarly, in SUNBEAM, the adjusted mean numbers of GdE brain MRI lesions over 12 months in patients in the ozanimod 1 mg and interferon beta-1a treatment groups were 0.160 (95% CI, 0.106 to 0.242) and 0.433 (95% CI, 0.295 to 0.635), respectively. This corresponded to a 62.973% (95% CI, 46.406 to 74.419; P < 0.0001) reduction in the number of GdE brain MRI lesions in favour of ozanimod 1.0 mg (Table 14).

The results for the number of GdE brain MRI lesions were supported by multiple pre-specified sensitivity analyses for the individual studies (at 12 months for SUNBEAM and at 24 months for RADIANCE Part B). These sensitivity analyses were consistent with the primary analyses and demonstrated similar results for ozanimod treatment group compared to interferon beta-1a (Table 40).

In both RADIANCE Part B and SUNBEAM the RRs and 95% CIs for the number of GdE brain MRI lesions were generally consistent across the subgroups (age, relapses in prior 12 months, baseline GdE lesions, baseline EDSS, and prior DMT), and the upper bound of the rate ratio of ozanimod 1 mg versus interferon beta-1a was lower than 1, with the exception of the subgroup of patients who were naive to DMTs in the SUNBEAM study, and patients with GdE lesions absent at baseline and patients older than 40 years of age in RADIANCE Part B (Table 41). Analysis for the subgroup of patients with a baseline EDSS score of more than 3.5 was not conducted in SUNBEAM due to the small number of patients and events in that subgroup.

In RADIANCE Part B, the proportions of patients who were GdE lesion-free at month 24 in the ozanimod 1 mg and interferon beta-1a treatment groups were 65.6 (95% CI, 61.1 to 70.1) and 56.2 (95% CI, 51.6 to 60.9), respectively. This corresponded to a difference in proportions of 9.4% (95% CI, 2.9 to 15.8; nominal P = 0.0047) in favour of ozanimod 1.0 mg (Table 43). Similarly, in SUNBEAM, the proportions of patients who were GdE lesion-free at month 12 in the ozanimod 1 mg and interferon beta-1a treatment groups were 74.05 (95% CI, 69.99 to 78.11) and 63.17 (95% CI, 58.70 to 67.64), respectively. This corresponded to a difference in proportions of 10.88% (95% CI, 4.84 to 16.92; nominal P = 0.0006) in favour of ozanimod 1.0 mg (Table 43).

Table 14: Number of GdE Brain Lesions on MRI – ITT Population

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Number of GdE brain MRI lesions at month 24 in the RADIANCE Part B study and at month 12 in the SUNBEAM study				
Number of patients contributing to the analysis	327	336	388	382
Adjusted mean (95% CI)[a]	0.176 (0.116 to 0.266)	0.373 (0.256 to 0.543)	0.160 (0.106 to 0.242)	0.433 (0.295 to 0.635)
Rate ratio (ozanimod/interferon beta-1a) (95% CI)[a]	0.471 (0.306 to 0.725)	Reference	0.370 (0.256 to 0.536)	Reference
Percent reduction (95% CI)[a]	52.944 (27.530 to 69.445)	Reference	62.973 (46.406 to 74.419)	Reference
P value[a]	0.0006		< 0.0001	

CI = confidence interval; GdE = gadolinium-enhanced; ITT = intention-to-treat.

[a] Based on the negative binomial regression model, adjusted for region (Eastern Europe versus rest of the world), age at baseline, and the baseline number of GdE lesions. The natural log transformation of the number of available MRI scans at 24 months in the RADIANCE Part B study and at 12 months in the SUNBEAM study (1 scan per patient) was used as an offset term.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

In RADIANCE Part B, the mean (SD) normalized brain volume at baseline was similar among treatment groups at 1,441.949 (79.228) cm^3 for the ozanimod 1 mg group and 1,449.581 (77.156) cm^3 for the interferon beta-1a group. The mean (SD) percent change in normalized brain volume on MRI scans from baseline to month 24 was −0.850 (0.928) for the ozanimod 1 mg group compared with −1.092 (0.991) for the interferon beta-1a group; the nominal P value for the between-group difference was less than 0.0001 in favour of ozanimod 1.0 mg (Table 44).

In SUNBEAM, the mean (SD) normalized brain volume at baseline was similar among treatment groups at 1,455.980 (77.941) cm^3 for the ozanimod 1 mg group and 1,443.355 (78.731) cm^3 for the interferon beta-1a group. The mean (SD) percent change in normalized brain volume on MRI scans from baseline to month 12 was −0.42 (0.654) for the ozanimod 1 mg group compared with −0.64 (0.696) for the interferon beta-1a group; the nominal P value for the between-group difference was less than 0.0001 in favour of ozanimod 1.0 mg (Table 44).

Composite Outcomes: NEDA (Relapses and Imaging)

In RADIANCE Part B, the proportions of patients with NEDA through month 24 in the ozanimod 1 mg and interferon beta-1a treatment groups were 24.2 (95% CI, 19.5 to 28.8) and 17.0 (95% CI, 13.0 to 21.0), respectively. This corresponded to a difference in proportions of 7.2% (95% CI, 1.1 to 13.3; nominal P = 0.0244) in favour of ozanimod 1.0 mg.

In SUNBEAM, the proportions of patients with NEDA through month 24 in the ozanimod 1 mg and interferon beta-1a treatment groups were 26.8 (95% CI, 22.3 to 31.2) and 22.5 (95% CI, 18.3 to 26.8), respectively. This corresponded to a difference in proportions of 4.23% (95% CI, −1.90 to 10.35; nominal P = 0.1744), indicating no difference between treatment groups.

Health-Related Quality of Life

In the RADIANCE Part B and SUNBEAM studies, HRQoL was measured using the MSQOL-54 (Table 15).

In the RADIANCE Part B, the mean (SD) physical health composite summary scores on the MSQOL-54 at month 24 were 0.209 (12.321) for the ozanimod 1 mg group and −1.526 (12.319) for the interferon beta-1a group. This corresponded to a between-group difference of 1.345 (95% CI, −0.252 to 2.943; P = 0.0988), indicating insufficient evidence to show a difference between treatments. The mean (SD) mental health composite summary scores on the MSQOL-54 at month 24 were [redacted] for the ozanimod 1 mg group and [redacted] for the interferon beta-1a group. This corresponded to a between-group difference of [redacted].

In the SUNBEAM, the mean (SD) physical health composite summary scores on the MSQOL-54 at month 12 were 1.925 (11.870) for the ozanimod 1 mg group and 0.046 (12.578) for the interferon beta-1a group. This corresponded to a between-group difference of 1.642 (95% CI, 0.104 to 3.180; nominal P = 0.0364), in favour of ozanimod 1.0 mg. [redacted]

Table 15: Change from Baseline in MSQOL-54 Summary Scores – ITT Population

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Change from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study in physical health composite summary of the MSQOL-54				
n	433	441	443	445
Mean (SD)	0.209 (12.321)	−1.526 (12.319)	1.925 (11.870)	0.046 (12.578)
Difference in means (95% CI)[a]	1.345 (−0.252 to 2.943)	Reference	1.642 (0.104 to 3.180)	Reference
P value[a]	0.0988		0.0364[b]	
[redacted]				

CI, confidence interval; EDSS = Expanded Disability Status Scale; ITT = intention-to-treat; IVRS = interactive voice response system; MSQOL-54 = Multiple Sclerosis Quality of Life-54 items; SD = standard deviation.

[a] Difference in means and P value for comparison between the ozanimod and interferon beta-1a 30 mcg treatment groups are based on an analysis of covariance model, adjusted for region (Eastern Europe versus rest of the world), EDSS category per IVRS, and the baseline summary score of interest. Missing data were imputed using a mixed-effects regression model (random slope and intercept).

[b] P value has not been adjusted for multiple testing.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

Mobility

The MSFC, T25FW, and the 9-HPT were used to inform mobility-related outcomes included in the SUNBEAM and RADIANCE Part B studies.

The changes in MSFC z score, MSFC z score including LCLA, MSFC component T25FW z score, MSFC component 9-HPT z score, MSFC component T25FW actual time (seconds), and MSFC component 9-HPT actual time (seconds) from baseline to month 24 and month 12 in the SUNBEAM and RADIANCE Part B studies are presented in Table 45. There was insufficient evidence to show a difference between treatment groups for any of the outcomes assessed in either study.

Cognitive Function

Cognitive function was evaluated using the PASAT in the RADIANCE Part B study and the SDMT in the SUNBEAM study.

The change in MSFC component PASAT-3 z score and MSFC component PASAT-3 total correct responses from baseline to month 24 in the RADIANCE Part B study are presented in Table 45. There was insufficient evidence to show a difference between treatment groups for this outcome.

The change in MSFC component SDMT z score and MSFC component SDMT total correct responses from baseline to month 12 in the SUNBEAM study are presented in Table 45. The mean changes from baseline in the SDMT total correct responses at month 12 were 1.1 and −0.4 for ozanimod 1 mg and interferon beta-1a, respectively, with a between-group difference of 0.111 (95% CI, 0.039 to 0.182; nominal P = 0.0016) in favour of ozanimod 1.0 mg. The corresponding SDMT z scores at month 12 had mean values of 0.073 and −0.029 for ozanimod 1 mg, and interferon beta-1a, respectively; with nominal P values of 0.0024.

Symptoms of Multiple Sclerosis

Visual disturbance assessed using the LCLA instrument was the only outcome related to the symptoms of MS. Other specific outcomes related to the symptoms of MS, such as fatigue, and cognition, were not reported in any of the included studies for this review.

Change in z score in the LCLA, change in number of letters correct in the LCLA for the 100% chart, and change in number of letters correct for LCLA for the 2.5% chart from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study are presented in Table 45. There was insufficient evidence to show a difference between treatment groups for any of the outcomes assessed in either study.

Ability to Work or Attend School

Specific outcomes related to the ability to work or attend school were not reported in any of the studies included in this review.

Use of Rescue Medication

While methylprednisolone 1 g per day for a maximum of 5 consecutive days was permitted as rescue medication, data specific to the use of rescue medication were not reported.

Disability Progression or Improvement

The third rank-ordered key secondary efficacy end point, the time to onset of disability progression, was defined as a sustained worsening of 1.0 points or more in EDSS scores, confirmed after 3 months, and after 3 months and 6 months. This was pre-specified as a pooled analysis of RADIANCE Part B and SUNBEAM.

In the RADIANCE Part B study, a low event rate was observed across treatment groups. The number of patients with disability progression confirmed at 3 months was 54 (12.5%) in the ozanimod 1 mg group, and 50 (11.3%) in the interferon beta-1a group. The number of patients with disability progression confirmed at 6 months was 42 (9.7%) in the ozanimod 1 mg group, and 29 (6.6%) in the interferon beta-1a group. The risk of disability progression after 3 and 6 months was low in all groups and not statistically significantly lower for the ozanimod 1 mg group compared with the interferon beta-1a group. Similar results were observed in the SUNBEAM study (Table 46).

In the pooled analysis, a low percentage of patients experienced disability progression in the ozanimod 1 mg and interferon beta-1a groups. The number of patients with disability progression confirmed at 3 months was 67 (7.6%) in the ozanimod 1 mg group, and 69 (7.8%) in the interferon beta-1a group. The number of patients with disability progression confirmed at 6 months was 51 (5.8%) in the ozanimod 1 mg group, and 36 (4.0%) in the interferon beta-1a group. The risk of disability progression after 3 months and 6 months was low in all groups and not statistically significantly lower for the ozanimod 1 mg group compared with the interferon beta-1a group.

Harms

Only those harms identified in the review protocol are reported below. See Table 16 for detailed harms data.

Adverse Events

In the RADIANCE Part B study, the majority of patients reported at least 1 treatment-emergent AE, with 324 patients (74.7%) in the ozanimod 1 mg group and 365 patients (83.0%) in the interferon beta-1a group experiencing at least 1 treatment-emergent AE. In the SUNBEAM study, 268 patients (59.8%) in the ozanimod 1 mg group and 336 patients (75.5%) in the interferon beta-1a group experienced at least 1 treatment-emergent AE. The most commonly reported AEs overall were influenza-like illness (3.8% to 51.0%), nasopharyngitis (6.7% to 15.7%), headache (5.6% to 12.0%), upper respiratory tract infection (4.0% to 8.4%), increased ALT (1.8% to 6.0%), and pyrexia (1.1% to 6.4%). In RADIANCE Part B, nasopharyngitis and increased ALT were reported in a greater proportion of patients in the ozanimod 1 mg group compared with the interferon beta-1a group (nasopharyngitis, 15.7% versus 10.9%; increased ALT, 6.0% versus 4.5%), while in SUNBEAM, headache and increased ALT were reported in a greater proportion of patients in the ozanimod 1 mg group compared with the interferon beta-1a group (headache, 7.6% versus 5.6%; increased ALT, 4.7% versus 1.8%).

In both studies, influenza-like illness, upper respiratory tract infection, and pyrexia were reported in a greater proportion of patients in the interferon beta-1a group (influenza-like illness, 48.9% to 51.0%; upper respiratory tract infection, 4.4% to 8.4%; pyrexia, 6.3% to 6.4%) compared with the ozanimod 1 mg group (Influenza-like illness, 3.8% to 6.2%; upper respiratory tract infection, 4.0% to 7.8%; pyrexia, 1.1% to 2.5%). The overall higher incidence of AEs in the interferon beta-1a treatment group compared with the ozanimod treatment groups could be attributed to the predominance of influenza-like illness and pyrexia events.

Serious Adverse Events

In the RADIANCE Part B study, the incidence of SAEs was similar across treatment groups at 28 patients (6.5%) in the ozanimod 1 mg group; and 28 patients (6.4%) in the interferon beta-1a group. Serious AEs occurring in more than 1 patient in any treatment group were appendicitis (ozanimod 1 mg: 2 patients, 0.5%; interferon beta-1a: 2 patients, 0.5%), and ovarian cysts (ozanimod 1 mg: 2 patients, 0.5%; interferon beta-1a: 0 patients).

In the SUNBEAM study, the incidence of SAEs was similar across treatment groups at 13 patients (2.9%) in the ozanimod 1 mg group and 11 patients (2.5%) in the interferon beta-1a group. No SAE was reported in more than 1 patient in either treatment group.

Withdrawals Due to Adverse Events

In both studies, across treatment groups, few patients discontinued the study drug due to an AE.

In RADIANCE Part B, 13 patients (3.0%) in the ozanimod 1 mg group and 18 patients (4.1%) in the interferon beta-1a group discontinued the study drug due to AEs, with the most common reason for permanent discontinuation of the study drug in the ozanimod 1 mg group being liver-related lab abnormalities (discontinuation was protocol-mandated when an ALT or AST value exceeded 5 times the upper limit of normal). In the interferon

beta-1a group, the most common reason for discontinuing the study drug due to an AE was influenza-like illness.

In the SUNBEAM study, 13 patients (2.9%) in the ozanimod 1 mg group and 16 patients (3.6%) in the interferon beta-1a group discontinued the study drug due to AEs, with the most common reason in the ozanimod 1 mg group being increased ALT, back pain, and headache (2 patients each). In the interferon beta-1a group, the most common reason for discontinuing the study drug due to an AE was influenza-like illness.

Mortality

In RADIANCE Part B, a single death due to chronic kidney failure in the ozanimod 1 mg group occurred 157 days after treatment discontinuation on study day 647 and was considered unrelated to study drug.

No deaths were reported during the SUNBEAM study.

Notable Harms

In the RADIANCE Part B study, AEs of special interest were reported by 1 patient each, except for increased ALT (6 patients [1.4%] in the ozanimod 1 mg group and 8 patients [1.8%] in the interferon beta-1a group), increased AST (5 patients [1.1%] in the interferon beta-1a group), increased transaminases (2 patients [0.5%] in the ozanimod 1 mg group), increased blood pressure increased (3 patients [0.7%] in the ozanimod 1 mg group), and macular edema (2 patients [0.5%] in the interferon beta-1a group).

In the SUNBEAM study, each AE of special interest was reported by 1 patient, except for increased ALT and increased blood pressure, which were reported in 3 patients (0.7%) and 4 patients (0.9), respectively, in the ozanimod 1 mg group.

Table 16: Summary of Harms

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 434)	Interferon beta-1a 30 mcg (N = 440)	Ozanimod 1 mg (N = 448)	Interferon beta-1a 30 mcg (N = 445)
Patients with ≥ 1 adverse event				
n (%)	324 (74.7)	365 (83.0)	268 (59.8)	336 (75.5)
Most common events,[a] n (%)				
Nasopharyngitis	68 (15.7)	48 (10.9)	30 (6.7)	36 (8.1)
Headache	44 (10.1)	53 (12.0)	34 (7.6)	25 (5.6)
Upper respiratory tract infection	34 (7.8)	37 (8.4)	18 (4.0)	24 (5.4)
Orthostatic hypotension	30 (6.9)	27 (6.1)	8 (1.8)	1 (0.2)
Increased alanine aminotransferase	26 (6.0)	20 (4.5)	21 (4.7)	8 (1.8)
Influenza-like illness	27 (6.2)	215 (48.9)	17 (3.8)	227 (51.0)
Hypertension	24 (5.5)	14 (3.2)	6 (1.3)	4 (0.9)
Increased gamma-glutamyl transferase	25 (5.8)	9 (2.0)	15 (3.3)	2 (0.4)
Pharyngitis	17 (3.9)	15 (3.4)	11 (2.5)	5 (1.1)
Urinary tract infection	19 (4.4)	17 (3.9)	17 (3.8)	10 (2.2)
Back pain	18 (4.1)	14 (3.2)	17 (3.8)	9 (2.0)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 434)	Interferon beta-1a 30 mcg (N = 440)	Ozanimod 1 mg (N = 448)	Interferon beta-1a 30 mcg (N = 445)
Fatigue	16 (3.7)	12 (2.7)	4 (0.9)	4 (0.9)
Arthralgia	15 (3.5)	6 (1.4)	5 (1.1)	8 (1.8)
Depression	15 (3.5)	15 (3.4)	8 (1.8)	10 (2.2)
Insomnia	12 (2.8)	14 (3.2)	9 (2.0)	6 (1.3)
Bronchitis	15 (3.5)	11 (2.5)	8 (1.8)	6 (1.3)
Pyrexia	11 (2.5)	28 (6.4)	5 (1.1)	28 (6.3)
Abdominal pain upper	14 (3.2)	6 (1.4)	6 (1.3)	3 (0.7)
Rhinitis	10 (2.3)	10 (2.3)	9 (2.0)	3 (0.7)
Pain in extremity	8 (1.8)	12 (2.7)	7 (1.6)	6 (1.3)
Sinusitis	9 (2.1)	16 (3.6)	4 (0.9)	3 (0.7)
Paresthesia	8 (1.8)	9 (2.0)	3 (0.7)	4 (0.9)
Anxiety	10 (2.3)	7 (1.6)	4 (0.9)	10 (2.2)
Hypercholesterolemia	6 (1.4)	9 (2.0)	11 (2.5)	5 (1.1)
Influenza	5 (1.2)	9 (2.0)	4 (0.9)	5 (1.1)
Respiratory tract infection	9 (2.1)	15 (3.4)	9 (2.0)	6 (1.3)
Increased aspartate aminotransferase	8 (1.8)	12 (2.7)	8 (1.8)	5 (1.1)
Toothache	9 (2.1)	9 (2.0)	2 (0.4)	4 (0.9)
Oral herpes	3 (0.7)	10 (2.3)	3 (0.7)	2 (0.4)
Anemia	2 (0.5)	10 (2.3)	7 (1.6)	9 (2.0)
Oropharyngeal pain	2 (0.5)	12 (2.7)	4 (0.9)	2 (0.4)
Respiratory tract infection viral	6 (1.4)	8 (1.8)	15 (3.3)	3 (0.7)
Patients with ≥ 1 serious adverse event				
n (%)	28 (6.5)	28 (6.4)	13 (2.9)	11 (2.5)
Most common events,[b] n (%)				
Appendicitis	2 (0.5)	2 (0.5)	1 (0.2)	0
Ovarian cysts	2 (0.5)	0	0	0
Patients who stopped treatment due to adverse events				
n (%)	13 (3.0)	18 (4.1)	13 (2.9)	16 (3.6)
Most common events,[b] n (%)				
Macular edema	0	2 (0.5)	1 (0.2)	1 (0.2)
Urticaria	2 (0.5)	0	0	0
Influenza-like illness	0	4 (0.9)	0	8 (1.8)
Increased alanine aminotransferase	2 (0.5)	3 (0.7)	2 (0.4)	0
Increased aspartate aminotransferase	1 (0.2)	2 (0.5)	0	0
Back pain	0	0	2 (0.4)	1 (0.2)
Headache	0	0	2 (0.4)	0
Deaths				
n (%)	1 (0.2)	0	0	0
Cause of death				

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 434)	Interferon beta-1a 30 mcg (N = 440)	Ozanimod 1 mg (N = 448)	Interferon beta-1a 30 mcg (N = 445)
Chronic kidney failure	1 (0.2)	0	0	0
Notable harms, n (%)				
Infections and infestations				
Herpes zoster	1 (0.2)	0	0	1 (0.2)
Varicella-zoster virus infection	1 (0.2)	0	0	0
Corynebacterium Infection	0	0	1 (0.2)	0
Abscess limb	0	0	0	1 (0.2)
Hepatitis C	0	0	0	1 (0.2)
Bradycardia	0	0	0	0
Liver-function tests				
Increased alanine aminotransferase	6 (1.4)	8 (1.8)	3 (0.7)	1 (0.2)
Increased aspartate aminotransferase	0	5 (1.1)	0	0
Increased transaminases	2 (0.5)	0	0	1 (0.2)
Liver-function test abnormal	0	1 (0.2)	1 (0.2)	1 (0.2)
Effects in pregnancy				
Vanishing twin syndrome	1 (0.2)	0	0	0
Placental polyp	1 (0.2)	0	0	0
Spontaneous abortion	0	0	1 (0.2)	0
Increased blood pressure	3 (0.7)	1 (0.2)	4 (0.9)	1 (0.2)
Pulmonary function test decreased	1 (0.2)	0	0	0
Eye disorder				
Macular edema	1 (0.2)	2 (0.5)	0	1 (0.2)
Macular hole	0	1 (0.2)	0	0
Maculopathy	0	0	0	1 (0.2)
Neoplasms (benign, malignant, and unspecified, including cysts and polyps)				
Basal cell carcinoma	1 (0.2)	0	1 (0.2)	0
Breast cancer	1 (0.2)	0	0	0
Invasive breast carcinoma	1 (0.2)	0	0	0
Chronic lymphocytic leukemia	0	1 (0.2)	0	0

[a] Frequency greater than or equal to 2% of patients.

[b] Frequency greater than or equal to 2 patients.

Source: Clinical Study Reports for RADIANCE Part B and SUNBEAM trials.[11,12]

Critical Appraisal

Internal Validity

Randomization in the RADIANCE Part B and SUNBEAM studies was conducted using appropriate methods with adequate measures to conceal treatment allocation (i.e., centrally by using an interactive voice response system). Randomization was stratified by EDSS (≤ 3.5 versus > 3.5) and country. Key baseline and demographic characteristics were generally balanced between the ozanimod and interferon groups in both studies. The study

treatments in both RADIANCE Part B and SUNBEAM studies were administered in a double-blind manner. Because ozanimod and interferon beta-1a require a different route of administration (oral and IM, respectively) a double-dummy design was used to preserve blinding. The matching placebo oral capsules were identical to ozanimod capsules, and the matching placebo injections were identical to interferon beta-1a injections.

Differences in the AE profiles related to the administration of the study drugs could have allowed some patients and investigators to infer which active treatment had been administered. For example, flu-like symptoms are one of the most common AEs associated with the administration of interferon beta products and could potentially unmask treatment assignment. The approved labels for beta interferon products recommend acetaminophen or ibuprofen for relief of these symptoms. Influenza-like illness was reported by 48.9% to 51.0% of patients in the interferon beta-1a treatment groups, in comparison with 3.8% to 6.2% in the ozanimod 1 mg treatment groups. Both phase III studies recommended the prophylactic use of acetaminophen (paracetamol) or ibuprofen (or alternatively, naproxen or Aspirin if a patient could not take acetaminophen or ibuprofen) within 1 hour prior to each use of an injectable study drug and then periodically thereafter for the 24 hours following each injection. This recommendation to use acetaminophen or ibuprofen prophylactically was aimed at reducing potential bias with respect to patients or investigators being potentially unblinded to treatment assignment. However, it was not reported how many patients followed this recommendation, and whether the patient who received prophylactic treatment had reduced flu-like symptoms. Fatigue is also a known AE associated with beta interferon treatment, and it is not clear whether this AE could unmask the participant. The ARR was determined using confirmed relapses accompanied by objective neurological worsening as revealed by an examination by a blinded EDSS evaluator. To maintain blinding, a "dual assessor" approach used an independent blinded EDSS reviewer to evaluate efficacy. The treating investigator managed the safety to prevent potential unblinding of the independent EDSS assessor as a result of observed efficacy, AEs, or laboratory changes. The protocol required that the blinded assessor who provided efficacy assessments (including EDSS) for a patient did not have access to other data for that patient (including prior EDSS data, AE reports, or laboratory findings). In addition, to minimize bias in outcome ascertainment and study results for MRI end points, both studies used a blinded, centralized MRI reading centre to evaluate MRI paraments (i.e., lesion counts, lesion volume, and brain volume). Laboratory results for total white blood cell counts and their differential parameters (including absolute lymphocyte counts) were also blinded to the treating investigator, the blinded EDSS efficacy assessor, and all site personnel after the onset of study treatment. However, these AEs may have allowed certain patients and/or investigators to surmise the assigned treatment, and subsequently may have had an impact on patient-reported outcomes (e.g., HRQoL) or AEs.

Except for the primary outcome and the 3 key secondary outcomes that were adjusted for multiple testing using a hierarchical testing procedure, other secondary outcomes, subgroup analyses, and exploratory outcomes were analyzed with no control for multiplicity of testing. As a result, firm conclusions cannot be drawn for these additional analyses without increasing the risk of type I error for these end points. As a result, other secondary outcomes, subgroup analyses, and exploratory outcomes should be interpreted cautiously. In addition, while subgroup analyses in both studies were pre-specified, it is important to note that neither study was powered for subgroup effects.

The disposition of patients who were screened and enrolled in RADIANCE Part B and SUNBEAM was appropriately reported. In both trials, the rate of withdrawal was

disproportionate, with more patients discontinuing in the interferon beta-1a groups (8.0% and 15.1%) compared with the ozanimod 1 mg groups (6.5% and 10.4%). This difference between the treatment groups is an indication that the rate of withdrawal may have been influenced by unblinding or post-randomization events.

Patients could have been previously treated with an interferon product, with prior usage reported for interferon beta-1a (10.4%) and interferon beta-1b (9.3%). Patients who had ceased treatment with interferon beta-1a were excluded from the study. This may have resulted in an enriched population of patients who were likely to tolerate interferon beta-1a; however, this level of detail was not reported in the reasons for screening failure. It is also possible that patients previously treated with an interferon product could have inferred their allocated study treatment based on the presence or absence of familiar adverse events.

RADIANCE Part B and SUNBEAM utilized a Poisson regression model for the primary analysis based on the assumption that relapse counts display a Poisson distribution. A known drawback of this model is that it does not account for over-dispersion commonly observed in MS relapse data as this model has a structured mean-variance relationship. The negative binomial model handles over-dispersion count data. Both studies' pre-specified sensitivity analyses did include negative binomial regression modelling to compare relapse rates, and results from these sensitivity analyses were consistent with the primary analysis.

[redacted]. The imputation methodologies in 2 of the pre-specified sensitivity analyses allowed a patient who dropped out of the study early to have a lesion number value imputed as the average lesion number of the patients who had completed a longer duration of the study; that is, patients who remained in the trial for longer periods likely experienced greater cumulative treatment effects than the patients who were earlier dropouts, which could also introduce a potential bias into the analysis. As the dropout rate was higher for the interferon beta-1a group, this would likely overestimate the effect in the interferon beta-1a group, which would likely bias results conservatively against ozanimod. In summary, although ozanimod 1 mg achieved statistical significance in the reduction of lesion numbers over interferon beta-1a group, neither the estimates of the lesion numbers nor the P values provide certainty with respect to their accuracy.

External Validity

Both RADIANCE Part B and SUNBEAM included primarily Eastern European centres, enrolled exclusively White patients, and included few North American centres and only a single Canadian patient from 1 centre. The clinical expert consulted by CADTH for this review noted that standard care in Eastern Europe may differ from Canada's in that a greater proportion of patients with MS may be treatment-naive. However, the clinical expert did not expect any difference in how MS progresses between Eastern European and North American populations.

The majority of study participants were female, which is consistent with relapsing MS populations. Diagnosis of MS was based on 2010 revised McDonald criteria, which is consistent with Canadian clinical practice. The clinical expert consulted by CADTH suggested that the patients enrolled in the pivotal trials were reasonably reflective of

patients encountered in routine Canadian practice. Patients were required to have an EDSS score of 0 to 5.0 to be eligible for the RADIANCE Part B and SUNBEAM studies. Although common in clinical trials for MS, this criterion excludes a number of patients with more severe disability who could be eligible to receive ozanimod in clinical practice. The efficacy and safety of ozanimod in such patients is uncertain. Approximately 30% of patients across all treatment groups in both studies had been previously treated with a DMT, while the majority of patients (70%) in both trials had no exposure to any disease-modifying MS treatments. The clinical expert consulted by CADTH suggested that the place in therapy for ozanimod is likely as a first-line agent or as an option when switching between treatments. Both studies excluded patients who were older than 55 years of age, patients with a disease duration of more than 15 years and an EDSS score of at least 2.0, and patients with contraindications to gadolinium contrast. The clinical expert indicated that such patients could be eligible to receive ozanimod in clinical practice.

Type 2 diabetes mellitus and macular edema were not exclusionary; however, diabetic uveitis or retinopathy or other comorbid conditions due to diabetes were exclusionary conditions for this study, limiting the generalizability of the study results to these patients.

The eligibility criteria excluded participants with specific cardiac conditions given the known cardiac liability of S1P receptor modulators; however, participants who had stable disease and were judged to be not at significant risk through trial participation could enroll in the trial, and cardiology consultation was performed for these cases. The clinical expert consulted by CADTH indicated that obtaining an electrocardiogram prior to initiating treatment with ozanimod to determine whether pre-existing conduction abnormalities are present would not be an issue in clinical practice. The expert did not anticipate that screening requirements would limit access to ozanimod given that only small numbers of patients would need to see a cardiologist.

Interferon beta-1a is considered an appropriate comparator by the clinical expert consulted by CADTH, and is aligned with guidance from the EMA, which states that a superiority trial versus a first-line DMT, such as an interferon beta, is an appropriate trial design.[10] The dose of interferon beta-1a used in the RADIANCE Part B and SUNBEAM studies is consistent with recommendations in the Canadian product monograph (i.e., 30 mcg injected intramuscularly once per week).[23] Similarly, ozanimod in the ozanimod 1 mg group was administered in accordance with recommendations in the product monograph.[9] The clinical expert consulted by CADTH indicated that the dosage of interferon beta-1a was consistent with Canadian practice and the dose of ozanimod likely reflects how this drug will be used in Canada.

The duration of the SUNBEAM study was 12 months, which is shorter than the typical 2-year trials for MS; and is not sufficient for long-term safety evaluation. The RADIANCE Part B study was 24 months in duration, which the clinical expert consulted for this review indicated it was sufficient to observe whether the treatment had an effect. However, it is likely that patients would be taking this treatment long-term, and therefore the results as observed at month 24 may be limited in their applicability to chronic use of ozanimod in clinical practice. An ongoing OLE study (DAYBREAK) is expected to provide evidence regarding the long-term efficacy and safety of ozanimod; data from the interim analyses up to a cut-off date of June 30, 2018, was provided by the sponsor, and is summarized in the long-term extension studies section.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

Ozanimod was previously compared to interferon beta-1a in 2 clinical trials. However, no head-to-head comparison of ozanimod against other relevant DMTs used to treat RRMS was available for this review. As there was no direct evidence comparing ozanimod to other therapies for RRMS, a review of indirect evidence was undertaken. CADTH conducted a literature search to identify potentially relevant ITCs in patients with RRMS, and reviewed the sponsor's submission to CADTH. The Ovid MEDLINE database was searched using a combination of MeSH (Medical Subject Headings) and keywords. The main search concept was RRMS. A filter was applied to limit the study type to NMAs. Retrieval was not limited by publication date or language. Titles, abstracts, and full-text articles were screened for inclusion by 1 reviewer based on the population, intervention, comparator, and outcome criteria as outlined in Table 4.

One sponsor-submitted ITC[13] and 1 published ITC by Swallow et al.[14] that was identified in a literature search were summarized and critically appraised. The sponsor-submitted ITC was used to inform the pharmacoeconomic model.

Description of Indirect Comparisons

The sponsor submitted an ITC[13] to evaluate the relative clinical efficacy and safety of ozanimod 1 mg to cladribine, dimethyl fumarate, fingolimod, teriflunomide, alemtuzumab, natalizumab, ocrelizumab, glatiramer acetate, interferon beta-1a, interferon beta-1b, and peginterferon beta-1a in adult patients with RRMS. The sponsor performed a systematic review to identify relevant studies for inclusion in the ITC. Nine outcomes were analyzed, including ARR, CDP12, CDP24, discontinuation events, AEs, SAEs, new GdE lesions, new or newly enlarging T2 lesions at 12 months, and new or newly enlarging T2 lesions at 24 months.

The article by Swallow et al.[14] included an MAIC that compared ozanimod with fingolimod in patients with RRMS.

The populations, interventions, comparators, outcomes, and designs of studies included in the sponsor's ITC and the ITC by Swallow et al.[14] are provided in Table 17.

Table 17: Study Selection Criteria and Methods for Indirect Treatment Comparisons

	Sponsor-submitted ITC	ITC by Swallow et al. (2020)[14]
Population	Patients with RRMS with or without prior interferon or disease-modifying antirheumatic drug treatment	Patients with relapsing multiple sclerosis
Intervention	• Ozanimod 0.5 mg once daily or 1.0 mg once daily • Alemtuzumab (Lemtrada) first treatment course 12 mg/day for 5 consecutive days; second treatment course 12 mg/day for 3 consecutive days administered 12 months after the first initial treatment course • Cladribine 3.5 mg/kg • Dimethyl fumarate (Tecfidera) 240 mg twice a day • Fingolimod (Gilenya) 0.5 mg once daily • Glatiramer acetate (Copaxone and generic) 20 mg/mL once daily or 40 mg/mL 3 times per week	Ozanimod 1.0 mg once daily

	Sponsor-submitted ITC	ITC by Swallow et al. (2020)[14]
	• Interferon beta-1a (Rebif) 44 mcg 3 times a week or 22 mcg 3 times a week • Interferon beta-1a (Avonex) 30 mcg once per week • Interferon beta-1b (Betaseron; Betaferon) 250 mcg every other day • Natalizumab (Tysabri) 300 mg every 4 weeks • Ocrelizumab (Ocrevus) 600 mg every 6 months • Peginterferon beta-1a (Plegridy) 125 mcg every 2 weeks • Teriflunomide (Aubagio) • 7 mg once daily or 14 mg once daily	
Comparator	Placebo or any intervention listed above	Fingolimod 0.5 mg once daily
Outcome	• ARR • CDP at 12 weeks • CDP at 24 weeks • Overall discontinuation • AE • SAE • New GdE lesions • New or newly enlarging T2 lesions at 12 months • New or newly enlarging T2 lesions at 24 months	• ARR • Confirmed CDP at 3 months • Confirmed CDP at 6 months • Change in blood pressure from baseline • AEs • AEs leading to discontinuation • SAE • Patient death • Liver enzymes (ALT) at least 3 times the upper limit of normal • Macular edema
Study design	Randomized controlled trials	Randomized controlled trials
Publication characteristics	Publication in English	Not reported
Exclusion criteria	• Non-randomized studies • No outcomes of interest reported • Treatments in combination with other RRMS or non-RRMS drugs or non-pharmacotherapeutic treatments (e.g., acupuncture) • Single-arm studies or studies examining different dosages of the same drug without placebo or active treatment comparators • Studies without full-text publications • Conference abstracts	Not reported
Databases searched	• MEDLINE • Embase • CDSR • CENTRAL • clinicaltrials.gov • WHO ICTRP	Not reported
Selection process	Articles screened independently by 2 researchers	Not reported
Data extraction process	Data extraction was performed by 2 independent reviewers and compared for discrepancies	Not reported
Quality assessment	NICE quality assessment checklist for parallel-group randomized controlled trials	Not reported

AE = adverse event; ARR = annualized relapse rate; CDP = confirmed disability progression; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; GdE = gadolinium-enhanced; ICTRP = International Clinical Trials Registry Platform; ITC = indirect treatment comparison; NICE = National Institutes for Health and Care Excellence; RRMS = remitting-relapsing multiple sclerosis; SAE = serious adverse event.

Source: Sponsor-submitted indirect treatment comparison[13] and Swallow et al. (2020).[14]

Methods of Sponsor-Submitted Indirect Treatment Comparison

Objectives

In the absence of head-to-head clinical trials comparing all relevant MS therapies, the objective of this ITC was to generate comparative efficacy and safety data for ozanimod relative to currently existing medications for the treatment of RRMS.

Study Selection Methods

Multiple electronic databases such as MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform databases were searched from inception to October 10, 2017, for the initial search, and from January 1, 2017, to June 12, 2019, for the search update. Manual searching of references of published systematic reviews, meta-analyses, and HTA documents was also conducted to identify publications that may not have been identified from the electronic searches.

Studies were included if they were RCTs in patients with RRMS that included at least 1 treatment of interest, reported 1 or more of the required efficacy and safety end points, enrolled patients who were at least 18 years of age unless outcomes for adult patients are reported as subgroups, and were published in English. Studies were excluded if they were non-randomized, did not report outcomes of interest, single-arm in design, or examined different dosages of the same drug without placebo or active treatment comparators, without full-text publications, or conference abstracts. Studies of treatments in combination with other RRMS or non-RRMS drugs or non-pharmacotherapeutic treatments (e.g., acupuncture) were also excluded.

Titles and abstracts were reviewed for potential study inclusion. At least 2 reviewers independently selected abstracts for full-text review and noted at least 1 reason for abstract exclusion. Any discrepancies between reviewers were resolved by consensus and/or in conjunction with a third reviewer. At least 2 reviewers reviewed the selected full-text articles according to the inclusion and exclusion criteria, compiling the final study sample for data extraction.

A form was developed for use in data extraction. The extraction form was pilot-tested on a small number of included studies and revised. Extraction was performed by 2 independent reviewers and compared for discrepancies. Data for each outcome were collected at baseline and at all time points available within the randomized controlled period (i.e., before early escape or crossover). If multiple sources of the same data were reported (e.g., from a journal publication and from clinicaltrials.gov), all sources were reviewed and reconciled to optimize quantity and quality of data extraction. Additional ARR data of the number of relapses and the total number of person-years of treatment exposure were collected separately from data tables within a previously published ITC by the Institute for Clinical and Economic Review (ICER)[71] and published study data, when necessary. ICER data[71] were prioritized because the authors collected data from study publications as well as from direct contact with manufacturers to obtain unreported data. When data were not available from the ICER report or reported in this format in publications, the total number of relapses from the reported ARR, the number of patients, and the duration of follow-up were estimated. For example, a reported ARR of 0.33 for a population of 50 patients followed for 2 years is equal to a total of 33 relapses (0.33 relapses per year per patient × 2 years × 50 patients) and 100 person-years of exposure.

Risk of bias was assessed using the NICE quality assessment checklist for parallel-group RCTs.[72] However, the authors of the sponsor-submitted ITC did not provide a plan to investigate the impact of studies that were considered to be of low quality or have a high risk of bias.

The efficacy outcomes assessed were ARR, CDP12, CDP24, new GdE lesions, new or newly enlarging T2 lesions at 12 months, new or newly enlarging T2 lesions at 24 months, overall discontinuations, AEs, and SAEs. The definitions for the outcomes' ARR, CDP, and discontinuation events used in the studies were not provided.

Indirect Treatment Comparison Analysis Methods

The authors of the submitted ITC used a Bayesian NMA approach. Fixed-effect and random-effects models were evaluated, and selection was determined by the deviance information criterion (DIC) model-fit statistics. Lower DIC values indicate a better fit to the data. When the DIC values were not substantially different, the fixed-effects model was preferred.

Vague prior distributions (e.g., normal with mean of 0 and variance of 105) on model parameters were used to ensure the model outcomes would be determined primarily by the clinical trial data. These were selected using the recommended priors in NICE Technical Support Document 2.[73] Posterior outcome distributions were based on at least 20,000 simulations after a burn-in of at least 20,000 runs. Convergence was assessed by visual inspection of the WinBUGS autocorrelation and history results; however, convergence diagnostics were not reported. Nor was it reported how many chains were used or if any sensitivity analyses were carried out for the prior distributions used.

ARR effects were analyzed using the total number of relapses and the total patient-years of drug exposure for each treatment arm. The ARR model assumption was that the relapse rate was constant over the follow-up period, but different for each treatment. The observed number of events was assumed to follow the Poisson distribution, a common distribution for representing count data.

The CDP and discontinuation events were analyzed using the total number of CDP events observed and the time over which those events occurred. In this analysis, the time to a CDP or discontinuation event is assumed to follow the exponential survival distribution, in which there is a constant risk, or hazard, of progression or discontinuation. Alternate methodologies for analyzing CDP data were used; these included the adjustment for the observed placebo response in placebo-controlled trials, independent analysis of CDP12 and CDP24, and analysis of CDP12 and CDP24 in a single model.

The proportion of patients experiencing an AE is a binary outcome in which the treatment effect is measured using log odds ratios relative to placebo. These were modelled using the binomial likelihood and the logit link function according to NICE Technical Support Document 2.[73]

For lesion counts, continuous data based on sample means and standard errors were analyzed using the normal likelihood and the normal link function (NICE Technical Support Document 2).[73] For studies where standard errors were not available, they were imputed using the sample-size weighted average of the available standard errors. The mean difference between each treatment and placebo is the NMA output.

Heterogeneity in the treatment effects (i.e., RR or mean difference) was assessed for pairs of treatment comparisons with 2 or more studies for the ARR, CDP12, CDP24, discontinuation, and AE outcomes. Comparisons with Q statistic P values of less than 0.1 were considered to demonstrate significant heterogeneity. The I^2 statistic was also calculated based on the Q statistic, which can be interpreted as the proportion of total variability explained by heterogeneity (i.e., between-study variance), rather than chance. Values for I^2 of less than 30% are generally considered as mild heterogeneity while an I^2 of greater than 50% indicates the presence of substantial heterogeneity. Heterogeneity was not assessed for new GdE lesions, new or newly enlarging T2 lesions at 12 months, and new or newly enlarging T2 lesions at 24 months.

Network inconsistency of the ARR and CDP NMAs was evaluated by constructing a meta-analysis estimating only direct comparison evidence without the influence of the network or indirect treatment effects. The magnitude of inconsistency for individual comparisons was demonstrated by plotting the posterior mean deviance of the individual data points in the inconsistency (or direct evidence model) against their posterior mean deviance in the NMA model. Data points that fell far from of the 45-degree line indicated differences between the 2 models and highlighted loops in which inconsistency was present.

Sensitivity analyses were conducted with various subsets of the study data, excluding studies contributing to heterogeneity and/or consistency for the ARR and CDP outcomes.

Table 18 presents a summary of the methods used for the ITC.

Table 18: Sponsor-Submitted Indirect Treatment Comparison Analysis Methods

	Sponsor-submitted indirect treatment comparison
Methods	Fixed-effects and random-effects models under a Bayesian framework
Priors	Vague prior distributions (e.g., normal with mean 0 and variance 10)[5]
Assessment of model fit	Deviance information criterion
Assessment of consistency	Posterior mean residual deviance
Assessment of convergence	Only visual inspection, no calculations provided
Outcomes	ARR, CDP at 12 and 24 months, discontinuation, AEs, SAEs, lesion counts
Follow-up time points	Up to 24 months
Sensitivity analyses	Conducted with various subsets of the study data, excluding studies contributing to heterogeneity and/or consistency for the ARR and CDP outcomes
Subgroup analysis	Not conducted
Methods for pairwise meta-analysis	Not reported

AE = adverse event; ARR = annualized relapse rate; CDP = confirmed disability progression; SAE = serious adverse event.

Source: Sponsor-submitted indirect treatment comparison.[13]

Results of Sponsor-Submitted ITC

Out of a total of 2,551 articles identified from the systematic literature search, 105 records (representing 47 RCTs) were included in the ITC. The adult patient populations included in the trials were not restricted by geographic region, gender, race, or line of therapy. Variability was noted for a number of study characteristics. The publication dates for the studies were between 1987 and 2018; this included 6 studies published prior to 2000. The studies ranged in duration from 16 weeks to 2 years. The sample sizes ranged from 6 to 943 patients in treatment arms. The mean duration of disease ranged between 1.0 and 8.3

years. The mean age of patients was between 28.1 and 40.6 years and the proportion of female patients ranged between 33% and 81%. The diagnostic criteria varied between studies, as 9 studies utilized McDonald's 2001 diagnostic criteria, 19 utilized McDonald's 2005 criteria, 7 utilized McDonald's 2010 criteria, 11 utilized Poser's diagnostic criteria, and 1 study used both Poser's and McDonald's 2005 criteria. The majority of trials enrolled patients with a baseline EDSS score equal to or less than 6 who had at least 1 or 2 relapses in the past year or 2, respectively. The mean EDSS score at baseline ranged from 1.9 to 3.5. A summary of the study characteristics and patient's baseline characteristics for each of the included studies is presented in Table 19 and Table 20.

Risk of bias was assessed using the NICE quality assessment checklist for parallel-group RCTs. Of the 47 included RCTs, all had appropriate or unclear randomization procedures, 43 had appropriate or unclear concealment of treatment allocation, 41 had well-balanced baseline prognostic factors, 22 reported blinded patients and providers and/or outcome assessors, 33 did not have an imbalance in dropouts, 44 reported all outcomes measured, and 41 included an appropriate ITT analysis. No studies were excluded based on the assessment of bias.

Table 19: Characteristics of Trials Included in the ITC

Trial name or author, year of publication	Intervention	Study duration	Inclusion criteria	MS criteria
Alemtuzumab (Lemtrada)				
Cohen 2012b/CARE-MS I	Alemtuzumab (Lemtrada), 12 mg Interferon beta-1a (Rebif), 44 mcg	24 months	EDSS 0 to 3.0; ≥ 1 relapse in past year and ≥ 2 relapses in past 2 years; disease duration at most 5 years	McDonald 2005
Coles 2008/CAMMS223	Alemtuzumab (Lemtrada), 12 mg Interferon beta-1a (Rebif), 44 mcg	36 months	≥ 2 clinical episodes in the last 2 year; no previous DMT	McDonald 2001
Coles 2012/CARE-MS II	Alemtuzumab (Lemtrada), 12 mg Interferon beta-1a (Rebif), 44 mcg	24 months	Disease duration ≤ 10 years; ≥ 2 attacks in the last 2 years and ≥ 1 attack in the last year	McDonald 2005
Cladribine				
Giovannoni 2010/CLARITY	Placebo Cladribine, 3.5 mg/kg	96 weeks	EDSS 0 to 5.5; ≥ 1 relapse in last year; < 2 failed DMTs within 3 months; no prior immunosuppressants	McDonald 2001
Dimethyl fumarate (Tecfidera)				
Fox 2012/CONFIRM	Placebo Dimethyl fumarate (Tecfidera), 240 mg (b.i.d.) Glatiramer acetate (Copaxone), 20 mg	96 weeks	EDSS 0 to 5; ≥ 1 relapse in last year OR ≥ 1 GdE lesion in past 6 weeks	McDonald 2005

Trial name or author, year of publication	Intervention	Study duration	Inclusion criteria	MS criteria
Gold 2012/DEFINE	Placebo	96 weeks	EDSS 0 to 5; ≥ 1 relapse in past year OR ≥ 1 GdE lesion within 6 months	McDonald 2005
	Dimethyl fumarate (Tecfidera), 240 mg (b.i.d.)			
Saida 2019	Placebo	24 weeks	EDSS 0 to 5; Age 18 to 55; From East Asia; ≥ 1 relapse in last 12 months or 1 GdE lesion within 6 weeks	McDonald 2005
	Dimethyl fumarate (Tecfidera), 240 mg (b.i.d.)			
Fingolimod (Gilenya)				
Calabresi 2014a/FREEDOMS II	Placebo	24 months	EDSS 0 to 5.5; ≥ 1 relapse per year for 1 or 2 years; no relapse in last 30 days	McDonald 2005
	Fingolimod (Gilenya), 0.5 mg			
Cohen 2010/TRANSFORMS	Fingolimod (Gilenya), 0.5 mg	12 months	EDSS 0 to 5.5; ≥ 1 relapse in past year or ≥ 2 relapses in past 2 years	McDonald 2005
	Interferon beta-1a (Avonex) 30 mcg			
Comi 2017/GOLDEN	Fingolimod (Gilenya), 0.5 mg	18 months	EDSS 0 to 5; age 18 to 60; ≥ 1 relapse in past year or 2 relapses in past 2 years or disease activity on MRI in past 6 months; no relapses in past 30 days	McDonald 2005
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg			
Kappos 2010/FREEDOMS	Placebo	24 months	EDSS 0 to 5.5; ≥ 1 relapse in past year or ≥ 2 in the last 2 years; no relapse in last 30 days	McDonald 2005
	Fingolimod (Gilenya), 0.5 mg			
Saida 2012	Placebo	6 months	EDSS 0 to 6.0; ≥ 1 relapse in the previous year OR ≥ 2 relapses in the previous 2 years OR ≥ 1 GdE lesion in last 30 days; ≥ 1 T2-weighted brain lesion	McDonald 2005
	Fingolimod (Gilenya), 0.5 mg			
Glatiramer acetate (Copaxone), 20 mg				
Boiko 2018	Placebo	12 months	EDSS 0 to 5.5; age 18 to 55; ≥ 1 relapse or ≥ 1 GdE lesion	McDonald 2005
	Glatiramer acetate (Generic), 20 mg			
	Glatiramer acetate (Copaxone), 20 mg			
Bornstein 1987	Placebo	24 months	EDSS 0 to 6; age 20 to 35; ≥ 2 exacerbations in last 2 years	Poser
	Glatiramer acetate (Copaxone), 20 mg			
Cadavid 2009/BECOME	Glatiramer acetate (Copaxone), 20 mg	2 years	EDSS 0 to 5.5, confirmed disease activity in last 6 months	McDonald 2005
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg			

Trial name or author, year of publication	Intervention	Study duration	Inclusion criteria	MS criteria
Calabrese 2012	Glatiramer acetate (Copaxone), 20 mg	2 years	EDSS ≦ 5; no previous immunosuppressive therapy	McDonald 2005
	Interferon beta-1a (Avonex) 30 mcg			
	Interferon beta-1a (Rebif), 44 mcg			
Cohen 2015/ GATE	Placebo	9 months	EDSS 0 to. 5.5; ≥ 1 relapse in past year; 1 to 15 GdE T1 lesions	McDonald 2010
	Glatiramer acetate (Copaxone), 20 mg			
	Glatiramer acetate (generic), 20 mg			
Johnson 1995/Copolymer 1 Trial	Placebo	24 months	EDSS 0 to 5.0; Age 18 to 45 years; ≥ 2 documented relapses in last 2 years; onset of first relapse ≥ 1 year before randomization; no prior copolymer 1 or immunosuppressives	Poser
	Glatiramer acetate (Copaxone), 20 mg			
Lublin 2013/CombiRx	Glatiramer acetate (Copaxone), 20 mg	36 months	EDSS 0 to 5.5; ≥ 2 relapses in last 3 years	McDonald 2001
	Interferon beta-1a (Avonex) 30 mcg			
Mikol 2008/REGARD	Glatiramer acetate (Copaxone), 20 mg	96 weeks	EDSS 0 to 5.5; ≥ 1 relapse in last year	McDonald 2001
	Interferon beta-1a (Rebif), 44 mcg			
O'Connor 2009/BEYOND	Glatiramer acetate (Copaxone), 20 mg	2 years	EDSS 0 to 5; ≥ 1 relapse in last year; treatment-experienced	McDonald 2001
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg			
Comi 2001/EU/C GASG	Placebo	9 months	EDSS 0 to 5; diagnosis of MS for ≥ 1 year; ≥ 1 documented relapse in prior 2 years; ≥ 1 enhancing lesion	Poser
	Glatiramer acetate (Copaxone), 40 mg			
Khan 2013/GALA	Placebo	12 months	EDSS 0 to 5.5; ≥ 1 relapse in a 1-year period within the last 2 years OR ≥ 1 relapse within 12 to 24 months with ≥ 1 GdE lesion within 12 months	McDonald 2005
	Glatiramer acetate (Copaxone), 40 mg			
Interferon beta-1a (Avonex) 30 mcg				
Durelli 2002/INCOMIN	Interferon beta-1a (Avonex) 30 mcg	24 months	EDSS 1 to 3.5; Age 18 to 50 years; ≥ 2 clinically documented relapses last 2 years; no previous systemic treatment or	Poser
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg			

Trial name or author, year of publication	Intervention	Study duration	Inclusion criteria	MS criteria
			immunosuppressive drugs (except corticosteroids)	
Etemadifar 2006	Interferon beta-1a (Avonex) 30 mcg Interferon beta-1a (Rebif), 44 mcg Interferon beta-1b (Betaseron; Betaferon), 250 mcg	24 months	EDSS 0 to 5; ≥ 2 relapses in previous 2 years	Poser
Jacobs 1996/MSCRG	Placebo Interferon beta-1a (Avonex) 30 mcg	104 weeks	EDSS 1 to 3.5; ≥ 2 exacerbations in the last 3 years; no prior interferon or immunosuppressives	Poser
Mokhber 2015/ IRCT201404195280N16	Interferon beta-1a (Avonex) 30 mcg Interferon beta-1a (Rebif), 44 mcg Interferon beta-1b (Betaseron; Betaferon), 250 mcg	12 months	Definite MS	McDonald 2010
Panitch 2002/EVIDENCE	Interferon beta-1a (Avonex) 30 mcg Interferon beta-1a (Rebif), 44 mcg	48 weeks	EDSS 0 to 5.5; interferon-naive; ≥ 2 exacerbations in prior 2 years	Poser
Vollmer 2014/BRAVO	Placebo Interferon beta-1a (Avonex) 30 mcg	24 months	EDSS 0 to 5.5; ≥ 1 relapse in a 1-year period within the last 2 years	McDonald 2005
Interferon beta-1a (Rebif)				
PRISMS 1998	Placebo Interferon beta-1a (Rebif), 44 mcg Interferon beta-1a (Rebif), 22 mcg	24 months	EDSS 0 to 5.0; ≥ 1 year MS duration; ≥ 2 relapses in last 2 years	Poser
De Stefano 2010, 2012/ IMPROVE	Placebo Interferon beta-1a (Rebif), 44 mcg	16 weeks	EDSS 0 to 5.5; ≥ 1 relapse AND ≥ 1 GdE lesions in the last 6 months	McDonald 2001
Singer 2012/REFORMS	Interferon beta-1a (Rebif), 44 mcg Interferon beta-1b (Betaseron; Betaferon), 250 mcg	12 weeks	Age 18 to 60 years; no prior interferon beta use; no DMTs in last 3 months	McDonald 2005 or Poser

Trial name or author, year of publication	Intervention	Study duration	Inclusion criteria	MS criteria
Interferon beta-1b (Betaseron; Betaferon)				
IFNb MSSG 1993	Placebo Interferon beta-1b (Betaseron; Betaferon), 8 mIU	2 years	EDSS 0 to 5.5; ≥ 2 exacerbations in last 2 years	Poser
Knobler 1993	Placebo Interferon beta-1b (Betaseron; Betaferon), 250 mcg	24 weeks	EDSS 0 to 5.5; 2 prior exacerbations in the past 2 years	Poser
Natalizumab (Tysabri), 300 mg				
Polman 2006/AFFIRM	Placebo Natalizumab (Tysabri), 300 mg	2 years or more	EDSS 0 to 5; ≥ 1 relapse in last year	McDonald 2001
Saida 2017	Placebo Natalizumab (Tysabri), 300 mg	24 weeks	EDSS: 0 to 5.5; ≥ 1 relapse in last year	McDonald 2005
Ocrelizumab (Ocrevus)				
Hauser 2017a/OPERA I	Interferon beta-1a (Rebif), 44 mcg Ocrelizumab (Ocrevus), 600 mg	96 weeks	EDSS 0 to 5.5; ≥ 2 relapses in last 2 years; disease duration ≥ 10 years with an EDSS < 2 excluded	McDonald 2010
Hauser 2017b/OPERA II	Interferon beta-1a (Rebif), 44 mcg Ocrelizumab (Ocrevus), 600 mg	96 weeks	EDSS 0 to 5.5	McDonald 2010
Kappos 2011	Placebo Interferon beta-1a (Avonex) 30 mcg Ocrelizumab (Ocrevus), 600 mg	48 weeks	EDSS 1 to 6; ≥ 2 relapses in the last 3 years with ≥ 1 in the last year; ≥ 6 T2 lesions per MRI OR ≥ 2 relapses in prior year; disease duration ≥ 15 years with EDSS ≤ 2 excluded	McDonald 2001
Ozanimod				
Cohen 2016/RADIANCE PART A	Placebo Ozanimod, 0.5 mg Ozanimod, 1.0 mg	24 weeks	EDSS 0 to 5; ≥ 1 relapse in past year or ≥ 1 relapse in past 2 years and ≥ 1 GdE T1 lesion	McDonald 2010
RADIANCE PART B	Interferon beta-1a (Avonex) 30 mcg Ozanimod, 0.5 mg Ozanimod, 1.0 mg	24 months	EDSS 0 to 5.5; ≥ 1 relapse in the last 12 months OR 1 relapse in the last 24 months with ≥1 GdE lesion	McDonald 2010
SUNBEAM	Interferon beta-1a (Avonex) 30 mcg Ozanimod, 0.5 mg Ozanimod, 1.0 mg	13.1 months	EDSS 0 to 5; ≥ 1 relapse past year or ≥ 2 in past 2 years AND ≥ 1 GdE lesion; MS duration ≥ 15 years with EDSS ≤ 2 excluded	McDonald 2010

Trial name or author, year of publication	Intervention	Study duration	Inclusion criteria	MS criteria
Peginterferon beta-1a (Plegridy), 125 mcg every other week				
Calabresi 2014b/ADVANCE	Placebo	48 weeks	EDSS 0 to 5; ≥ 2 relapses in the last 3 years and ≥ 1 in the last year	McDonald 2005
	Peginterferon beta-1a (Plegridy), 12 5 mcg every other week			
Teriflunomide (Aubagio)				
Confavreux 2014/TOWER	Placebo	48 weeks	EDSS 0 to 5.5; ≥ 1 relapse in past year or ≥ 2 in prior 2 years; no relapse in last 30 days	McDonald 2005
	Teriflunomide (Aubagio), 14 mg			
	Teriflunomide (Aubagio), 7 mg			
O'Connor 2006	Placebo	36 weeks	EDSS 0 to 6; ≥ 2 relapses in the last 3 years with 1 in the last year	Poser
	Teriflunomide (Aubagio), 14 mg			
	Teriflunomide (Aubagio), 7 mg			
O'Connor 2011/TEMSO	Placebo	108 weeks	EDSS 0 to 5.5; ≥ 2 relapses in last 2 years; no relapses in last 60 days	McDonald 2001
	Teriflunomide (Aubagio), 14 mg			
	Teriflunomide (Aubagio), 7 mg			
Vermersch 2014/TENERE	Interferon beta-1a (Rebif), 44 mcg	48 weeks	EDSS < 5.5; relapse-free for last 30 days	McDonald 2005
	Teriflunomide (Aubagio), 14 mg			
	Teriflunomide (Aubagio), 7 mg			

b.i.d. = twice daily; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhanced.

Source: Sponsor-submitted ITC.[13]

Table 20: Summary of Patient Characteristics for the 47 Included Trials

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
Alemtuzumab (Lemtrada)									
Cohen 2012b/CARE-MS I	Alemtuzumab (Lemtrada), 12 mg	376	33.0 (8.03)	65			2.1 (1.4)	2.0 (0.81)	1 year: 1.8 (0.8)
	Interferon beta-1a (Rebif), 44 mcg	187	33.2 (8.48)	65			2.0 (1.3)	2.0 (0.79)	1 year: 1.8 (0.8)
Coles 2008/CAMMS223	Alemtuzumab (Lemtrada), 12 mg	112	31.9 (8.0)	64.3				1.9 (0.74)	
	Interferon beta-1a (Rebif), 44 mcg	111	32.8 (8.8)	64				1.9 (0.83)	
Coles 2012/CARE-MS II	Alemtuzumab (Lemtrada), 12 mg	426	34.8 (8.36)	66	100		4.5 (2.68)	2.7 (1.26)	1 year: 1.7 (0.86)
	Interferon beta-1a (Rebif), 44 mcg	202	35.8 (8.77)	65	100		4.7 (2.86)	2.7 (1.21)	1 year: 1.5 (0.75)
Cladribine									
Giovannoni 2010/CLARITY	Placebo	437	38.7 (9.9)	65.9		8.9 (7.4)		2.9 (1.3)	
	Cladribine, 3.5 mg/kg	433	37.9 (10.3)	68.8		7.9 (7.2)		2.8 (1.2)	
Dimethyl fumarate (Tecfidera)									
Fox 2012/CONFIRM	Placebo	363	36.9 (9.2)	69		4.8 (5.0)		2.6 (1.2)	1 year: 1.4 (0.8)
	Dimethyl fumarate (Tecfidera), 240 mg (b.i.d.)	359	37.8 (9.4)	68		4.9 (5.1)		2.6 (1.2)	1 year: 1.3 (0.6)
	Glatiramer acetate (Copaxone), 20 mg	350	36.7 (9.1)	71		4.4 (4.7)		2.6 (1.2)	1 year: 1.4 (0.6)
Gold 2012/DEFINE	Placebo	408	38.5 (9.1)	75	42	5.8 (5.8)		2.48 (1.24)	1 year: 1.3 (0.7)

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
	Dimethyl fumarate (Tecfidera), 240 mg (b.i.d.)	410	38.1 (9.1)	72.2	40	5.6 (5.4)		2.4 (1.29)	1 year: 1.3 (0.7)
Saida 2019	Placebo	113	36.0 (7.5)	74	57			1.9 (1.3)	1 year: 1.4 (0.7), 3 years: 2.3 (1.5)
	Dimethyl fumarate (Tecfidera), 240 mg (b.i.d.)	111	37.3 (8.3)	70	57			2.2 (1.3)	1 year: 1.4 (0.7), 3 years: 2.5 (1.7)
Fingolimod (Gilenya)									
Calabresi 2014a/FREEDOMS II	Placebo	355	40.1 (8.4)	81	73		10.6 (7.9)	2.4 (1.3)	1 year: 1.5 (0.9), 2 years: 2.2 (1.5)
	Fingolimod (Gilenya), 0.5 mg	358	40.6 (8.4)	77	74		10.4 (8.0)	2.4 (1.3)	1 year: 1.4 (0.9), 2 years: 2.2 (1.4)
Cohen 2010/TRANSFORMS	Fingolimod (Gilenya), 0.5 mg	431	36.7 (8.8)	65.4	55.2		7.5 (6.2)	2.24 (1.33)	1 year: 1.5 (1.2), 2 years: 2.3 (2.2)
	Interferon beta-1a (Avonex) 30 mcg	435	36 (8.3)	67.8	56.3		7.4 (6.3)	2.19 (1.26)	1 year: 1.5 (0.8), 2 years: 2.3 (1.2)
Comi 2017/GOLDEN	Fingolimod (Gilenya), 0.5 mg	80	40.23 (9.09)	71.25	52.5	4.97 (6.67)		2.78 (1.34)	1 year: 1.45 (0.79), 2 years: 1.90 (0.84)

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg	28	37.64 (9.29)	67.86	46.43	4.71 (6.47)		2.09 (1.05)	1 year: 1.18 (0.48), 2 years: 1.54 (0.84)
Kappos 2010/FREEDOMS	Placebo	418	37.2 (8.6)	71.3			8.1 (6.4)	2.5 (1.3)	1 year: 1.4 (0.7), 2 years: 2.2 (1.2)
	Fingolimod (Gilenya), 0.5 mg	425	36.6 (8.8)	69.6			8.0 (6.6)	2.3 (1.3)	1 year: 1.5 (0.8), 2 years: 2.1 (1.1)
Saida 2012	Placebo	57	35 (8.9)	68.4			8.2 (7.3)	2.1 (1.7)	1 year: 1.7 (1.6), 2 years: 2.8 (3.0)
	Fingolimod (Gilenya), 0.5 mg	57	35 (9)	70.2			8.2 (6.8)	2.3 (1.9)	1 year: 1.4 (1.0), 2 years: 2.2 (1.4)
Glatiramer acetate (Copaxone), 20 mg									
Boiko 2018	Placebo	28	4 (median)						1 year: 1.21 (0.42)
	Glatiramer acetate (Generic), 20 mg	61	5 (median)						1 year: 1.28 (0.49)
	Glatiramer acetate (Copaxone), 20 mg	61	3 (median)						1 year: 1.28 (0.64)
Bornstein 1987	Placebo	23	31.1	60		6.4		3.1	2 years: 3.9
	Glatiramer acetate (Copaxone), 20 mg	25	30	56		4.9		2.9	2 years: 3.8
Cadavid 2009/BECOME	Glatiramer acetate (Copaxone), 20 mg	39	36 (22 to 55; range)	64		1.2		2	

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg	36	36 (18 to 49; range)	75		0.9		2	
Calabrese 2012	Glatiramer acetate (Copaxone), 20 mg	48	38.9 (10.2)	72.9		5.5 (6.1)		2.1 (1.1)	
	Interferon beta-1a (Avonex) 30 mcg	47	34.8 (9.6)	68		5.3 (5.1)		1.9 (0.8)	
	Interferon beta-1a (Rebif), 44 mcg	46	35.9 (9.1)	69.5		5.7 (4.9)		1.9 (1.0)	
Cohen 2015/ GATE	Placebo	84	32.6 (8.7)	67.9	88.1		5.7 (6.0)	2.7 (1.2)	2 years: 1.9 (0.9)
	Glatiramer acetate (Copaxone), 20 mg	357	33.8 (9)	66.7	82.6		6.4 (6.0)	2.7 (1.2)	2 years: 1.8 (0.9)
	Glatiramer acetate (generic), 20 mg	353	32.6 (8.6)	66	84.1		5.5 (5.3)	2.6 (1.2)	2 years: 1.9 (0.9)
Johnson 1995/Copolymer 1 Trial	Placebo	126	34.3 (6.5)	76.2		6.6 (5.1)		2.4 (1.3)	2 years: 2.9 (1.1)
	Glatiramer acetate (Copaxone), 20 mg	125	34.6 (6)	70.4		7.3 (4.9)		2.8 (1.2)	2 years: 2.9 (1.3)
Lublin 2013/CombiRx	Glatiramer acetate (Copaxone), 20 mg	259	39 (9.5)	71.4		1.0 (2.9)		1.9 (1.2)	1 year: 1.6 (0.7)
	Interferon beta-1a (Avonex) 30 mcg	250	37.6 (10.2)	69.2		1.4 (4.0)		2.0 (1.2)	1 year: 1.7 (0.9)
Mikol 2008/REGARD	Glatiramer acetate (Copaxone), 20 mg	378	36.8 (9.5)	72				2.33 (1.31)	
	Interferon beta-1a (Rebif), 44 mcg	386	36.7 (9.8)	69				2.35 (1.28)	
O'Connor 2009/BEYOND	Glatiramer acetate (Copaxone), 20 mg	448	35.2 (27 to 43; IQR)	68.3		5.1		2.28	1 year: 1.6

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg	897	35.8 (28 to 43; IQR)	69.9		5.3		2.35	1 Year: 1.6
Comi 2001/EU/C GASG	Placebo	120	34.0 (7.5)			8.3 (5.5)		2.4 (1.2)	2 years: 2.5 (1.4)
	Glatiramer acetate (Copaxone), 40 mg	119	34.1 (7.4)			7.9 (5.5)		2.3 (1.1)	2 years: 2.8 (1.8)
Khan 2013/GALA	Placebo	461	38.1 (9.2)	67.9			7.6 (6.4)	2.7 (1.2)	1 year: 1.3 (0.6), 2 years: 1.9 (0.9)
	Glatiramer acetate (Copaxone), 40 mg	943	37.4 (9.4)	68			7.7 (6.7)	2.8 (1.2)	1 year: 1.3 (0.6), 2 years: 1.9 (0.9)
Interferon beta-1a (Avonex) 30 mcg									
Durelli 2002/INCOMIN	Interferon beta-1a (Avonex) 30 mcg	92	34.9 (7.9)	62		6.7 (5.4)		1.96 (0.7)	2 years (annualized): 1.38 (0.52)
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg	96	38.8 (7.1)	68.8		5.9 (4.2)		1.97 (0.7)	2 years (annualized): 1.52 (0.67)
Etemadifar 2006	Interferon beta-1a (Avonex) 30 mcg	30	28.1 (1.2)	80		2.9 (2.3)		1.9 (1.1)	1 year: 2.0 (0.8)
	Interferon beta-1a (Rebif), 44 mcg	30	27.4 (1.2)	77		3.0 (2.2)		2.1 (1.0)	1 year: 2.4 (1.0)
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg	30	29.9 (1.4)	70		3.7 (2.3)		1.9 (0.7)	1 year: 2.2 (0.7)

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
Jacobs 1996/MSCRG	Placebo	143	36.9 (0.64; SE)	72		6.4 (0.49; SE)		2.3 (0.07; SE)	1 year: 1.2 (0.05, SE)
	Interferon beta-1a (Avonex) 30 mcg	158	36.7 (0.57; SE)	75		6.6 (0.46; SE)		2.4 (0.06; SE)	1 year: 1.2 (0.05, SE)
Mokhber 2015/ IRCT201404195280N16	Interferon beta-1a (Avonex) 30 mcg	20	31.11 (6.76)	60					
	Interferon beta-1a (Rebif), 44 mcg	22	27.78 (8.01)	60.9					
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg	23	28.95 (8.78)	72.7					
Panitch 2002/EVIDENCE	Interferon beta-1a (Avonex) 30 mcg	338	37.4	74.6		6.7		2.3	2 years: 2.6
	Interferon beta-1a (Rebif), 44 mcg	339	38.3	74.9		6.5		2.3	2 years: 2.6
Vollmer 2014/BRAVO	Placebo	450	37.5	71.3		1.2	4.7	2.5	1 year: 1 (1 to 2) (median, [IQR]) 2 years: 2 (1 to 2) (median, [IQR])
	Interferon beta-1a (Avonex) 30 mcg	447	38.5	68.7		1.4	5.3	2.5	1 year: 1 (1 to 2) (median, [IQR]) 2 years: 2 (1 to 2) (median, [IQR])
Interferon beta-1a (Rebif)									
PRISMS 1998	Placebo	187	34.6	75		4.3		2.4 (1.2)	2 years: 3 (1.3)

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
	Interferon beta-1a (Rebif), 44 mcg	184	35.6	66		6.4		2.5 (1.3)	2 years: 3 (1.1)
	Interferon beta-1a (Rebif), 22 mcg	189	34.8	67		5.4		2.5 (1.2)	2 years: 3 (1.1)
De Stefano 2010, 2012/ IMPROVE	Placebo	60	35.2 (10.5)	70					
	Interferon beta-1a (Rebif), 44 mcg	120	34.0 (7.8)	73					
Singer 2012/REFORMS	Interferon beta-1a (Rebif), 44 mcg	65	40.26 (9.80)	70.8		1.01 (2.35)	4.51 (6.70)		1 year: 1.36 (0.52) out of 55 with relapse
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg	64	40.78 (9.56)	68.8		1.93 (4.02)	5.74 (6.66)		1 year: 1.30 (0.46) out of 50 with relapse
Interferon beta-1b (Betaseron; Betaferon)									
IFNb MSSG 1993	Placebo	123	36 (0.6; SE)	71.5		3.9 (0.3; SE)		2.8 (0.1; SE)	2 years: 3.6 (0.1, SE)
	Interferon beta-1b (Betaseron; Betaferon), 8 mIU	124	35.2 (0.6; SE)	69.4		4.7 (0.4; SE)		3.0 (0.1; SE)	2 years: 3.4 (0.2, SE)
Knobler 1993	Placebo	7	34.5	71		7		3.1	
	Interferon beta-1b (Betaseron; Betaferon), 250 mcg	6	35.4	33		4.2		2.7	
Natalizumab (Tysabri), 300 mg									
Polman 2006/AFFIRM	Placebo	315	36.7 (7.8)	67		6		2.3 (1.2)	1 year: 1.5 (0.77)
	Natalizumab (Tysabri), 300 mg	627	35.6 (8.5)	72		5		2.3 (1.2)	1 year 1.53 (0.91)
Saida 2017	Placebo	47	35.1 (8.2)	68	85	5.1 (4.9)	6.8 (5.5)	2.1 (1.5)	1 year: 1.9 (1.0)

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
	Natalizumab (Tysabri), 300 mg	47	37.7 (8.6)	72	91	5.9 (5.0)	8.7 (5.7)	2.5 (1.6)	1 year: 2.0 (1.2)
Ocrelizumab (Ocrevus)									
Hauser 2017a/OPERA I	Interferon beta-1a (Rebif), 44 mcg	411	36.9 (9.3)	66.2		3.71 (4.63)	6.25 (5.98)	2.75 (1.29)	1 year: 1.33 (0.64)
	Ocrelizumab (Ocrevus), 600 mg	410	37.1 (9.3)	65.9		3.82 (4.80)	6.74 (6.37)	2.86 (1.24)	1 year: 1.31 (0.65)
Hauser 2017b/ OPERA II	Interferon beta-1a (Rebif), 44 mcg	418	37.4 (9)	67		4.13 (5.07)	6.68 (6.13)	2.84 (1.38)	1 year: 1.34 (0.73)
	Ocrelizumab (Ocrevus), 600 mg	417	37.2 (9.1)	65		4.15 (4.95)	6.72 (6.10)	2.78 (1.30)	1 year: 1.32 (0.69)
Kappos 2011	Placebo	54	38 (8.8)	67	30	2.7	4.8	3.2 (1.4)	
	Interferon beta-1a (Avonex) 30 mcg	54	38.1 (9.3)	59	31	3.3	5.3	3.1 (1.5)	
	Ocrelizumab (Ocrevus), 600 mg	55	35.6 (8.5)	64	53	3.6	6.5	3.5 (1.5)	
Ozanimod									
Cohen 2016/RADIANCE PART A	Placebo	88	39.0 (8.7)	70		8.1 (7.0)	4.6 (5.1)	2.9 (1.3)	1 year: 1.3 (0.6), 2 years: 1.8 (1.0)
	Ozanimod, 0.5 mg	87	38.1 (9.2)	69		6.0 (6.4)	6.0 (6.4)	2.9 (1.3)	1 year: 1.5 (1.2), 2 years: 2.0 (1.8)
	Ozanimod, 1.0mg	83	38.4 (9.8)	71		6.2 (5.8)	3.6 (4.4)	2.9 (1.2)	1 year: 1.3 (0.7), 2 years: 1.9 (1.1)

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
RADIANCE PART B	Interferon beta-1a (Avonex) 30 mcg	441	35.1 (9.07)	68.9	92.3	3.63 (4.613)	6.36 (6.065)	2.49 (1.158)	1 year: 1.3 (0.58), 2 years: 1.8 (0.86)
	Ozanimod, 0.5 mg	439	35.4 (8.82)	65.4	92	3.5 (4.207)	6.23 (5.547)	2.48 (1.166)	1 year: 1.4 (0.64), 2 years: 1.8 (0.9)
	Ozanimod, 1.0 mg	433	36 (8.89)	67.2	92.8	3.97 (5.171)	6.92 (6.201)	2.55 (1.145)	1 year: 1.3 (0.56), 2 years: 1.7 (0.82)
SUNBEAM	Interferon beta-1a (Avonex) 30 mcg	448	35.9 (9.11)	67	95.3	3.71 (4.361)	6.88 (5.877),	2.62 (1.138)	1 year: 1.3 (0.55), 2 years: 1.7 (0.84)
	Ozanimod, 0.5 mg	451	36 (9.43)	69	92.5	3.70 (4.518)	7.16 (6.255),	2.65 (1.135)	1 year: 1.3 (0.57), 2 years: 1.7 (0.84)
	Ozanimod, 1.0mg	447	34.8 (9.24)	63.3	94.4	3.60 (4.193)	6.85 (6.449)	2.61 (1.160)	1 year: 1.3 (0.57), 2 years: 1.8 (0.86)
Peginterferon beta-1a (Plegridy), 125 mcg every other week									
Calabresi 2014b/ADVANCE	Placebo	500	36.3 (9.7)	72	17	3.5 (4.6)	6.3 (6.3)	2.44 (1.18)	1 year: 1.6 (0.67), 3 years: 2.6 (1.0)
	Peginterferon beta-1a (Plegridy), 125 mcg every other week	512	36.9 (9.8)	71	17	4.0 (5.1)	6.9 (6.6)	2.47 (1.26)	1 year: 1.6 (0.67), 3 years: 2.9 (0.99)
Teriflunomide (Aubagio)									

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
Confavreux 2014/TOWER	Placebo	389	38.1 (9.1)	70	35		7.64 (6.7)	2.69 (1.36)	1 year: 1.4 (0.8), 2 Years: 2.1 (1.1)
	Teriflunomide (Aubagio), 14 mg	372	38.2 (9.4)	69	34		8.18 (6.73)	2.71 (1.35)	1 year: 1.4 (0.7), 2 years: 2.1 (1.2)
	Teriflunomide (Aubagio), 7 mg	408	37.4 (9.4)	74	30		8.18 (6.75)	2.71 (1.39)	1 year: 1.4 (0.7), 2 years: 2.1 (1.1)
O'Connor 2006	Placebo	61	39.2 (8.7)	67		4.4 (5.7)		2.5	1 year: 1, 3 years: 3
	Teriflunomide (Aubagio), 14 mg	57	40.1 (9.1)	78.9		5.4 (6.2)		2	1 year: 1, 3 years: 3
	Teriflunomide (Aubagio), 7 mg	61	40.1 (9.3)	75		6.0 (5.6)		2.5	1 year: 1, 3 years: 2
O'Connor 2011/TEMSO	Placebo	363	38.4 (9)	75.8			8.6 (7.1)	2.68 (1.34)	1 year: 1.4 (0.7), 2 years: 2.2 (1)
	Teriflunomide (Aubagio), 14 mg	359	37.8 (8.2)	71			8.7 (6.7)	2.67 (1.24)	1 year: 1.3 (0.7), 2 years: 2.2 (1)
	Teriflunomide (Aubagio), 7 mg	366	37.4 (9)	69.7			8.8 (6.8)	2.68 (1.34)	1 year: 1.4 (0.7), 2 years: 2.3 (1.2)

Trial name or author, year of publication	Intervention	N	Mean age, years (SD)	Female (%)	Prior treatment (%)	Mean disease duration (SD)	Mean symptom duration, years (SD)	Mean EDSS score (SD)	Mean prior relapses (SD)
Vermersch 2014/TENERE	Interferon beta-1a (Rebif), 44 mcg	104	37 (10.6)	68.3			7.7 (7.6)	2.0 (1.2)	1 year: 1.2 (1.0), 2 years: 1.7 (1.1)
	Teriflunomide (Aubagio), 14 mg	111	36.8 (10.3)	70.3			6.6 (7.6)	2.3 (1.4)	1 year: 1.4 (0.8), 2 years: 1.7 (0.9)
	Teriflunomide (Aubagio), 7 mg	109	35.2 (9.2)	64.2			7.0 (6.9)	2.0 (1.2)	1 year: 1.3 (0.8), 2 years: 1.7 (0.9)

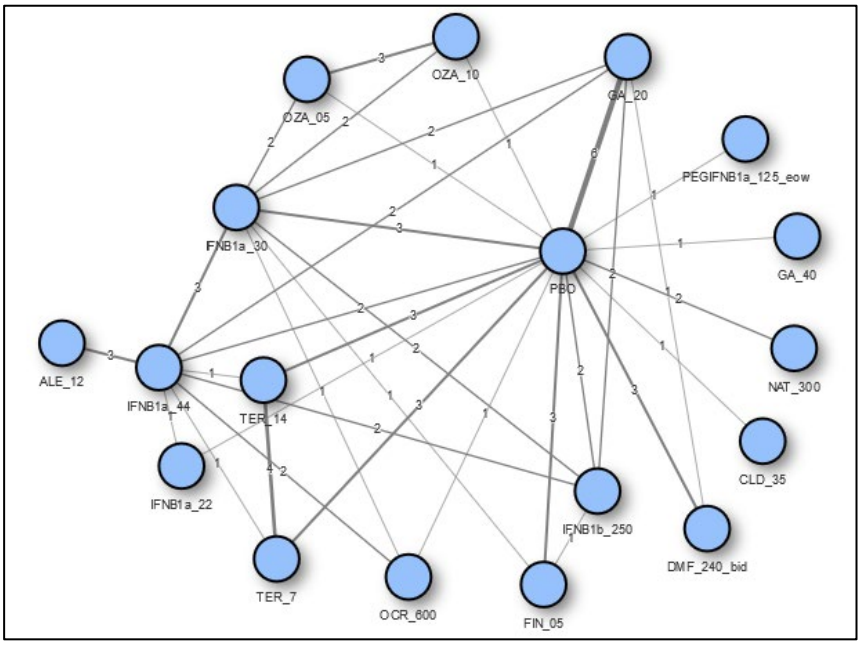
b.i.d. = twice daily; IQR = interquartile range; SD = standard deviation; SE = standard error.

Source: Sponsor-submitted indirect treatment comparsion.[13]

Annualized Relapse Rate

Forty-six studies and 18 treatments were included in the ARR network (Figure 4).

Figure 4: Network of Studies Included in the Annualized Relapse Rate Analysis



ALE = alemtuzumab; CLD = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB1a = interferon beta-1a; IFNB1b = interferon beta-1b; NAT = natalizumab; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEGIFNB1a = peginterferon beta-1a; TER = teriflunomide.

Source: Sponsor-submitted indirect treatment comparsion.[13]

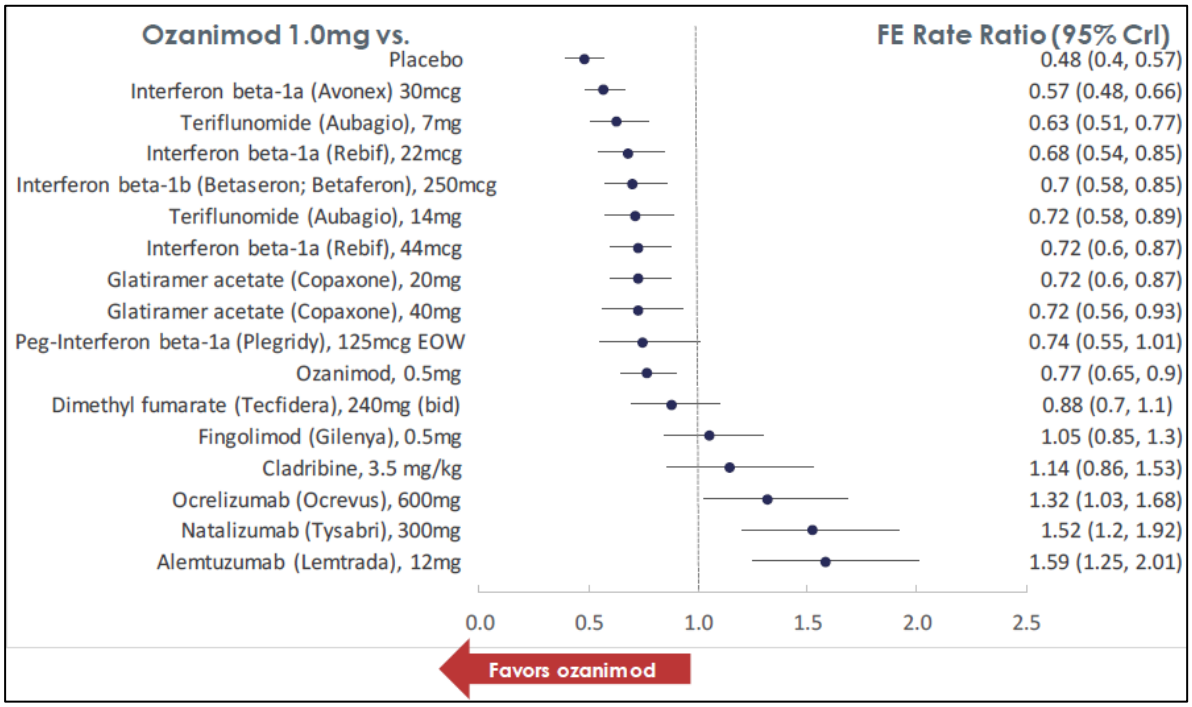
The DIC was 182.303 for the fixed-effects model and 87.426 for the random-effect model. The results of the NMA are presented for the fixed-effects model as an RR and 95% credible interval (CrI) for ozanimod 1.0 mg versus comparators. Results in which the RR and the 95% CrI were less than 1 indicate that ozanimod 1.0 mg was superior to the comparator at reducing the ARR, while results in which the RR and 95% CrI were greater than 1 indicate that the comparator was superior to the ozanimod 1.0 mg at reducing the ARR. Results in which the number 1 is within the CrI indicate that no treatment was favoured.

Ozanimod 1.0 mg was favoured for the ARR outcome when compared to Avonex (RR, 0.57; 95% CrI, 0.48 to 0.66), teriflunomide 7 mg (RR, 0.63; 95% CrI, 0.51 to 0.77), teriflunomide 14 mg (RR, 0.72; 95% CrI, 0.58 to 0.89), Rebif 22 mcg (RR, 0.68; 95% CrI, 0.54 to 0.85), Rebif 44 mcg (RR, 0.72; 95% CrI, 0.6 to 0.87), glatiramer acetate 20 mg (RR, 0.72; 95% CrI, 0.6 to 0.87), glatiramer acetate 40 mcg (RR, 0.72; 95% CrI, 0.56 to 0.93), and Betaseron (RR, 0.7; 95% CrI, 0.58 to 0.85). Ozanimod 1.0 mg was not favoured for the ARR outcome when compared to alemtuzumab (RR, 1.59; 95% CrI, 1.25 to 2.01), natalizumab (RR, 1.52; 95% CrI, 1.2 to 1.92), and ocrelizumab (RR, 1.32; 95% CrI, 1.03 to 1.68). When ozanimod 1.0 mg was compared with peginterferon beta-1a, dimethyl fumarate, fingolimod, and cladribine, no treatment was favoured (Figure 5).

Results from the random-effects model were similar to those from the fixed-effects model, except that no treatment was favoured when ozanimod 1.0 mg was compared with ocrelizumab.

Three ARR scenarios in the fixed-effects model were considered as sensitivity analyses. Bornstein (1987) was removed from scenario 1 because of high heterogeneity; Vermersch (2014) and Comi (2017) were removed from scenario 2 because of potential inconsistency; and studies with a duration of less than 1 year were removed from scenario 3. The results relative to placebo remained largely unchanged in all 3 scenario analyses; however, results for the comparison of ozanimod 1.0 mg against comparators were not reported.

Figure 5: Network Meta-Analysis Results for the Annualized Relapse Rate Analysis (Rate Ratio)[a]



CrI = credible interval; EOW = every other week; FE = fixed-effect.

[a] The network meta-analysis model was based on a Poisson distribution.

Source: Sponsor-submitted indirect treatment comparsion.[13]

Confirmed Disability Progression

The CDP12 network included 22 studies and 18 treatments (Figure 6) and the CDP24 network included 23 studies and 15 treatments (Figure 7). The 3 treatments for which CDP12 outcomes were reported and CDP24 outcomes were not reported were glatiramer acetate 40 mg, interferon beta-1a 22 mcg, and peginterferon beta-1a 125 mcg.

For CDP12, the DIC was 93.72 for the fixed-effects model and 95.22 for the random-effects model. For CDP24, the DIC was 95.5 for the fixed-effects model and 95.7 for the random-effects model. The fixed-effects model was chosen as the base-case results. The results of the NMA for the CDP12 and CDP24 are presented as an HR of ozanimod 1.0 mg versus comparators. Results in which the HR and 95% CrI were less than 1 indicate that ozanimod

1.0 mg was superior to the comparator in reducing CDP, while results in which the HR and 95% CrI were greater than 1 indicate that the comparator was superior to ozanimod 1.0 mg in reducing CDP. Results in which the number 1 was within the CrI indicate that no treatment was favoured.

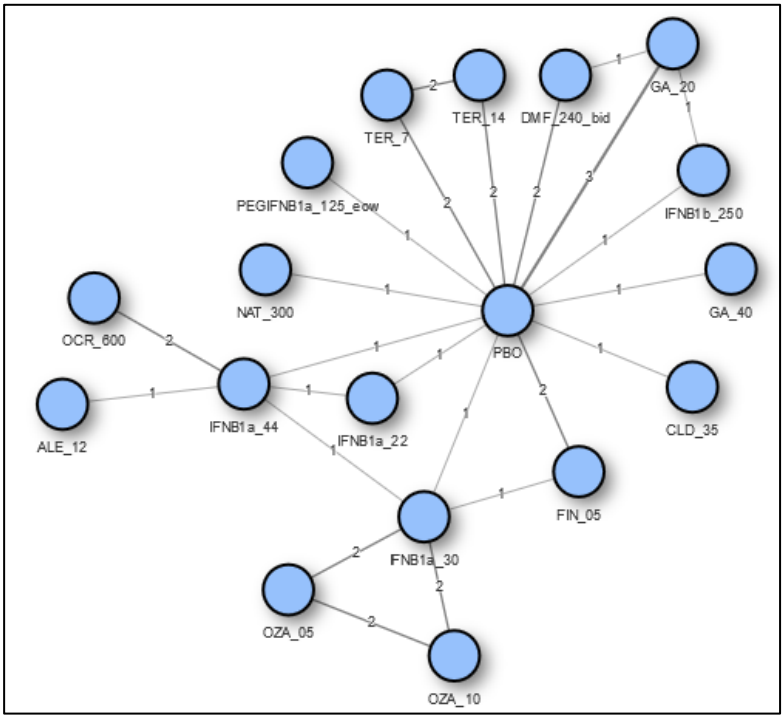
In the fixed-effects model for CDP12, ozanimod 1.0 mg was not favoured when compared to alemtuzumab and ocrelizumab. When ozanimod 1.0 mg was compared to glatiramer acetate, interferon beta-1a (Avonex), interferon beta-1a (Rebif), interferon beta-1b, fingolimod, teriflunomide, cladribine, dimethyl fumarate, peginterferon beta-1a, and natalizumab no treatment was favoured (Figure 8). Results from the random-effects model were similar to those from the fixed-effects model.

In the fixed-effects model for CDP24, ozanimod 1.0 mg was not favoured when compared to cladribine, alemtuzumab, interferon beta-1b, natalizumab, and ocrelizumab. When ozanimod 1.0 mg was compared to glatiramer acetate, interferon beta-1a (Avonex), interferon beta-1a (Rebif), fingolimod, teriflunomide, and dimethyl fumarate, no treatment was favoured (Figure 9). Results from the random-effects model for CDP24 were similar to those from the fixed-effects model, with the only difference being that, when ozanimod 1.0 mg was compared with cladribine and ocrelizumab, no treatment was favoured.

Three scenarios in the fixed-effects model were considered as sensitivity analyses for CDP12 and CDP24. For CDP12, inconsistent studies were removed from scenario 1, those being Calabresi (2014a), Bornstein (1987), Vollmer (2014), PRISMS (1998), IFNb MSSG (1993), and Panitch (2002). For CDP24, the inconsistent studies that were removed were Vollmer (2014), Jacobs (1996), IFNb MSSG (1993), Panitch (2002), Cadavid (2009), and Durelli (2002). In this scenario analysis, the HR of disability progression of ozanimod 1.0 mg relative to placebo worsened over the base-case CDP12 (0.95 versus 0.81); however, results for the comparison of ozanimod 1.0 mg against comparators were not reported.

In the second scenario analysis, when CDP24 data were missing, CDP12 values were used if available, and in the third scenario analysis, the treatment-specific relationship between CDP12 and CDP24 from studies where both outcomes were available was calculated, and then used to estimate the missing CDP24 data from reported CDP12 data in the analysis. The results relative to placebo were similar to the base-case analysis in these 2 scenarios analyses; however, results for the comparison of ozanimod 1.0 mg against comparators was not reported.

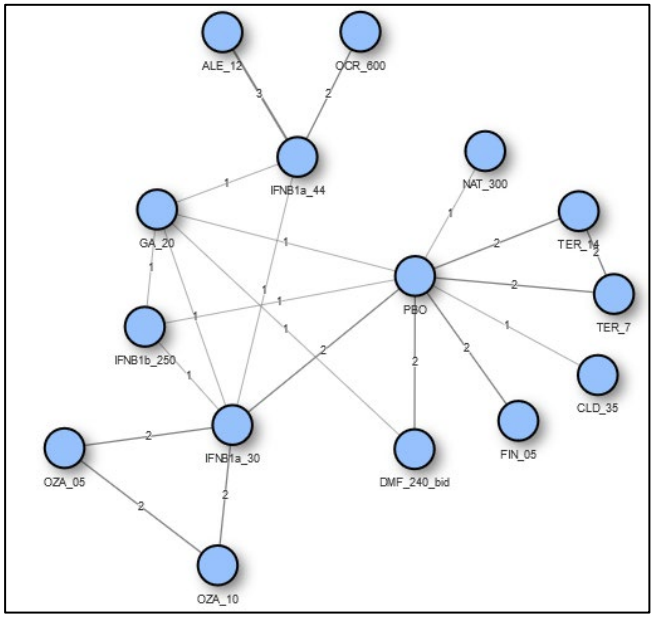
Figure 6: Network of Studies Included in the Confirmed Disability Progression After 12 Weeks Analysis



ALE = alemtuzumab; CLD = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB1a = interferon beta-1a; IFNB1b = interferon beta-1b; NAT = natalizumab; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEGIFNB1a = peginterferon beta-1a; TER = teriflunomide.

Source: Sponsor-submitted indirect treatment comparison.[13]

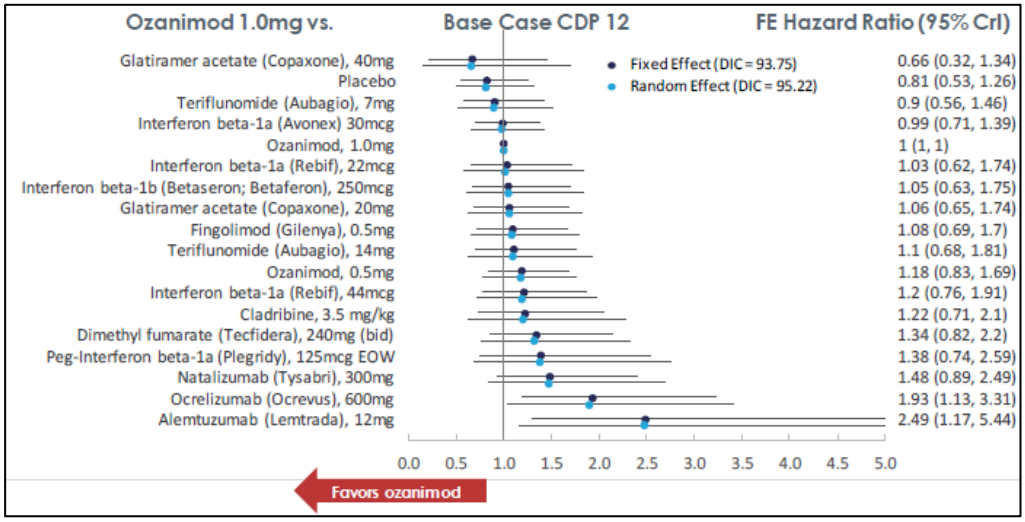
Figure 7: Network of Studies Included in the Confirmed Disability Progression After 24 Weeks Analysis



ALE = alemtuzumab; CLD = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB1a = interferon beta-1a; IFNB1b = interferon beta-1b; NAT = natalizumab; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEGIFNB1a = peginterferon beta-1a; TER = teriflunomide.

Source: Sponsor-submitted indirect treatment comparison.[13]

Figure 8: Network Meta-Analysis Results for the Confirmed Disability Progression at 12 Weeks Analysis (Hazard Ratio)[a]

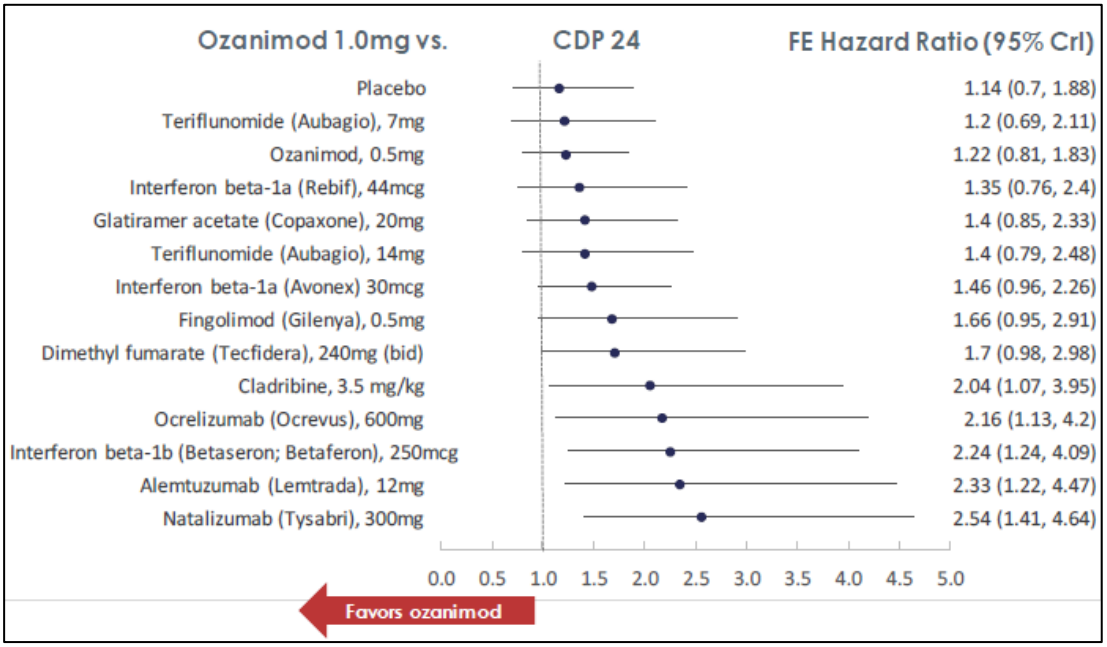


CDP = confirmed disability progression; CrI = credible interval; DIC = deviance information criterion; EOW = every other week; FE = fixed-effect.

[a] CDP events were analyzed using the total number of CDP events observed and the duration of time in which those events occurred. In this analysis, the time to CDP was assumed to follow the exponential survival distribution.

Source: Sponsor-submitted indirect treatment comparison.[13]

Figure 9: Network Meta-Analysis Results for the Confirmed Disability Progression at 24 Weeks Analysis (Hazard Ratio)[a]



CDP = confirmed disability progression; CrI = credible interval; FE = fixed-effect.

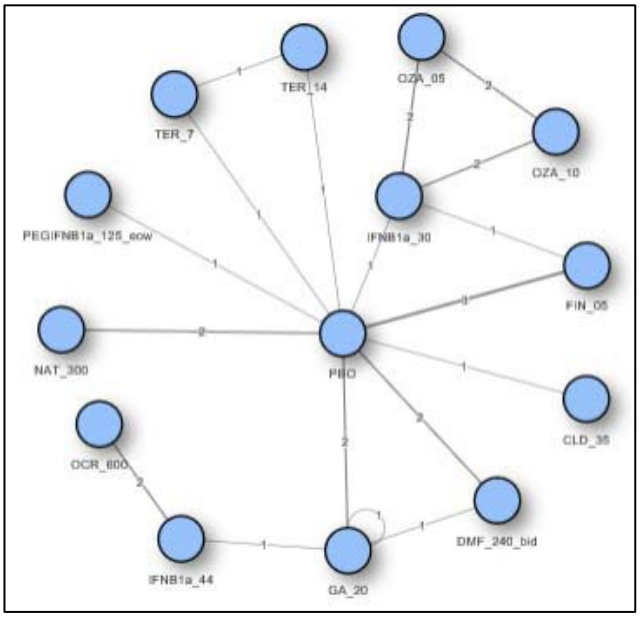
[a] CDP events were analyzed using the total number of CDP events observed and the duration of time in which those events occurred. In this analysis, the time to CDP was assumed to follow the exponential survival distribution.

Source: Sponsor-submitted indirect treatment comparison.[13]

Lesion Counts

Eighteen studies and 14 therapies were included in the network for GdE lesions (Figure 10). Nine studies and 10 therapies were included in the network for T2 new or newly enlarging lesions at 12 months (Figure 11). Eleven studies and 11 therapies were included in the network for T2 new or newly enlarging lesions at 24 months (Figure 12).

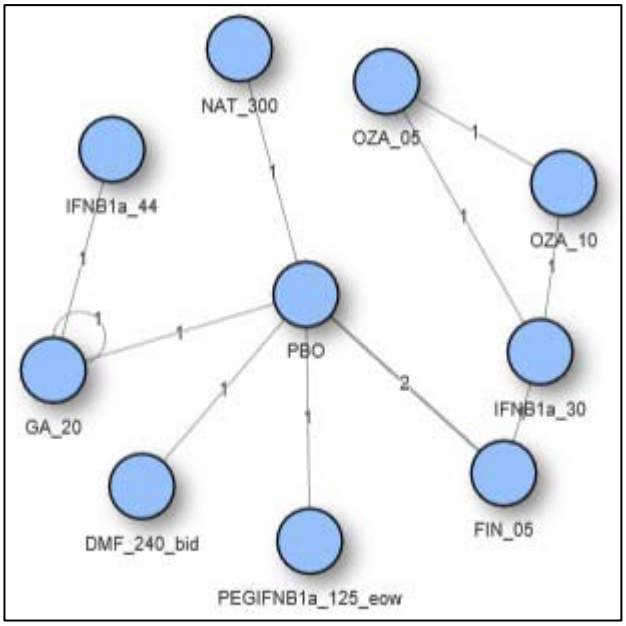
Figure 10: Network of Studies Included in the GdE Lesion Analysis



ALE = alemtuzumab; CLD = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB1a = interferon beta-1a; IFNB1b = interferon beta-1b; NAT = natalizumab; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEGIFNB1a = peginterferon beta-1a; TER = teriflunomide.

Source: Sponsor-submitted indirect treatment comparison.[13]

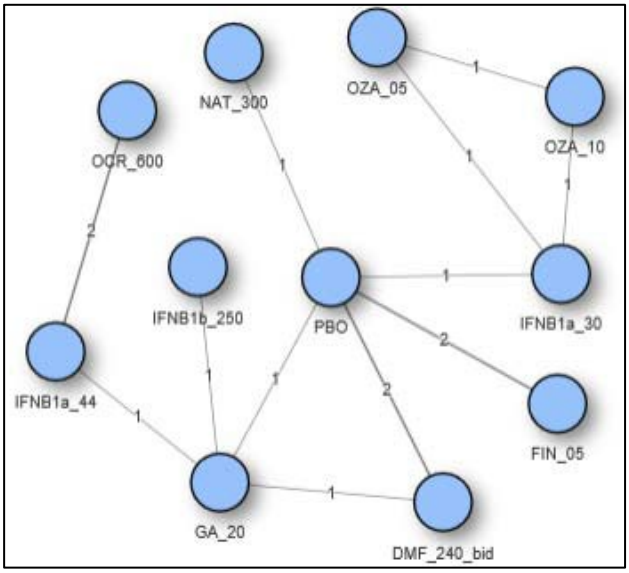
Figure 11: Network of Studies Included in the T2 New or Newly Enlarging Lesions at 12 Months Analysis



ALE = alemtuzumab; CLD = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB1a = interferon beta-1a; IFNB1b = interferon beta-1b; NAT = natalizumab; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEGIFNB1a = peginterferon beta-1a; TER = teriflunomide.

Source: Sponsor-submitted indirect treatment comparsion.[13]

Figure 12: Network of Studies Included in the T2 New or Newly Enlarging Lesions at 24 Months Analysis



ALE = alemtuzumab; CLD = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB1a = interferon beta-1a; IFNB1b = interferon beta-1b; NAT = natalizumab; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEGIFNB1a = peginterferon beta-1a; TER = teriflunomide.

Source: Sponsor-submitted indirect treatment comparison.[13]

For the new GdE lesion analysis, the DIC was 84.362 for the fixed-effects model and 83.689 for the random-effects model. The results of the NMA are presented for the fixed-effects model as the treatment difference and 95% CrI of ozanimod 1.0 mg versus comparators. Results in which treatment difference and the 95% CrI were less than 0 indicate that ozanimod 1.0 mg was superior to the comparator at preventing new GdE lesions, while results in which the RR and 95% CrI were greater than 0 indicate that the comparator was superior to ozanimod 1.0 mg at preventing new GdE lesions. Results in which the number 0 was within the CrI indicate that no treatment was favoured. Ozanimod 1.0 mg was favoured for the new GdE lesion outcome when compared with Avonex and fingolimod. When ozanimod 1.0 mg was compared with teriflunomide, interferon beta-1a (Rebif), glatiramer acetate, peginterferon beta-1a, dimethyl fumarate, cladribine, ocrelizumab, natalizumab, and alemtuzumab, no treatment was favoured (Table 21). Results from the RE model were similar to those from the fixed-effects model, the only difference being that no treatment was favoured when ozanimod 1.0 mg was compared with fingolimod.

For the T2 new or newly enlarging lesions at 12 months, the DIC was 37.987 for the fixed-effects model and 38.781 for the random-effects model. For the T2 new or newly enlarging lesions at 24 months, the DIC was 45.057 for the fixed-effects model and 45.64 for the random-effects model. The results of the NMA are presented for the fixed-effects model as the treatment difference and 95% CrI of ozanimod 1.0 mg versus comparators. Results in which treatment difference and the 95% CrI were less than 0 indicate that ozanimod 1.0 mg was superior to the comparator in preventing new or newly enlarging lesions, while results in which the RR and 95% CrI were greater than 0 indicate that the comparator was superior to ozanimod 1.0 mg in preventing new or newly enlarging lesions. Results in which the number 0 was within the CrI indicate that no treatment was favoured.

Ozanimod 1.0 mg was favoured for the T2 new or newly enlarging lesions at 12 months outcome when compared with glatiramer acetate, Rebif, Avonex, and fingolimod. When ozanimod 1.0 mg was compared with peginterferon beta-1a, dimethyl fumarate, and natalizumab, no treatment was favoured (Table 21). Results from the random-effects model were in the same direction as those from the fixed-effects model; in the former, ozanimod 1.0 mg was favoured only when compared with Avonex.

Ozanimod 1.0 mg was favoured for the T2 new or newly enlarging lesions at 24 months outcome when compared with Avonex. Ozanimod 1.0 mg was not favoured when compared to ocrelizumab, interferon beta-1b, and dimethyl fumarate. When ozanimod 1.0 mg was compared with fingolimod, natalizumab, interferon beta-1a (Rebif), and glatiramer acetate, no treatment was favoured. (Table 21). Results from the random-effects model were in the same direction as those from the fixed-effects model; in the random-effects model, ozanimod 1.0 mg was favoured when compared with Avonex but not when compared with dimethyl fumarate.

Table 21: Network Meta-Analysis Results for New GdE Lesions, T2 New or Newly Enlarging Lesions at 12 Months and at 24 Months[a]

	Mean treatment difference (95% CrI) fixed-effects model		
Ozanimod 1.0 relative to:	**New GdE lesions**	**T2 new or newly enlarging lesions at 12 months**	**T2 new or newly enlarging lesions at 24 months**
Placebo	**−1.09 (−1.44 to −0.74)**	**−5.73 (−7.58 to −3.9)**	**−6.81 (−9.48 to −4.12)**
Interferon beta-1a (Avonex) 30 mcg	**−0.56 (−0.77 to −0.34)**	**−2.8 (−4.4 to −1.2)**	**−5.21 (−7.58 to −2.82)**
Interferon beta-1a (Rebif), 22 mcg	NR	NR	NR
Interferon beta-1b (Betaseron; Betaferon), 250 mcg	NR	NR	**4.76 (0.78 to 9.17)**
Glatiramer acetate (Copaxone), 40 mg	NR	NR	NR
Teriflunomide (Aubagio), 14 mg	−0.01 (−0.49 to 0.46)	NR	NR
Interferon beta-1a (Rebif), 44 mcg	0.1 (−0.52 to 0.84)	**−3.92 (−6 to −1.84)**	3.27 (−0.72 to 7.7)
Glatiramer acetate (Copaxone), 20 mg	0.14 (−0.45 to 0.81)	**−4.19 (−6.24 to −2.14)**	3.46 (−0.52 to 7.87)
Peginterferon beta-1a (Plegridy), 125 mcg every other week	0.11 (−0.38 to 0.61)	1.56 (−0.87 to 3.96)	NR
Dimethyl fumarate (Tecfidera), 240 mg twice daily	0.43 (−0.17 to 1.04)	2.36 (−1.11 to 5.8)	**6.48 (2.53 to 10.57)**
Fingolimod (Gilenya), 0.5 mg	**−0.29 (−0.58 to 0)**	**−1.8 (−3.5 to −0.09)**	0.24 (−2.69 to 3.16)
Cladribine, 3.5 mg/kg	−0.3 (−0.68 to 0.08)	NR	NR
Ocrelizumab (Ocrevus), 600 mg	0.42 (−0.2 to 1.17)	NR	**4.55 (0.55 to 8.99)**
Natalizumab (Tysabri), 300 mg	0.09 (−0.47 to 0.66)	−0.85 (−2.96 to 1.3)	2.3 (−1.01 to 5.55)
Alemtuzumab (Lemtrada), 12 mg	NR	NR	NR

CrI = credible interval; GdE = gadolinium-enhanced; NR = not reported.

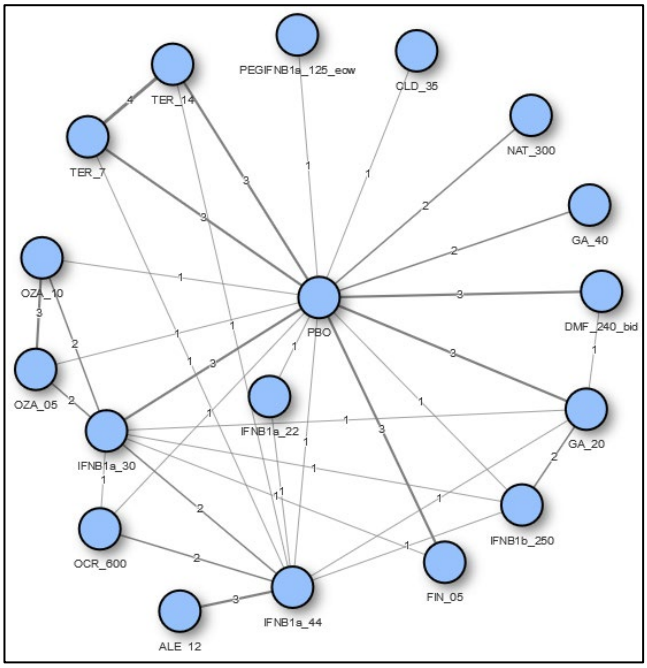
[a] For lesion counts, continuous data based on sample means and standard errors were analyzed using the normal likelihood and the normal link function.

Source: Sponsor-submitted indirect treatment comparsion.[13]

Discontinuation, adverse events, and serious adverse events

The network of discontinuation included 41 studies and 18 treatments (Figure 13). Twenty-six studies and 17 treatments were included in the AE network (Figure 14). Thirty-one studies reported SAEs, including 21 treatments.

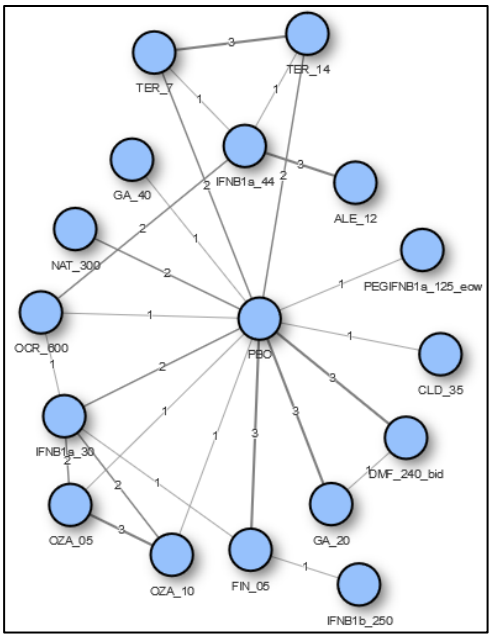
Figure 13: Network of Studies Included in the Discontinuation Analysis



ALE = alemtuzumab; CLD = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB1a = interferon beta-1a; IFNB1b = interferon beta-1b; NAT = natalizumab; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEGIFNB1a = peginterferon beta-1a; TER = teriflunomide.

Source: Sponsor-submitted indirect treatment comparison.[13]

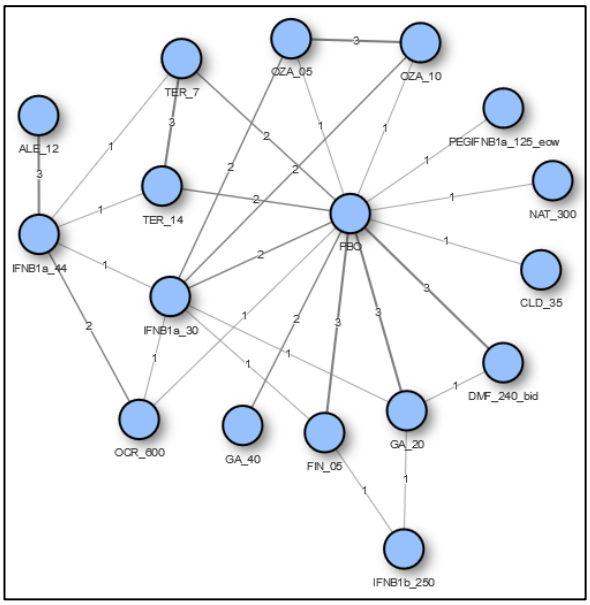
Figure 14: Network of Studies Included in the Adverse Events Analysis



ALE = alemtuzumab; CLD = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB1a = interferon beta-1a; IFNB1b = interferon beta-1b; NAT = natalizumab; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEGIFNB1a = peginterferon beta-1a; TER = teriflunomide.

Source: Sponsor-submitted indirect treatment comparsion.[13]

Figure 15: Network of Studies Included in the Serious Adverse Events Analysis



ALE = alemtuzumab; CLD = cladribine; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFNB1a = interferon beta-1a; IFNB1b = interferon beta-1b; NAT = natalizumab; OCR = ocrelizumab; OZA = ozanimod; PBO = placebo; PEGIFNB1a = peginterferon beta-1a; TER = teriflunomide.

Source: Sponsor-submitted indirect treatment comparsion.[13]

For discontinuation, the DIC was 168.87 for the fixed-effects model and 166.74 and for the random-effects model. The fixed-effects model was chosen as the base-case results. The results of the NMA for discontinuation are presented as the HR of ozanimod 1.0 mg versus comparators. Results in which the HR and 95% CrI were less than 1 indicate that ozanimod 1.0 mg had a lower annualized rate of discontinuation compared with the comparator, while results in which the HR and 95% CrI were greater than 1 indicate that the comparator had a lower annualized rate of discontinuation compared with ozanimod 1.0 mg. Results in which the number 1 was within the CrI indicate that no treatment was favoured. Ozanimod 1.0 mg was favoured when compared with peginterferon beta-1a, interferon beta-1a (Rebif) 22 mcg and 44 mcg, glatiramer acetate 40 mg, and interferon beta-1a (Avonex) 30 mcg, and was not favoured when compared to alemtuzumab 12 mg. When ozanimod 1.0 mg was compared with teriflunomide, placebo, dimethyl fumarate, ocrelizumab, and glatiramer acetate 20 mg, fingolimod, natalizumab, and interferon beta-1b, no treatment was favoured (Table 22). Results from the random-effects model were in the same direction as those from the fixed-effects model; in the random-effects model, ozanimod 1.0 mg was favoured when compared with peginterferon beta-1a, and interferon beta-1a (Rebif) 44 mcg and was not favoured when compared with alemtuzumab.

For AEs, the DIC was 114.727 for the fixed-effects model and 114.879 for the random-effects model. For SAEs, the DIC was 117.373 for the fixed-effects model and 117.385 for the random-effects model. The fixed-effects model was chosen as the base-case results for AEs and SAEs.

The results of the NMA for discontinuation are presented as the odds ratio of ozanimod 1.0 mg versus comparators. Results in which the odds ratio and 95% CrI were less than 1 indicate that patients on ozanimod 1.0 mg had lower odds of experiencing an AE or SAE than those on the comparator, while results in which the odds ratio and 95% CrI were greater than 1 indicate that patients on the comparator had lower odds of experiencing an AE or SAE than those on ozanimod 1.0 mg. Results in which the number 1 was within the CrI indicate that no treatment was favoured.

For AE, ozanimod 1.0 mg was favoured when compared with cladribine, dimethyl fumarate, glatiramer acetate 40 mg, Avonex, peginterferon beta-1a, and alemtuzumab, and no treatment was favoured when ozanimod 1.0 mg was compared to the rest of the treatments (Table 22). Results from the random-effects model were similar to those from the fixed-effects model.

For SAEs, in both the fixed-effects and random-effects models, no treatment was favoured when ozanimod 1.0 mg was compared to other treatments (Table 22).

Table 22: Network Meta-Analysis Results for Discontinuations, Adverse Events and Serious Adverse Events

Ozanimod 1.0 relative to:	Annualized HR (95% CrI) fixed-effects model	Median odds ratio (95% CrI) fixed-effects model	
	Discontinuations	Adverse events	Serious adverse events
Placebo	0.73 (0.51 to 1.05)	0.98 (0.74 to 1.32)	0.84 (0.49 to 1.44)
Interferon beta-1a (Avonex) 30 mcg	**0.72 (0.53 to 0.96)**	**0.53 (0.43 to 0.65)**	1.07 (0.68 to 1.69)
Interferon beta-1a (Rebif), 22 mcg	**0.51 (0.27 to 0.98)**	NR	NR
Interferon beta-1b (Betaseron; Betaferon), 250 mcg	1.18 (0.76 to 1.82)	2.08 (0.89 to 4.89)	1.38 (0.72 to 2.65)
Glatiramer acetate (Copaxone), 40 mg	**0.56 (0.33 to 0.95)**	**0.61 (0.42 to 0.89)**	0.75 (0.36 to 1.54)
Teriflunomide (Aubagio), 14 mg	0.71 (0.48 to 1.06)	0.77 (0.51 to 1.16)	0.77 (0.42 to 1.42)
Interferon beta-1a (Rebif), 44 mcg	**0.52 (0.34 to 0.79)**	0.66 (0.34 to 1.25)	0.95 (0.47 to 1.9)
Glatiramer acetate (Copaxone), 20 mg	0.92 (0.63 to 1.35)	1.2 (0.79 to 1.83)	1.15 (0.65 to 2.02)
Peginterferon beta-1a (Plegridy), 125 mcg every other week	**0.42 (0.25 to 0.7)**	**0.32 (0.19 to 0.53)**	1.26 (0.66 to 2.42)
Dimethyl fumarate (Tecfidera), 240 mg twice daily	0.74 (0.49 to 1.11)	**0.58 (0.36 to 0.91)**	1.07 (0.6 to 1.9)
Fingolimod (Gilenya), 0.5 mg	0.99 (0.67 to 1.47)	0.77 (0.53 to 1.13)	0.86 (0.49 to 1.52)
Cladribine, 3.5 mg/kg	1.22 (0.7 to 2.14)	**0.65 (0.42 to 1)**	0.63 (0.3 to 1.33)
Ocrelizumab (Ocrevus), 600 mg	0.89 (0.55 to 1.44)	0.67 (0.35 to 1.25)	1.24 (0.57 to 2.68)
Natalizumab (Tysabri), 300 mg	1 (0.6 to 1.65)	1.61 (0.84 to 3.15)	1.5 (0.46 to 5.11)
Alemtuzumab (Lemtrada), 12 mg	**2.2 (1.3 to 3.73)**	**0.26 (0.11 to 0.62)**	0.91 (0.43 to 1.93)

CrI = credible interval; HR = hazard ratio; NR = not reported.

Source: Sponsor-submitted indirect treatment comparsion.[13]

Critical Appraisal of Sponsor-Submitted Indirect Treatment Comparison

The sponsor's rationale for conducting the ITC (i.e., an absence of head-to-head studies that compared ozanimod 1 mg against all relevant MS therapies) and the objectives of the ITC (efficacy and safety data for ozanimod relative to currently existing medications for the treatment of RRMS) were clearly reported. According to the clinical expert consulted by CADTH for this review, the comparators and the dosages used were appropriate. However, glatiramer acetate injection (Glatect), and interferon beta-1b (Extavia), which were identified as comparators of interest in the protocol for this review, were not included in the sponsor-submitted ITC. A comprehensive systematic review was performed with a 2-stage dual-selection process, whereby articles were first selected based on titles and abstracts and then full-text articles were retrieved and their inclusion criteria examined. The criteria and key terms used in the literature search were provided and it was clear that the literature screening and data extraction were conducted in duplicate with methods in place to assess discrepancies. However, the potential for publication bias was not reported and the literature search used was limited to English-language trials. The risk of bias was assessed using the NICE quality assessment checklist for parallel-group RCTs,[72] and detailed results of these assessments were provided. Key efficacy outcomes for HRQoL or symptoms were not included in the analysis. While safety outcomes (AEs and SAEs) were assessed, mortality, withdrawals due to AEs, and notable harms were not reported. For most of the studies included in the ITC, the risk of bias was low. Some studies had an unclear or high

risk of bias primarily because the studies were open-label or had a single assessor. Evidence-network diagrams for the outcomes assessed were presented.

Clinical heterogeneity was present in the analysis due to variations in study phase, blinding, diagnostic criteria, publication date, and mean duration of disease. In addition, no definitions for "relapse" and "disease progression" were provided, making it impossible to know whether the definition for these 2 outcomes was consistent across studies. Heterogeneity may have been reduced by specifying additional inclusion criteria for studies, such as requiring data on the study phase, blinding status, diagnostic criteria, follow-up duration, and mean duration of disease. The clinical expert consulted for this review indicated that prior treatment, disease duration, and disease activity could have an impact on response to treatment. However, the sponsor-submitted ITC did not perform sensitivity analyses by removing outlier studies that had effect modifiers that could influence the results.

Strengths included the performance and comparison of both the RE and FE models and the assessment of the consistency assumption. However, an important difference identified between the trials included in the NMA was the ARR in the placebo arms of the trials, which was the common reference treatment across most of the trials. The ARR in the placebo arm of the trials included in the NMA ranged from 0.25 to 1.785. The sponsor did not use an NMA meta-regression model for placebo response, as meta-regression models impose a common interaction effect between baseline risk and relative effectiveness that account for variation in reference-arm response across trials. While adjusting for placebo response may be the preferred approach, there are limitations to this approach, because it assumes that study and patient characteristics that are effect modifiers of the relative treatment effect are also prognostic factors of the outcome with placebo. Given that the extent to which placebo response is an adequate proxy for specific characteristics or effect modifiers is unclear, uncertainty remains.

While the risk of bias for the included studies was assessed, the authors of the sponsor-submitted ITC did not provide a plan to investigate the impact of studies that were considered to be of low quality or have a high risk of bias.

Several sensitivity analyses were conducted for the ARR, CDP1, and CDP 24 outcomes. However, for most of the analyses only results against placebo were reported, and the CADTH reviewers were unable to comment on the impact of these sensitivity analyses. No sensitivity analyses were conducted for the remaining outcomes.

For lesion counts, continuous data based on sample means and standard errors were analyzed using the normal likelihood and the normal link function. However, in both the RADIANCE Part B and SUNBEAM studies, a negative binomial regression model was used, which seems more appropriate for this kind of outcome.

The heterogeneity and consistency of statistical analyses were not provided for the mean lesion counts, reducing the certainty of the results synthesized.

Methods of MAIC by Swallow et al.[14]

Objectives

In the absence of a head-to-head randomized trial between the S1P receptor modulating agents (ozanimod and fingolimod) in the treatment of RMS, the objective of this ITC was to

indirectly compare the key safety and efficacy outcomes between these 2 therapies using an MAIC.

Study Selection Methods

Methods used to conduct the systematic review and to select studies for inclusion in the ITC were not reported, nor were the eligibility criteria for study inclusion and exclusion provided. Also, the information sources used and how the study selection process and data extraction were conducted were not reported. A quality assessment of the included studies was not conducted.

Individual patient data from the RADIANCE Part B and SUNBEAM ozanimod trials were used in this analysis. In addition, the published summary-level data from the FREEDOMS, FREEDOMS II, and TRANSFORMS fingolimod phase III trials were used, along with pooled safety data from the FREEDOMS, FREEDOMS II, and TRANSFORMS trials, as well as the trial data reported in clinicaltrials.gov.[14] However, how it was decided to include these trials in the analysis was not reported.

Safety and efficacy outcomes assessed at 1 and 2 years included AEs and AEs leading to discontinuation, any SAE, patient death, liver enzymes (ALT) at least 3 times the upper limit of normal, macular edema, ARR, and 3-month and 6-month confirmed CDP.

ITC Analysis Methods

An anchor-based comparison was conducted for 1-year safety and efficacy outcomes using the interferon beta-1a arm as an anchor. Because of a lack of data comparing fingolimod versus interferon beta-1a at 2 years, the comparisons of 2-year outcomes were non-anchored.

For each treatment comparison, an MAIC was used to adjust for baseline patient differences. Patients in the ozanimod trials were assigned weights such that the weighted-mean baseline patient characteristics in the ozanimod trials exactly matched those reported for the fingolimod trials. To estimate the weights for the propensity of enrolment in the ozanimod trials versus the fingolimod trials, a logistic regression model using the method of moments was used.

All MAICs adjusted for cross-trial differences in the following baseline characteristics: sex, age, duration since the first symptoms of MS, EDSS score, relapses within the previous year, relapses within the last 2 years, prior DMT use, and absence of GdE lesions.

Baseline patient characteristics before and after matching were compared between the ozanimod and fingolimod groups. Comparisons of binary variables before matching were conducted via chi-square tests. Wald tests were used for the comparisons of binary variables after matching and the comparisons of continuous variables both before and after matching. A P value of 0.05 was used to determine statistical significance.

For the comparisons of 1-year outcomes, both ozanimod 1 mg dose groups from RADIANCE Part B and SUNBEAM were pooled. The ozanimod clinical trials and the TRANSFORMS trial all included a randomized comparison to interferon beta-1a. For the comparisons of 2-year outcomes, the patient group receiving ozanimod 1 mg from RADIANCE Part B was used. The fingolimod groups were pooled across the FREEDOMS and FREEDOMS II studies.

Results of MAIC by Swallow et al.[14]

Summary of Included Studies

Five studies were included in this analysis: the RADIANCE Part B and SUNBEAM ozanimod trials and 3 fingolimod phase III trials (FREEDOMS, FREEDOMS II, and TRANSFORMS).

Patients in all trials were between 18 and 55 years of age. Several differences between the trials existed. In the ozanimod trials, an RMS diagnosis was based on the 2010 revised McDonald criteria, while in the fingolimod trials, RMS diagnosis was based on the 2005 revised McDonald criteria. The fingolimod trials required either 1 confirmed relapse during the prior year or at least 2 during the prior 2 years, while the ozanimod trials required either 1 documented relapse in the prior year or 1 in the prior 2 years, along with GdE lesions. The upper EDSS score threshold for inclusion in the fingolimod trials was 5.5, whereas the upper threshold was a score of 5.0 in the ozanimod trials.

The baseline characteristics for the studies included in the 1-year outcomes indicated clinically relevant differences between patients receiving ozanimod (N = 882) and those receiving fingolimod (N = 429). These differences included shorter MS duration, less prior use of a DMT, fewer relapses within the previous 2 years, and higher EDSS scores at baseline in the patients enrolled in the RADIANCE Part B and SUNBEAM trials than in patients enrolled in the TRANSFORMS trial. After adjustment, baseline averages for included patient characteristics were balanced between the ozanimod and fingolimod trials (Table 23).

Table 23: Anchor-Based Comparison of Baseline Characteristics Between the Ozanimod 1 mg and Fingolimod 0.5 mg Trials for 1-Year Outcomes[a]

Characteristic	Before matching				After matching			
	RADIANCE Part B and SUNBEAM		TRANSFORMS		RADIANCE Part B and SUNBEAM		TRANSFORMS	
	Ozanimod 1 mg (N = 882)	Interferon beta-1a (N = 885)	Fingolimod 0.5 mg (N = 429)	Interferon beta-1a (N = 431)	Ozanimod 1 mg (N = 276)	Interferon beta-1a (N = 317)	Fingolimod 0.5 mg (N = 429)	Interferon beta-1a (N = 431)
Age, mean (SD), years	35.4 (9.1)	35.6 (9.1)	36.7 (8.8)	36.0 (8.3)	36.7 (9.2)	36.0 (9.4)	36.7 (8.8)	36.0 (8.3)
Female, n (%)	576 (65.3)	602 (68.0)	281 (65.4)	292 (67.8)	65.4	67.8	65.4	67.8
Duration of MS since first symptom, mean (SD), years	6.9 (6.3)	6.6 (6.0)	7.5 (6.2)	7.4 (6.3)	7.5 (6.5)	7.4 (6.4)	7.5 (6.2)	7.4 (6.3)
Relapses within previous year, mean (SD)	1.3 (0.6)	1.3 (0.6)	1.5 (1.2)	1.5 (0.8)	1.5 (0.7)	1.5 (0.7)	1.5 (1.2)	1.5 (0.8)
Relapses within previous 2 years, mean (SD)	1.7 (0.8)	1.7 (0.9)	2.3 (2.2)	2.3 (1.2)	2.3 (1.2)	2.3 (1.2)	2.3 (2.2)	2.3 (1.2)
EDSS score, mean (SD)	2.6 (1.2)	2.6 (1.2)	2.2 (1.3)	2.2 (1.3)	2.2 (1.1)	2.2 0.1)	2.2 (1.3)	2.2 (1.3)
Patients with prior DMTs, n (%)	252 (28.6)	276 (31.2)	237 (55.2)	243 (56.3)	55.2	56.3	55.2	56.3
Absence of GdE lesions, n (%)	488 (55.3)	475 (53.7)	289 (67.4)	272 (63.1)	67.4	63.1	67.4	63.1
Lymphocyte count at baseline, mean (SD), 1,000/µL	1.8 (0.6)	1.9 (0.6)	1.8 (0.5)	1.7 (0.5)	1.8 (0.6)	1.7 (0.5)	1.8 (0.5)	1.7 (0.5)

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhanced; MS = multiple sclerosis; SD = standard deviation.

[a] For this analysis, the fingolimod and interferon beta-1a arms from the TRANSFORMS trial were compared to the pooled ozanimod 1 mg and interferon beta-1a arms from the RADIANCE Part B and SUNBEAM trials.

Source: Swallow et al. (2020).[14]

The baseline characteristics for the studies included in the 2-year outcomes indicated clinically relevant differences between patients receiving ozanimod (N = 434) compared with those receiving fingolimod (N = 783). These differences included shorter MS duration, less prior use of DMTs, and fewer relapses within the previous 2 years in patients enrolled in the RADIANCE Part B and SUNBEAM trials than in patients enrolled in the FREEDOMS I and II trials. After adjustment, baseline averages for included patient characteristics were balanced between the ozanimod and fingolimod trials (Table 24).

Table 24: Non-Anchor–Based Comparison of Baseline Characteristics Between the Ozanimod 1 mg and Fingolimod 0.5 mg Trials for 2-year Outcomes[a]

	Before matching		After matching	
	RADIANCE Part B	FREEDOMS I and II	RADIANCE Part B	FREEDOMS I and II
Characteristics	Ozanimod 1 mg (N = 434)	Fingolimod 0.5 mg (N = 783)	Ozanimod 1 mg (ESS = 158)	Fingolimod 0.5 mg (N = 783)
Age, mean (SD), years	36.0 (8.9)	38.4 (8.8)	38.4 (8.9)	38.4 (8.8)
Female, n (%)	292 (67.3)	571 (72.9)	72.9	72.9
Duration of MS since first symptom, mean (SD), years	6.9 (6.2)	9.1 (7.4)	9.1 (7.0)	9.1 (7.4)
Relapses within previous year, mean (SD)	1.3 (0.6)	1.5 (0.8)	1.5 (0.7)	1.5 (0.8)
Relapses within previous 2 years, mean (SD)	1.7 (0.8)	2.1 (1.2)	2.1 (1.1)	2.1 (1.2)
EDSS score, mean (SD)	2.6 (1.1)	2.3 (1.3)	2.3 (1.2)	2.3 (1.3)
Patients with prior DMTs, n (%)	123 (28.3)	445 (56.8)	56.8	56.8
Absence of GdE lesions, n (%)	255 (58.8)	482 (61.6)	61.6	61.6

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhanced; SD = standard deviation.

Source: Swallow et al.[14] © 2020 Elyse Swallow. Reprinted in accordance with CC BY-NC-ND 4.0.

Results

After adjustment for baseline patient characteristics (age, sex, duration of MS since first symptom, relapses within previous year, relapses within the previous 2 years, EDSS scores, prior DMT use, and absence of GdE lesions), the effective sample size in the ozanimod 1 mg group for the comparison of 1-year safety and efficacy outcomes was 276, indicating greater loss in precision and greater influence of subsets of the patients in the RADIANCE Part B and SUNBEAM trials.

The analysis of 1-year outcomes found no statistically significant differences in ARRs (the ARR ratio for ozanimod versus fingolimod was 1.08 [95% CI, 0.64 to 1.82]) and the difference between the proportion of patients with CDP at 3 months and those CDP-free at 3 months between ozanimod and fingolimod was 1.1% (95% CI, −4.4 to 6.5). Ozanimod was associated with a statistically significantly lower risk of any AEs and a lower risk of abnormal liver enzyme (ALT) elevations compared with fingolimod. There were no differences between the treatment groups in AEs leading to discontinuation, death, any SAE, infection SAEs, neoplasm SAEs, cardiac SAEs, and macular edema (Table 25). A comparison of ozanimod and fingolimod for 6-month CDP at 1 year was not feasible as data were not reported in the fingolimod trial.

Table 25: Anchored Comparison of 1-Year Safety and Efficacy Outcomes for Ozanimod 1 mg and Fingolimod 0.5 mg

Outcome	Adjusted risk difference for ozanimod 1 mg versus fingolimod 0.5 mg		
	Δ	95% CI	P value
AE leading to discontinuation (%)[a]	−1.2	(−5.7 to 3.3)	0.61
Death (%)[a]	0.0	(0.0 to 0.0)	–
Any AE (%)[a]	−9.9	(−18.0 to −1.8)	< 0.05[b]
Any SAE (%)[a]	0.4	(−4.4 to 5.3)	0.86
Infection SAE (%)[a]			
Appendicitis	0.6	(−0.1 to 1.2)	0.1
Herpes virus infection (serious)	0.0	(−0.6 to 0.6)	1.0
Neoplasm SAE (%)[a]			
Basal cell carcinoma	−0.5	(−1.4 to 0.4)	0.27
Melanoma	−0.7	(−1.5 to 0.1)	0.08
Breast cancer	−0.5	(−1.2 to 0.2)	0.14
Cardiac SAE (%)[a]			
Bradycardia or sinus bradycardia	−0.4	(−1.1 to 0.3)	0.23
Atrioventricular block, first degree	−0.2	(−0.6 to 0.2)	0.35
Atrioventricular block, second degree	−0.2	(−0.6 to 0.2)	0.35
Myocardial infarction	−0.2	(−0.5 to 0.2)	0.32
Liver enzymes: ALT ≥ 3 × ULN (%)[a]	−6.8	(−10.6 to −3.1)	< 0.001[b]
Macular edema (%)[a]	−0.3	(−1.0 to −0.5)	0.50
Annualized relapse rate[c]	1.08	(0.64 to 1.82)	0.78
Proportion free of CDP at 3 months (%)[a]	1.1	(−4.4 to 6.5)	0.72

AE = adverse event; ALT = alanine aminotransferase; CDP = confirmed disability progression; SAE = serious adverse event; ULN = upper limit of normal.

[a] Difference in the proportion of patients with events.

[b] Denotes a statistically significant difference.

[c] Annualized relapse rate ratios for ozanimod versus fingolimod.

Source: Swallow et al.[14] © 2020 Elyse Swallow. Reprinted in accordance with CC BY-NC-ND 4.0.

After adjustment for baseline patient characteristics (age, sex, duration of MS since first symptom, relapses within previous year, relapses within previous 2 years, EDSS scores, prior DMT use, and absence of GdE lesions), the effective sample size in the ozanimod 1 mg group for the comparison of 2-year safety and efficacy outcomes was 158, indicating greater loss in precision and greater influence of subsets of the patients in the RADIANCE Part B study.

The analysis of 2-year outcomes revealed no statistically significant differences in ARRs. The ARR for ozanimod versus fingolimod was 1.06 (95% CI, 0.70 to 1.62) and the difference between the proportion of patients with CDP at 3 months and those CDP-free at 3 months between ozanimod and fingolimod was 5.2% (95% CI, −1.3 to 11.7), and the difference between the proportion of patients with CDP at 3 months and those CDP-free at 6 months between ozanimod and fingolimod was 0.9% (95% CI, −4.8 to 6.7). Ozanimod was associated with a statistically significantly lower risk of any AE and AEs leading to discontinuation, basal cell carcinoma, bradycardia, and abnormal liver enzyme elevations

compared with fingolimod. There were no differences between the treatment groups in death, any SAE, infection SAEs, and macular edema (Table 26).

Table 26: Unanchored Comparison of 2-Year Safety and Efficacy outcomes for Ozanimod 1 mg Versus Fingolimod 0.5 mg

Outcome	Adjusted risk difference for ozanimod 1 mg versus fingolimod 0.5 mg		
	Δ	95% CI	P value
AE leading to discontinuation (%)[a]	−7.4	(−12.3 to −2.5)	< 0.01[b]
Death (%)[a]	0.0	(0.0 to 0.1)	0.34
Any AE (%)[a]	−22.7	(−29.2 to −16.2)	< 0.001[b]
Any SAE (%)[a]	−4.7	(−9.8 to 0.5)	0.07
Infection SAE (%)[a]			
Appendicitis	−0.1	(−0.6 to 0.5)	0.83
Herpes virus infection (serious)	−0.3	(−0.7 to 0.1)	0.12
Neoplasm SAE (%)[a]			
Basal cell carcinoma	−1.8	(−2.7 to −0.9)	< 0.001[b]
Melanoma	−0.1	(−0.3 to 0.1)	0.38
Breast cancer	0	(−0.3 to 0.3)	0.96
Cardiac SAE (%)[a]			
Bradycardia or sinus bradycardia	−0.5	(−1.0 to 0.0)	< 0.05[b]
Atrioventricular block, first degree	0	(0.0 to 0.0)	–
Atrioventricular block, second degree	0	(0.0 to 0.0)	–
Myocardial infarction	0	(0.0 to 0.0)	–
Liver enzymes: ALT ≥ 3 × ULN (%)[a]	−3.0	(−5.8 to −0.1)	< 0.05[b]
Macular edema (%)[a]	−0.4	(−0.8 to 0.0)	0.08
Annualized relapse rate[c]	1.06	(0.70 to 1.62)	0.78
Proportion free of CDP, 3 months (%)[a]	5.2	(−1.3 to 11.7)	0.12
Proportion free of CDP, 6 months (%)[a]	0.9	(−4.8 to 6.7)	0.76

AE = adverse event; ALT = alanine aminotransferase; CDP = confirmed disability progression; SAE = serious adverse event; ULN = upper limit of normal.

[a] Difference in the proportion of patients with events.

[b] Denotes a statistically significant difference.

[c] Annualized relapse rate ratios for ozanimod versus fingolimod.

Source: Swallow et al. (2020).[14]

Critical Appraisal of MAIC by Swallow et al.[14]

The ITC by Swallow et al.[14] had a number of limitations that threatened the internal and external validity of the findings. Because the methods used to identify and select the studies were not reported, it is not clear whether an appropriate systematic literature search was conducted. Also, nothing was reported regarding literature search screening and data extraction. There was no assessment of study quality or discussion of how any potential biases in the trials may affect the results of the MAIC.

The authors conducted a thorough review of the study design, inclusion and exclusion criteria, and patient population characteristics in the clinical trials, and identified a number of differences between studies that could threaten the validity of an NMA or unadjusted ITC. The MAIC analyses were feasible because individual patient data were available for the

RADIANCE Part B and SUNBEAM trials, and the comparator trials had sufficiently similar study designs.

The analyses have several limitations that affect internal and external validity. There are concerns regarding the overlap between the fingolimod and ozanimod trial populations and the availability of data to allow for matching. The small effective sample size of many analyses suggests that substantial differences exist between the patient populations in the ozanimod and fingolimod trials, in which, for the comparison between ozanimod and fingolimod for 1-year outcomes, the sample size is effectively reduced to 31% of the original sample size for RADIANCE Part B and SUNBEAM. For the 2-year outcomes, the sample size is effectively reduced to 36% of the original sample size for RADIANCE Part B. Definitions for the outcomes included in the analyses were not provided, making it impossible to know whether the definition for these outcomes was consistent across studies. Given these issues, there is substantial uncertainty in the MAIC results.

There is also substantial uncertainty in the MAIC results for the 2-year comparisons due to a lack of a common comparator arm, i.e., a non-anchored comparison of ozanimod and fingolimod. Due to this limitation, the results could be biased by any imbalance in prognostic factors or effect modifiers that have not been included in the weighting process. In addition, there was no assessment of residual bias accounted for by the MAIC analysis. Furthermore, individual level data were pooled between RADIANCE Part B and SUNBEAM, and comparison results were combined across TRANSFORM, FREEDOM I, and FREEDOM II, although there was no clear description for how this was done. Combining data and results across multiple studies when conducting an MAIC must be done carefully as is discussed in the NICE Decision Support Unit Technical Support Document.[18] The approach as described does not appear to align with that described by the Decision Support Unit, which could introduce further bias in the reported results.

Results from the MAIC for AEs should be interpreted with caution because event ascertainment and reporting may differ between trials.

No justification was provided as to why the ITC was conducted using an MAIC rather than an NMA. Also, no justification was provided for how the effect modifiers were chosen.

Summary

Two ITCs were identified, reviewed, and critically appraised; 1 was submitted and commissioned by the sponsor[13] and 1 published by Swallow et al.[14] was funded by the sponsor. The sponsor-submitted ITC[13] included a systematic review, and used a Bayesian NMA to evaluate the relative clinical efficacy and safety of ozanimod 1 mg compared to cladribine, dimethyl fumarate, fingolimod, teriflunomide, alemtuzumab, natalizumab, ocrelizumab, glatiramer acetate, interferon beta-1a, interferon beta-1b, and peginterferon beta-1a in adult patients with RRMS. No systematic review was carried out by Swallow et al.,[14] and an MAIC was used to compare ozanimod to fingolimod in patients with RRMS, with individual patient data from the RADIANCE Part B and SUNBEAM trials used to match and adjust patients to those included in the comparator trials.

The sponsor-submitted ITC[13] reported that ozanimod was favoured in reducing ARRs compared to many first-line therapies, including interferons, glatiramer acetate, and teriflunomide. When compared with therapies reserved for more active or severe disease, (i.e., ocrelizumab, alemtuzumab, and natalizumab), ozanimod was found to be less efficacious for reducing ARRs. In sensitivity analyses, results were largely insensitive to the

exclusion of studies with statistically significant heterogeneity for ARRs or short study duration.

For CDP12, results did not favour any treatment when comparing ozanimod to all treatments included in the network except for alemtuzumab and ocrelizumab, which were favoured over ozanimod. For CDP24, the NMA found that Betaseron, cladribine, alemtuzumab, natalizumab, and ocrelizumab were favoured when compared with ozanimod. Notably, results for CDP24 did not favour either treatment when comparing ozanimod and fingolimod, which are in the same class of S1P receptor modulators. A series of CDP scenario analyses was conducted to estimate the effect of different data assumptions on the model results. Imputation scenarios for missing CDP24 data produced results similar to those of the base-case analysis.

For the analysis of treatment discontinuation, it was reported that ozanimod was favoured when compared with many first-line injectable therapies, including most interferons. Results did not favour any treatment for discontinuation when comparing ozanimod and other oral first-line therapies, including teriflunomide and dimethyl fumarate, or between ozanimod and fingolimod, cladribine, ocrelizumab, and natalizumab. Only alemtuzumab was favoured over ozanimod for treatment discontinuation. For SAEs, the results did not favour any treatment. However, the analysis found ozanimod was associated with similar or lower odds of AEs compared with interferon beta-1a, glatiramer acetate, peginterferon beta-1a, dimethyl fumarate, and alemtuzumab.

Critical appraisal points of the sponsor-submitted ITC[13] involve the lack of reporting certain items that would better inform on the certainty of the indirect evidence. The sponsor-submitted ITC[13] could have used more sensitivity and subgroup analysis to satisfy the assumptions of transitivity and homogeneity, and the sponsor could have used a meta-regression to adjust for effect modifiers that could influence the results. Also, given that the sponsor-submitted NMA did not adjust for the ARR in the placebo arm, the comparison between ozanimod and other therapies for RRMS is subject to uncertainty. In addition, uncertainty remains around the long-term efficacy and tolerability of the various treatments for RRMS.

The MAIC by Swallow et al.[14] reported that ozanimod was associated with statistically significantly lower risks of adverse outcomes over 1 and 2 years of follow-up compared with fingolimod, and that ozanimod and fingolimod were comparable in terms of reducing ARRs and the proportion of patients with CPD. However, the analyses by Swallow et al.[14] have a number of limitations that affect internal and external validity. There are concerns regarding the overlap between the ozanimod and fingolimod trial populations, and the availability of data to allow for matching. The small effective sample size of many analyses further suggests that substantial differences exist between the patient populations in the ozanimod and fingolimod trials, in which the effective sample size was only 31% of RADIANCE Part B and SUNBEAM patients after matching. Definitions for the outcomes included in the analyses were not provided. Data were pooled and results were combined in a manner that was unclearly specified and likely does not align with recommendations by the NICE Decision Support Unit. Given these issues, there is substantial uncertainty in the MAIC results, and firm conclusions cannot be drawn from them. In addition, this MAIC is subject to the limitations of the sponsor-submitted ITC as the network for the NMA contains the same studies included in the MAIC. The identified sources of heterogeneity between the studies included in the MAIC would also be of concern with respect to introducing bias in

the NMA as NMAs are generally less robust to sources of heterogeneity compared to MAICs.

Other Relevant Evidence

This section includes submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

Long-term Extension Studies

The DAYBREAK study is an ongoing, long-term extension, phase III study that assesses long-term safety, tolerability, and efficacy of ozanimod 1 mg once daily in patients with RMS. The DAYBREAK study was ongoing at the time of this review. The sponsor provided data from an interim analyses up to June 30, 2018. The first patient was enrolled on October 16, 2015. The primary objective of this study was to evaluate the long-term safety and tolerability of ozanimod in patients with RMS. The secondary objective was to evaluate the long-term efficacy of ozanimod in patients with RMS. The DAYBREAK study has been summarized to provide evidence regarding the long-term safety and efficacy of ozanimod 1 mg once daily in patients with RMS.

Methods

The DAYBREAK study is a multi-site, OLE study of ozanimod hydrochloride 1 mg oral capsules administered to patients with RMS. The DAYBREAK study was conducted at 227 sites in 27 countries in North America, Europe, and South Africa, and New Zealand. Study participants who had completed 1 of the parent trials (Study RPC01-1001, RADIANCE Part A Extension, RADIANCE Part B, or SUNBEAM) were eligible to enroll in DAYBREAK.

Patients in the parent studies who were on placebo, interferon beta-1a 30 mcg, or ozanimod 0.5 mg switched to ozanimod 1 mg while those on ozanimod 1 mg continued with the same treatment. All patients received a daily oral dose for the study duration after the dose-escalation period, where applicable.

Due to the study design, patients were neither randomized nor blinded to the treatment.

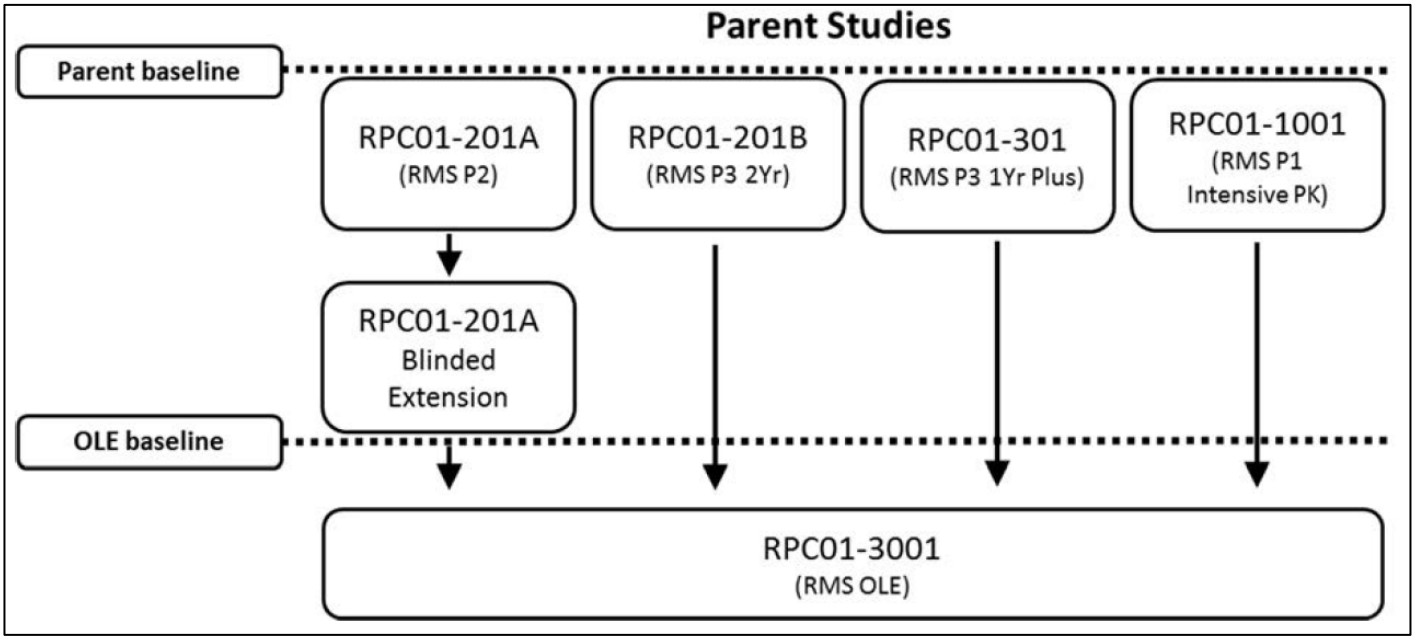
Populations

Patients with RMS were eligible to participate in DAYBREAK according to the enrolment criteria and completion of 1 of the parent studies. Figure 16 illustrates how eligible patients transitioned from the parent studies to the OLE study.

RPC01-1001 was a phase I, randomized, open-label, intensive, pharmacokinetic, 12-week study of patients with RMS in which patients were randomized to receive either ozanimod 0.5 mg or ozanimod 1 mg. The last patient visit was made on October 20, 2017. The RADIANCE Part A Extension was a blinded extension of the phase II, randomized, double-blind, parallel-group, placebo-controlled RADIANCE Part A study, in which patients were randomized to receive placebo, ozanimod 0.5 mg, or ozanimod 1 mg. The placebo-controlled phase lasted 24 weeks and the extension continued for up to an additional 96 weeks. During the extension study, placebo-treated patients were randomized 1:1 to receive either ozanimod 0.5 mg or ozanimod 1 mg while those treated with ozanimod continued with their assigned dose. The placebo-controlled period ended on April 13, 2014, while the extension phase continued until the OLE study became available for enrolment.

Its last patient visit was on May 11, 2016. RADIANCE Part B and SUNBEAM are the pivotal studies that met the inclusion criteria of this review protocol and have been summarized in previous sections.

Figure 16: Parent Studies and OLE Study



OLE = open-label study; RMS = relapsing multiple sclerosis; RPC01-201A = RADIANCE Part A; RPC01-201B = RADIANCE Part B; RPC01-301 = SUNBEAM; RPC01-3001 = DAYBREAK.

Source: Clinical Study Report for DAYBREAK.[44]

Patient eligibility criteria included not having a condition that would require withdrawal from 1 of the parent studies, not having conditions requiring treatment with a prohibited concomitant medication, not receiving treatment with CYP2C8 inhibitors or inducers at baseline or monoamine oxidase inhibitors 2 weeks prior to baseline, the ability to provide written informed consent, and compliance with the schedule of protocol assessments, and the use of contraception.

Table 27 summarizes the patient characteristics for DAYBREAK. In brief, 2,494 patients were included, of which 66.9% were female, 89.1% had RRMS, 99.2% were White, and 90.1% were from the Eastern European region. The mean age of the study population was 37.7 years (SD = 9.22; median = 38.0; range = 19 to 57) while the mean EDSS score at the OLE baseline was 2.56 (SD = 1.293; median = 2.00; range = 0.0 to 7.5).

Table 28 summarizes the MRI characteristics at the parent and OLE study baselines. At the OLE baseline, the mean GdE lesion count was 0.5 (SD = 1.8; median = 0.0; range = 0 to 46) and the mean T2 lesion count was 58.0 (SD = 41.63; median = 48.0; range = 0 to 313).

Table 29 summarizes the MS treatment history for the study population. In general, 771 patients (30.9%) had previously been treated for MS, while 706 (28.3%) had been treated with a DMT.

Table 27: Summary of Baseline Characteristics of DAYBREAK (OLE ITT Population)

	Pooled parent treatment groups					All patients (N = 2,494)
	Placebo → ozanimod 0.5 mg → ozanimod 1 mg (N = 37)	Placebo → ozanimod 1 mg → ozanimod 1 mg (N = 35)	Interferon beta-1a 30 mcg → ozanimod 1 mg (N = 740)	Ozanimod 0.5 mg → ozanimod 1 mg (N = 838)	Ozanimod 1 mg → ozanimod 1 mg (N = 844)	
Demographics						
Sex, n (%)						
Female	27 (73.0)	27 (77.1)	500 (67.6)	568 (67.8)	546 (64.7)	1,668 (66.9)
Age at OLE baseline (years)						
Mean (SD)	43.5 (8.21)	39.5 (8.53)	37.4 (9.06)	37.7 (9.24)	37.6 (9.32)	37.7 (9.22)
Median (range)	44.0 (23 to 57)	40.0 (22 to 53)	37.0 (19 to 57)	37.5 (19 to 57)	37.0 (19 to 57)	38.0 (19 to 57)
Race, n (%)						
White	37 (100)	35 (100)	738 (99.7)	826 (98.6)	838 (99.3)	2,474 (99.2)
Black	0	0	1 (0.1)	7 (0.8)	6 (0.7)	14 (0.6)
Asian	0	0	0	3 (0.4)	0	3 (0.1)
Other	0	0	1 (0.1)	2 (0.2)	0	3 (0.1)
Weight (kg), mean (SD)	70.20 (15.123)	69.46 (16.501)	70.14 (16.173)	70.27 (15.922)	70.58 (16.421)	70.32 (16.152)
BMI (kg/m^2), mean (SD)	24.60 (4.310)	24.30 (4.850)	24.22 (4.763)	24.39 (4.842)	24.37 (4.873)	24.34 (4.819)
Region						
North America	1 (2.7)	2 (5.7)	13 (1.8)	32 (3.8)	33 (3.9)	81 (3.2)
Canada	0	0	0	0	0	0
US	1 (2.7)	2 (5.7)	13 (1.8)	32 (3.8)	33 (3.9)	81 (3.2)
Western Europe	2 (5.4)	3 (8.6)	45 (6.1)	44 (5.3)	50 (5.9)	144 (5.8)
Eastern Europe	34 (91.9)	30 (85.7)	675 (91.2)	755 (90.1)	752 (89.1)	2,246 (90.1)
South Africa	0	0	5 (0.7)	5 (0.6)	6 (0.7)	16 (0.6)
New Zealand	0	0	2 (0.3)	2 (0.2)	3 (0.4)	7 (0.3)
Multiple sclerosis disease history						
Age at MS symptom onset (years)						
Mean (SD)	31.3 (8.67)	29.0 (9.26)	29.5 (8.78)	29.6 (9.10)	29.2 (8.74)	29.5 (8.88)
Median (range)	29.0 (16 to 50)	28.0 (16 to 49)	28.0 (10 to 53)	29.0 (9 to 54)	28.0 (9 to 52)	28.0 (9 to 54)
Age at MS diagnosis (years)						
Mean (SD)	35.2 (8.13)	32.9 (8.29)	32.5 (8.90)	32.9 (9.26)	32.4 (9.07)	32.6 (9.06)
Median (range)	37.0 (20 to 51)	34.0 (17 to 49)	32.0 (13 to 55)	32.0 (15 to 55)	31.0 (13 to 55)	32.0 (13 to 55)
Years since MS diagnosis						
Mean (SD)	5.2 (5.29)	3.5 (5.15)	3.7 (4.54)	3.5 (4.45)	3.8 (4.70)	3.7 (4.59)
Median (range)	4.0 (0 to 15)	1.0 (0 to 20)	1.7 (0 to 28)	1.6 (0 to 33)	1.9 (0 to 31)	1.7 (0 to 33)
Type of MS						
RRMS	0	0	732 (98.9)	745 (88.9)	745 (88.3)	2,222 (89.1)
SPMS	0	0	2 (0.3)	2 (0.2)	0	4 (0.2)

	Pooled parent treatment groups					All patients (N = 2,494)
	Placebo → ozanimod 0.5 mg → ozanimod 1 mg (N = 37)	Placebo → ozanimod 1 mg → ozanimod 1 mg (N = 35)	Interferon beta-1a 30 mcg → ozanimod 1 mg (N = 740)	Ozanimod 0.5 mg → ozanimod 1 mg (N = 838)	Ozanimod 1 mg → ozanimod 1 mg (N = 844)	
PRMS	0	0	6 (0.8)	9 (1.1)	15 (1.8)	30 (1.2)
Missing	37 (100)	35 (100)	0	82 (9.8)	84 (10.0)	238 (9.5)
EDSS score at parent baseline						
Mean (SD)	2.66 (1.179)	2.89 (1.340)	2.53 (1.152)	2.58 (1.174)	2.57 (1.142)	2.57 (1.160)
Median (range)	2.50 (1.0 to 5.0)	2.50 (1.0 to 5.0)	2.50 (0.0 to 5.0)	2.50 (0.0 to 6.0)	2.50 (0.0 to 5.0)	2.50 (0.0 to 6.0)
0 to 2.0	15 (40.5)	12 (34.3)	351 (47.4)	399 (47.6)	395 (46.8)	1,172 (47.0)
2.5 to 3.5	14 (37.8)	13 (37.1)	271 (36.6)	276 (32.9)	306 (36.3)	880 (35.3)
4.0 to 5.0	8 (21.6)	10 (28.6)	118 (15.9)	161 (19.2)	143 (16.9)	440 (17.6)
> 5.0	0	0	0	2 (0.2)	0	2 (<0.1)
EDSS score at OLE baseline						
Mean (SD)	2.85 (1.581)	3.00 (1.680)	2.52 (1.274)	2.57 (1.279)	2.56 (1.289)	2.56 (1.293)
Median (range)	2.50 (1.0 to 6.0)	3.00 (0.0 to 6.0)	2.00 (0.0 to 6.5)	2.50 (0.0 to 6.5)	2.00 (0.0 to 7.5)	2.00 (0.0 to 7.5)
0 to 2.0	17 (45.9)	14 (40.0)	374 (50.5)	416 (49.6)	431 (51.1)	1,252 (50.2)
2.5 to 3.5	9 (24.3)	11 (31.4)	242 (32.7)	273 (32.6)	264 (31.3)	799 (32.0)
4.0 to 5.0	7 (18.9)	5 (14.3)	100 (13.5)	120 (14.3)	119 (14.1)	351 (14.1)
>5.0	4 (10.8)	5 (14.3)	24 (3.2)	29 (3.5)	30 (3.6)	92 (3.7)
Number of relapses within the last 12 months prior to screening for parent study						
Mean (SD)	1.3 (0.70)	1.4 (0.65)	1.3 (0.55)	1.3 (0.64)	1.3 (0.57)	1.3 (0.60)
Median (range)	1.0 (0, 3)	1.0 (0, 3)	1.0 (0, 4)	1.0 (0, 5)	1.0 (0, 4)	1.0 (0, 5)
Number of relapses within the last 24 months prior to screening for parent study						
Mean (SD)	2.0 (1.25)	1.7 (0.78)	1.7 (0.87)	1.8 (0.96)	1.7 (0.84)	1.7 (0.90)
Median (range)	2.0 (1 to 6)	2.0 (1 to 3)	2.0 (1 to 6)	2.0 (1 to 14)	2.0 (1 to 5)	2.0 (1 to 14)

BMI = body mass index; ITT = intention-to-treat; MS = multiple sclerosis; OLE = open-label extension; PRMS = progressive relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SPMS = secondary progressive multiple sclerosis.

Note: Data are taken from parent study baseline information, unless otherwise stated.

Source: Clinical Study Report for DAYBREAK.[44]

Table 28: Summary of MRI Characteristics at Parent or OLE Baselines of DAYBREAK (OLE ITT Population)

	Pooled parent treatment groups					All patients (N = 2,494)
	Placebo → ozanimod 0.5 mg → ozanimod 1 mg (N = 37)	Placebo → ozanimod 1 mg → ozanimod 1 mg (N = 35)	Interferon beta-1a 30 mcg → ozanimod 1 mg (N = 740)	Ozanimod 0.5 mg → ozanimod 1 mg (N = 838)	Ozanimod 1 mg → ozanimod 1 mg (N = 844)	
GdE lesion count at parent baseline						
Mean (SD)	1.3 (2.83)	0.6 (1.37)	1.7 (3.31)	1.6 (3.05)	1.6 (3.05)	1.6 (3.11)
Median (range)	0.0 (0, 11)	0.0 (0, 6)	0.0 (0, 22)	0.0 (0, 26)	0.0 (0, 20)	0.0 (0, 26)
GdE lesion count at OLE baseline						
Mean (SD)	0.2 (1.32)	0.1 (0.40)	0.9 (2.70)	0.4 (1.25)	0.3 (1.15)	0.5 (1.80)
Median (range)	0.0 (0, 8)	0.0 (0, 2)	0.0 (0, 46)	0.0 (0, 15)	0.0 (0, 18)	0.0 (0, 46)
GdE lesion volume (cm^3) at parent baseline						
Mean (SD)	10.296 (8.319)	11.257 (9.959)	12.472 (14.074)	11.815 (13.833)	11.728 (13.248)	11.951 (13.595)
Median (range)	7.871 (0.781 to 30.695)	9.348 (0.057 to 39.620)	7.359 (0.057 to 99.706)	6.932 (0.000 to 105.251)	7.155 (0.000 to 131.626)	7.147 (0.000 to 131.626)
GdE lesion volume (cm^3) at OLE baseline						
Mean (SD)	10.517 (8.910)	11.246 (10.230)	12.976 (14.409)	12.104 (14.061)	11.875 (13.355)	12.250 (13.823)
Median (range)	7.113 (0.564 to 38.959)	8.309 (0.072 to 42.999)	8.238 (0.040 to 101.986)	6.940 (0.000 to 102.650)	7.123 (0.000 to 132.461)	7.265 (0.000 to 132.461)
T2 lesion count at parent baseline						
Mean (SD)	50.6 (38.38)	58.5 (38.94)	50.8 (35.56)	51.2 (35.57)	51.4 (36.46)	51.2 (35.94)
Median (range)	36.0 (5 to 191)	49.0 (3 to 153)	42.0 (1 to 202)	44.0 (0 to 222)	43.0 (0 to 222)	43.0 (0 to 222)
T2 lesion count at OLE baseline						
Mean (SD)	67.7 (62.81)	70.4 (58.40)	60.0 (43.18)	57.2 (40.20)	56.2 (39.49)	58.0 (41.63)
Median (range)	45.0 (6 to 297)	52.0 (3 to 313)	49.0 (1 to 232)	48.0 (0 to 267)	47.0 (0 to 226)	48.0 (0 to 313)
T2 lesion volume (cm^3) at parent baseline						
Mean (SD)	10.296 (8.319)	11.257 (9.959)	12.472 (14.074)	11.815 (13.833)	11.728 (13.248)	11.951 (13.595)
Median (range)	7.871 (0.781 to 30.695)	9.348 (0.057 to 39.620)	7.359 (0.057 to 99.706)	6.932 (0.000 to 105.251)	7.155 (0.000 to 131.626)	7.147 (0.000 to 131.626)
T2 lesion volume (cm^3) at OLE baseline						
Mean (SD)	10.517 (8.910)	11.246 (10.230)	12.976 (14.409)	12.104 (14.061)	11.875 (13.355)	12.250 (13.823)
Median (range)	7.113 (0.564 to 38.959)	8.309 (0.072 to 42.999)	8.238 (0.040 to 101.986)	6.940 (0.000 to 102.650)	7.123 (0.000 to 132.461)	7.265 (0.000 to 132.461)

GdE = gadolinium-enhanced; ITT = intention-to-treat; OLE = open-label extension; SD = standard deviation.

Source: Clinical Study Report for DAYBREAK.[44]

Table 29: Summary of MS Treatment History (OLE ITT Population)

	Pooled parent treatment groups					
	Placebo → ozanimod 0.5 mg → ozanimod 1 mg (N = 37)	Placebo → ozanimod 1 mg → ozanimod 1 mg (N = 35)	Interferon beta-1a 30 mcg → ozanimod 1 mg (N = 740)	Ozanimod 0.5 mg → ozanimod 1 mg (N = 838)	Ozanimod 1 mg → ozanimod 1 mg (N = 844)	All patients (N = 2,494)
Patients with any prior treatment for MS, n (%)[a]	15 (40.5)	11 (31.4)	236 (31.9)	258 (30.8)	251 (29.7)	771 (30.9)
Patients previously treated with a DMT, n (%)[b]	15 (40.5)	10 (28.6)	220 (29.7)	237 (28.3)	224 (26.5)	706 (28.3)
Glatiramer acetate	4 (10.8)	4 (11.4)	77 (10.4)	110 (13.1)	82 (9.7)	277 (11.1)
Interferon (unspecified)	1 (2.7)	0	0	3 (0.4)	1 (0.1)	5 (0.2)
Interferon beta-1a	7 (18.9)	7 (20.0)	84 (11.4)	80 (9.5)	81 (9.6)	259 (10.4)
Interferon beta-1b	3 (8.1)	2 (5.7)	64 (8.6)	57 (6.8)	66 (7.8)	192 (7.7)
Daclizumab	0	0	5 (0.7)	1 (0.1)	4 (0.5)	10 (0.4)
Dimethyl fumarate	0	0	1 (0.1)	1 (0.1)	3 (0.4)	5 (0.2)
Peginterferon beta-1a	2 (5.4)	0	12 (1.6)	9 (1.1)	10 (1.2)	33 (1.3)
Teriflunomide	0	0	10 (1.4)	11 (1.3)	12 (1.4)	33 (1.3)
Mitoxantrone hydrochloride	NR	NR	NR	NR	NR	NR
Patients previously treated with corticosteroids, n (%)	33 (89.2)	35 (100)	680 (91.9)	751 (89.6)	763 (90.4)	2,262 (90.7)
Patients with other MS medications prior to study treatment, n (%)	2 (5.4)	1 (2.9)	29 (3.9)	29 (3.5)	44 (5.2)	105 (4.2)

DMT = disease-modifying therapy; ITT = intent-to-treat; MS = multiple sclerosis; NR = not reported; OLE = open-label extension.

[a] Treatment history information was carried forward from the parent study and reflected the baseline information in parent studies. A history of previous treatments for MS was documented for the 2 years prior to the parent study.

[b] For disease-modifying therapy, reported terms interferon or interferon beta were categorized as interferon (unspecified); glatiramer as glatiramer acetate; and peginterferon as peginterferon beta-1a.

Source: Clinical Study Report for DAYBREAK.[44]

Interventions

All patients began study treatment on a 7-day dose-escalation regimen of ozanimod 0.25 mg from days 1 to 4, ozanimod 0.5 mg from days 5 to 7, and ozanimod 1 mg from day 8 until study completion. Patients from the RADIANCE Part A Extension or RPC01-1001 did not undergo the dose-escalation regimen if the time between their last dose of ozanimod in either of the previous 2 studies and the first dose in the OLE was less than 14 days.

In the ITT population, 82.5% of patients were taking at least 1 concomitant medication and were required to document the dose, date of administration, and reason for use in an electronic case-report form. The most common included sex hormones and modulators

(28.2%), analgesics (27.5%), anti-inflammatory and antirheumatics (25.7%), antibacterials (21.4%), vitamins (19.8%), and corticosteroids (19.7%).

The following concomitant medications were prohibited during the trial and the 28-day safety follow-up:

- approved or unapproved disease-modifying MS medications
- class Ia or III anti-arrythmia treatments, others that are known to prolong PR interval unless approved by the sponsor's representative
- systemic corticosteroid therapy or adrenocorticotropic hormone, except for treatment of relapse as outlined in the protocol
- live or live attenuated vaccines
- intravenous immunoglobulin or plasmapheresis
- immunosuppressive drugs that may deplete lymphocytes
- inhibitors of breast cancer resistance protein or monoamine oxidase, and inhibitors or inducers of CYP2C8.

Outcomes

The primary outcome measured in DAYBREAK was characterization of the long-term safety and tolerability of ozanimod 1 mg in patients with RMS. The secondary outcome was an investigation of the long-term efficacy of the study medication in the same population.

The efficacy end points explored in DAYBREAK include:

- primary efficacy analysis: ARR during the DAYBREAK study in the OLE ITT population for relapse confirmed by the treating investigator to meet the protocol definition of relapse
- supplementary efficacy analyses: ARRs of the phase III ITT populations (1) between the parent study to the OLE study, and (2) over time throughout the parent and OLE studies
- other efficacy analyses: time to first relapse; MRI outcomes (e.g., hyperintense T2-weighted brain lesions, GdE brain lesions); disability progression or improvement as defined by a sustained worsening of 1.0 point or more in an EDSS score from the OLE baseline, confirmed after 3 and 6 months; and changes in MSFC and MSQOL-54 scores.

The following harms outcomes were analyzed in DAYBREAK:

- incidence, relationship, and type of AEs
- SAEs, AEs leading to study withdrawal or temporary study drug discontinuation
- AEs of special interest (bradycardia, heart-conduction abnormalities, pulmonary effects, macular edema, hepatic effects, serious or opportunistic infections, and malignancy).

Statistical Analysis

Descriptive statistics were used to describe the number of patients (n), mean, SD, median, and range for continuous data. Categorical variables were recorded as counts and percentages. Two-sided 95% CIs were calculated, unless otherwise stated, and no statistical hypothesis testing was performed.

The adjusted ARR was calculated for the OLE ITT population using a negative binomial regression model with the same covariates as in the parent phase III studies.

Other efficacy end points, including percent change in brain volume, number of new or enlarging hyperintense T2-weighted brain MRI lesions, and number of GdE brain MRI lesions, were summarized by visit using descriptive statistics or counts and percentages as appropriate.

Analysis Populations

The OLE ITT population included all patients enrolled in the DAYBREAK study from parent studies, RPC01-1001, RADIANCE Part A Extension, RADIANCE Part B, and SUNBEAM who received at least 1 dose of open-label ozanimod.

The OLE safety population included all patients enrolled in the OLE study who received at least 1 dose of open-label ozanimod; i.e., the OLE ITT population.

The phase III ITT population included all patients enrolled in the OLE study from the phase III parent studies (RADIANCE Part B and SUNBEAM) who were randomized and received the investigational drug in the respective parent studies.

The phase III safety population included all patients enrolled in the OLE study from the phase III parent studies (RADIANCE Part B and SUNBEAM) who received at least 1 dose of the investigational drug in the parent studies.

Patient Disposition

Table 30 presents the detailed patient disposition for DAYBREAK. Of the 2,639 patients who completed the parent studies, 2,495 (84.6%) consented to participation in the OLE. Of the enrolled participants, 2,323 (93.1%) were ongoing while 172 (6.9%) had discontinued the study at the data cut-off date (June 30, 2018). Voluntary withdrawal (n = 91, 3.6%) from DAYBREAK was the most common reason for discontinuation, while others stopped due to AEs (n = 25, 1.0%), lack of efficacy (n = 24, 1.0%), other reasons (n = 13, 0.5%), physician decision (n = 4, < 0.002%), and use of prohibited medication (n = 1, < 0.0005%). Three deaths occurred; 2 during the study and 1 after the patient discontinued treatment. Twelve participants were lost to follow-up.

Table 30: Patient Disposition for DAYBREAK OLE Study

	Pooled parent treatment groups					All patients[a]
	Placebo → ozanimod 0.5 mg → ozanimod 1 mg	Placebo → ozanimod 1 mg → ozanimod 1 mg	Interferon beta-1a 30 mcg → ozanimod 1 mg	Ozanimod 0.5 mg → ozanimod 1 mg	Ozanimod 1 mg → ozanimod 1 mg	
Number of patients randomized in parent studies	41	42	891	994	975	2,948
Randomized and completed parent study, n (%)[b]	37 (90.2)	36 (85.7)	788 (88.4)	885 (89.0)	893 (91.6)	2,639 (89.5)
Consented to OLE study, n (%)[b]	37 (90.2)	35 (83.3)	741 (83.2)	838 (84.3)	844 (86.6)	2,495 (84.6)

	Pooled parent treatment groups					
	Placebo → ozanimod 0.5 mg → ozanimod 1 mg	Placebo → ozanimod 1 mg → ozanimod 1 mg	Interferon beta-1a 30 mcg → ozanimod 1 mg	Ozanimod 0.5 mg → ozanimod 1 mg	Ozanimod 1 mg → ozanimod 1 mg	All patients[a]
Ongoing at time of data cut-off, n (%)[c]	36 (97.3)	33 (94.3)	685 (92.4)	774 (92.4)	795 (94.2)	2,323 (93.1)
Discontinued study, n (%)[c]	1 (2.7)	2 (5.7)	56 (7.6)	64 (7.6)	49 (5.8)	172 (6.9)
AE	0	0	8 (1.1)	10 (1.2)	7 (0.8)	25 (1.0)
Lack of efficacy	0	0	4 (0.5)	14 (1.7)	6 (0.7)	24 (1.0)
Protocol violation	0	0	0	0	1 (0.1)	1 (< 0.1)
Lost to follow-up	0	0	4 (0.5)	3 (0.4)	5 (0.6)	12 (0.5)
Death	0	0	0	1 (0.1)	1 (0.1)	2 (< 0.1)
Voluntary withdrawal	1 (2.7)	2 (5.7)	34 (4.6)	32 (3.8)	22 (2.6)	91 (3.6)
Physician decision	0	0	1 (0.1)	1 (0.1)	2 (0.2)	4 (0.2)
Other	0	0	5 (0.7)	3 (0.4)	5 (0.6)	13 (0.5)
OLE ITT, n (%)[c]	37 (100)	35 (100)	740 (99.9)	838 (100.0)	844 (100.0)	2,494 (100.0)
OLE safety, n (%)[c,d]	37 (100)	35 (100)	736 (99.3)	840 (100.2)	846 (100.2)	2,494 (100.0)
Phase II ITT population, n (%)	NA	NA	741 (NA)	756 (NA)	760 (NA)	2,257 (NA)
Phase III safety population, n (%)	NA	NA	737 (NA)	758 (NA)	762 (NA)	2,257 (NA)

AE = adverse event; ITT = intention-to-treat; NA = not applicable; OLE = open-label extension.

[a] Five patients from the RPC01-201A placebo group did not continue into the double-blind extension period (i.e., placebo patients were not re-randomized to ozanimod 0.5 mg or ozanimod 1 mg) and are included in the column count for All patients.

[b] Denominators for percentages are the number of patients randomized in the parent study.

[c] Denominators for percentages are the number of patients enrolled in the OLE.

[d] Patients are included in the treatment group based on the treatment that they actually received in the parent studies.

Source: Clinical Study Report for DAYBREAK.[44]

Exposure to Study Treatments

As of the data cut-off date, 2,494 patients made up the ITT and safety populations for DAYBREAK and had a mean exposure of 19.0 months (SD = 4.2; median = 19.5; range = 0.03 to 32.5) to ozanimod 1 mg.

Efficacy

The results for the ARR are presented in Table 31. Most patients (2,046, 82.0%) had no confirmed relapses while 317 (12.7%) had a single relapse, 97 (3.9%) had 2 relapses, 28 (1.1%) had 3, and 6 patients (0.2%) had 4 or more during the OLE study. The adjusted ARR was 0.124 (95% CI, 0.101 to 0.152).

Table 31: Annualized Relapse Rate During DAYBREAK OLE – Negative Binomial Regression (ITT Population)

	Pooled parent treatment groups					All patients (N = 2,494)
	Placebo → ozanimod 0.5 mg → ozanimod 1 mg (N = 37)	Placebo → ozanimod 1 mg → ozanimod 1 mg (N = 35)	Interferon beta-1a 30 mcg → ozanimod 1 mg (N = 740)	Ozanimod 0.5 mg → ozanimod 1 mg (N = 838)	Ozanimod 1 mg → ozanimod 1 mg (N = 844)	
Patients with confirmed relapse, n (%)						
0	28 (75.7)	32 (91.4)	609 (82.3)	684 (81.6)	693 (82.1)	2,046 (82.0)
1	7 (18.9)	2 (5.7)	90 (12.2)	111 (13.2)	107 (12.7)	317 (12.7)
2	2 (5.4)	0	32 (4.3)	30 (3.6)	33 (3.9)	97 (3.9)
3	0	1 (2.9)	9 (1.2)	10 (1.2)	8 (0.9)	28 (1.1)
≥ 4	0	0	0	3 (0.4)	3 (0.4)	6 (0.2)
Adjusted ARR (95% CI)[a]	0.117 (0.053 to 0.255)	0.057 (0.021 to 0.157)	0.123 (0.095 to 0.158)	0.129 (0.101 to 0.164)	0.126 (0.099 to 0.161)	0.124 (0.101 to 0.152)

ARR = annualized relapse rate; CI, confidence interval; ITT = intent-to-treat; OLE = open-label extension.

[a] Based on the negative binomial regression model with parent treatment group, adjusted for region (Eastern Europe versus rest of world), age at parent baseline, and the parent baseline number of gadolinium-enhanced lesions. The natural log transformation of time on treatment was used as an offset term to adjust for patients having different exposure times.

Source: Clinical Study Report for DAYBREAK.[44]

The total number of relapses and adjusted ARR for each year of the first 5 years are found in Table 32. As of the data cut-off, open-label treatment with ozanimod led to sustained reductions in relapse rates.

Table 32: Summary of Annualized Relapse Rate Over Time During the Parent Study and DAYBREAK OLE Studies (Phase III ITT Populations)

Study period[a]	Year 0 to 1	Year 1 to 2	Year 2 to 3	Year 3 to 4	Year 4 to 5	Year 0 to data cut-off
Interferon beta-1a 30 mcg → ozanimod 1 mg						
Number of patients who entered the period	740	704	34	1	0	740
Number of relapses	126	56	0	0	0	182
Adjusted ARR (95% CI)[b]	0.146 (0.113 to 0.188)	0.114 (0.080 to 0.161)	NE (NE to NE)	NE (NE to NE)	NE (NE to NE)	0.130 (0.104 to 0.163)
Ozanimod 0.5 mg → ozanimod 1 mg						
Number of patients who entered the period	756	756	743	380	39	756
Number of relapses	179	124	111	23	0	437
Adjusted ARR (95% CI)[b]	0.202 (0.160 to 0.255)	0.139 (0.104 to 0.185)	0.131 (0.093 to 0.184)	NE (NE to NE)	NE (NE to NE)	0.155 (0.128 to 0.188)

Study period[a]	Year 0 to 1	Year 1 to 2	Year 2 to 3	Year 3 to 4	Year 4 to 5	Year 0 to data cut-off
Ozanimod 1 mg → ozanimod 1 mg						
Number of patients who entered the period	760	760	751	398	44	760
Number of relapses	149	114	107	30	1	401
Adjusted ARR (95% CI)[b]	0.169 (0.133 to 0.214)	0.129 (0.097 to 0.171)	0.124 (0.088 to 0.174)	NE (NE to NE)	NE (NE to NE)	0.141 (0.117 to 0.171)

ARR = annualized relapse rate; CI, confidence interval; ITT = intention-to-treat; NE = not estimable; OLE = open-label extension.

[a] Study period: from start of ozanimod exposure on day 1 through end of year 1, end of year 1 to end of year 2, and so on.

[b] Based on the negative binomial regression model with parent treatment group, adjusted for region (Eastern Europe versus rest of world), age at parent baseline, and the parent baseline number of gadolinium-enhanced lesions. The natural log transformation of time on treatment was used as an offset term to adjust for patients having different exposure times.

Source: Clinical Study Report of DAYBREAK.[44]

Supplementary efficacy outcomes are summarized in Table 33.

The median time to first confirmed relapse was not reached during the study period. However, for the 25th percentile, the time was shortest in the interferon beta-1a 30 mcg → ozanimod 1 mg group (413.0 days; 95% CI, 313.0 to 516.0), followed by the ozanimod 0.5 mg → ozanimod 1 mg group (603.0 days; 95% CI, 464.0 t, 748.0), and last, the ozanimod 1 mg → ozanimod 1 mg group (750.0 days; 95% CI, 564.0 to 944.0). The median time to onset of disability progression could not be estimated for the phase III ITT populations due to low rates of disease progression.

The mean (SD) number of new or enlarging T2 lesions at 24 months from parent study baseline were 10.4 (17.69), 6.4 (11.10), and 5.6 (11.88) for interferon beta-1a, ozanimod 0.5 mg, and ozanimod 1.0 mg, respectively (Table 33).

At 24 months from the OLE baseline, mean (SD) values for new T2 lesions were 2.3 (3.51), 2.6 (6.56), and 2.5 (5.39) for interferon beta-1a → ozanimod 1 mg, ozanimod 0.5 mg → ozanimod 1 mg, and ozanimod 1.0 mg → ozanimod 1 mg, respectively. The mean (SD) GdE MRI lesion counts at 24 months from the parent study baseline were 0.9 (2.46), 0.4 (1.31), and 0.3 (1.21) for interferon beta-1a, ozanimod 0.5 mg, and ozanimod 1.0 mg, respectively, compared to 0.1 (0.45), 0.3 (0.84), and 0.1 (0.42) at 24 months from the OLE baseline for interferon beta-1a → ozanimod 1 mg, ozanimod 0.5 mg → ozanimod 1 mg, and ozanimod 1.0 mg → ozanimod 1 mg, respectively.

The mean (SD) percent changes in brain volume at 24 months from the parent baseline were −1.085 (1.008), −0.763 (0.781), and −0.858 (0.930) for interferon beta-1a, ozanimod 0.5 mg, and ozanimod 1.0 mg, respectively, and −0.224 (0.917), −0.218 (0.937), and −0.178 (0.968) at 24 months from the OLE baseline for interferon beta-1a → ozanimod 1 mg, ozanimod 0.5 mg → ozanimod 1 mg, and ozanimod 1.0 mg → ozanimod 1 mg, respectively.

Table 33: Summary of Supplementary Efficacy Outcomes for Parent and DAYBREAK OLE Studies (Phase III ITT Population)

	Interferon beta-1a 30 mcg → ozanimod 1 mg	Ozanimod 0.5 mg → ozanimod 1 mg	Ozanimod 1 mg → ozanimod 1 mg
Number of patients	741	756	760
Time to first confirmed relapse, days			
Patients, n (%)	278 (37.5)	249 (32.9)	234 (30.9)
25th percentile, days (95% CI)	413.0 (313.0 to 516.0)	603.0 (464.0 to 748.0)	750.0 (564.0 to 944.0)
Median, days (95% CI)	NE (NE to NE)	NE (NE to NE)	NE (NE to NE)
Time to onset of sustained disability progression – 3-month confirmation, days			
Patients, n (%)	96 (13.0)	94 (12.4)	101 (13.3)
Median (95% CI)	NE (NE to NE)	NE ((NE to NE)	NE (NE to NE)
Time to onset of sustained disability progression – 6-month confirmation, days			
Patients, n (%)	75 (10.1)	75 (9.9)	87 (11.4)
Median (95% CI)	NE (NE to NE)	NE (NE to NE)	NE (NE to NE)
MRI outcomes			
New or enlarging hyperintense T2 MRI lesion count			
12 months from parent baseline			
Mean (SD)	6.7 (12.29)	4.5 (7.57)	3.8 (7.15)
Median (range)	2.0 (0 to 127)	2.0 (0 to 57)	1.0 (0 to 72)
24 months from parent baseline			
Mean (SD)	10.4 (17.69)	6.4 (11.10)	5.6 (11.88)
Median (range)	4.0 (0 to 105)	2.0 (0 to 86)	2.0 (0 to 103)
12 months from OLE baseline			
Mean (SD)	2.3 (4.42)	1.8 (4.16)	2.1 (5.37)
Median (range)	1.0 (0 to 43)	0.0 (0 to 36)	0.0 (0 to 65)
24 months from OLE baseline			
Mean (SD)	2.3 (3.51)	2.6 (6.56)	2.5 (5.39)
Median (range)	1.0 (0 to 16)	0.0 (0 to 31)	0.0 (0 to 25)
GdE MRI lesion count			
Parent baseline			
Mean (SD)	1.7 (3.31)	1.6 (3.15)	1.6 (3.07)
Median (range)	0.0 (0 to 22)	0.0 (0 to 26)	0.0 (0 to 20)
12 months from parent baseline			
Mean (SD)	0.7 (2.57)	0.4 (1.03)	0.2 (0.89)
Median (range)	0.0 (0 to 46)	0.0 (0 to 12)	0.0 (0 to 11)
24 months from parent baseline			
Mean (SD)	0.9 (2.46)	0.4 (1.31)	0.3 (1.21)
Median (range)	0.0 (0 to 20)	0.0 (0 to 15)	0.0 (0 to 14)
OLE baseline			
Mean (SD)	0.9 (2.70)	0.4 (1.22)	0.3 (1.20)
Median (range)	0.0 (0 to 46)	0.0 (0 to 15)	0.0 (0 to 18)

	Interferon beta-1a 30 mcg → ozanimod 1 mg	Ozanimod 0.5 mg → ozanimod 1 mg	Ozanimod 1 mg → ozanimod 1 mg
12 months from OLE baseline			
Mean (SD)	0.2 (0.58)	0.2 (1.08)	0.3 (1.29)
Median (range)	0.0 (0 to 8)	0.0 (0 to 20)	0.0 (0 to 26)
24 months from OLE baseline			
Mean (SD)	0.1 (0.45)	0.3 (0.84)	0.1 (0.42)
Median (range)	0.0 (0 to 2)	0.0 (0 to 5)	0.0 (0 to 2)
Normalized brain volume (cm^3) percent change			
Parent baseline			
Mean (SD)	1,445.803 (78.091)	1,448.978 (74.102)	1,448.330 (77.968)
Median (range)	1,451.163 (1,208.19 to 1,667.70)	1,452.358 (1,195.40 to 1,663.03)	1,451.482 (1,190.84 to 1,660.72)
12 months from parent baseline			
Mean (SD)	−0.613 (0.686)	−0.468 (0.609)	−0.433 (0.668)
Median (range)	−0.540 (−4.60 to 1.98)	−0.425 (−2.97 to 2.08)	−0.390 (−3.33 to 2.08)
24 months from parent baseline			
Mean (SD)	−1.085 (1.008)	−0.763 (0.781)	−0.858 (0.930)
Median (range)	–0.920 (−5.33 to 1.44)	−0.690 (−5.21 t 1.36)	−0.700 (−5.65 to 0.64)
OLE Baseline			
Mean (SD)	1,434.296 (80.592)	1,440.420 (75.405)	1,440.239 (79.238)
Median (range)	1,438.019 (1,176.17 to 1,662.37)	1,442.498 (1,194.21 to 1,654.05)	1,442.636 (1,185.48 to 1,645.57)
12 months from OLE Baseline			
Mean (SD)	−0.260 (0.798)	−0.301 (0.674)	−0.325 (0.656)
Median (range)	−0.275 (−2.79 to 2.51)	−0.310 (−2.68 to 2.70)	−0.350 (−3.47 to 1.97)
24 months from OLE Baseline			
Mean (SD)	−0.224 (0.917)	−0.218 (0.937)	−0.178 (0.968)
Median (range)	−0.240 (−2.13, 1.80)	−0.130 (−3.14 to 1.54)	0.000 (−4.69 to 1.59)

CI = confidence interval; ITT = intent-to-treat; NE = not estimable; OLE = open-label extension; SD = standard deviation.

Source: Clinical Study Report for DAYBREAK.[44]

Harms

Table 34 presents harms data for patients during the DAYBREAK study. Of the 2,494 patients in the OLE safety population, 1,704 (68.3%) experienced an AE. The most common AEs (≥ 5%) were nasopharyngitis (11.7%), headache (8.9%), lymphopenia (8.3%), upper respiratory tract infection (6.8%), and lymphocyte count decrease (6.6%).

A total of 144 patients (5.8%) had at least 1 SAE. The most common SAEs observed in more than 2 patients included acute pyelonephritis (5 patients), appendicitis (4), pneumonia (3) and uterine leiomyoma (5); other SAEs were reported in 1 or 2 patients each.

Thirty patients (1.2%) had AEs that caused them to discontinue ozanimod 1 mg, and 29 (1.2%) withdrew from the study due to AEs. The most common reasons for discontinuation were neoplasms (n = 7, 0.3%) and infections and infestations (n = 5, 0.2%).

There were 3 deaths, of which 2 took place during the study (1 craniocerebral injury and 1 pulmonary embolism), and a third occurred after the patient had permanently discontinued the drug without a specified cause of death.

Adverse events of special interest occurred in 34 patients (1.4%); infections and infestations, neoplasms, and eye disorders were the most common in 11 (0.4%), 8 (0.3%), and 5 (0.2%) patients, respectively.

Table 34: Summary of Harms in the DAYBREAK OLE Study (OLE ITT Population)

	Pooled parent treatment groups					All patients (N = 2,494)
	Placebo → ozanimod 0.5 mg → ozanimod 1 mg (N = 37)	Placebo → ozanimod 1 mg → ozanimod 1 mg (N = 35)	Interferon beta-1a 30 mcg → ozanimod 1 mg (N = 736)	Ozanimod 0.5 mg → ozanimod 1 mg (N = 840)	Ozanimod 1 mg → ozanimod 1 mg (N = 846)	
Number of patients	37	35	736	840	846	2,494
Patients with ≥ 1 adverse event						
n (%)	26 (70.3)	23 (65.7)	516 (70.1)	582 (69.3)	557 (65.8)	1,704 (68.3)
Most common events,[a] n (%)						
Nasopharyngitis	2 (5.4)	7 (20.0)	94 (12.8)	99 (11.8)	89 (10.5)	291 (11.7)
Headache	1 (2.7)	6 (17.1)	65 (8.8)	77 (9.2)	73 (8.6)	222 (8.9)
Lymphopenia	3 (8.1)	5 (14.3)	68 (9.2)	72 (8.6)	58 (6.9)	206 (8.3)
Upper respiratory tract infection	2 (5.4)	4 (11.4)	53 (7.2)	59 (7.0)	51 (6.0)	169 (6.8)
Decreased lymphocyte count	6 (16.2)	1 (2.9)	47 (6.4)	52 (6.2)	59 (7.0)	165 (6.6)
Increased gamma-glutamyl transferase	1 (2.7)	1 (2.9)	44 (6.0)	35 (4.2)	29 (3.4)	110 (4.4)
Back pain	4 (10.8)	1 (2.9)	25 (3.4)	31 (3.7)	33 (3.9)	94 (3.8)
Hypertension	3 (8.1)	1 (2.9)	31 (4.2)	33 (3.9)	22 (2.6)	90 (3.6)
Urinary tract infection	5 (13.5)	2 (5.7)	16 (2.2)	23 (2.7)	29 (3.4)	75 (3.0)
Respiratory tract infection	0	0	21 (2.9)	24 (2.9)	28 (3.3)	73 (2.9)
Bronchitis	0	2 (5.7)	16 (2.2)	27 (3.2)	22 (2.6)	67 (2.7)
Viral respiratory tract infection	0	0	16 (2.2)	26 (3.1)	23 (2.7)	65 (2.6)
Increased alanine aminotransferase	1 (2.7)	0	24 (3.3)	22 (2.6)	9 (1.1)	56 (2.2)
Influenza	0	2 (5.7)	14 (1.9)	24 (2.9)	16 (1.9)	56 (2.2)
Arthralgia	1 (2.7)	1 (2.9)	10 (1.4)	21 (2.5)	22 (2.6)	55 (2.2)
Depression	1 (2.7)	0	20 (2.7)	15 (1.8)	19 (2.2)	55 (2.2)
Anemia	2 (5.4)	2 (5.7)	14 (1.9)	17 (2.0)	15 (1.8)	50 (2.0)
Patients with ≥ 1 serious adverse event						
n (%)	3 (8.1) 1 (2.7)	1 (2.9)	46 (6.3)	53 (6.3)	41 (4.8)	144 (5.8)
Most common events[b], n (%)						
Pyelonephritis acute	0	0	4 (0.5)	1 (0.1)	0	5 (0.2)

	Pooled parent treatment groups					All patients (N = 2,494)
	Placebo → ozanimod 0.5 mg → ozanimod 1 mg (N = 37)	Placebo → ozanimod 1 mg → ozanimod 1 mg (N = 35)	Interferon beta-1a 30 mcg → ozanimod 1 mg (N = 736)	Ozanimod 0.5 mg → ozanimod 1 mg (N = 840)	Ozanimod 1 mg → ozanimod 1 mg (N = 846)	
Appendicitis	0	0	2 (0.3)	1 (0.1)	1 (0.1)	4 (0.2)
Pneumonia	0	0	1 (0.1)	0	2 (0.2)	3 (0.1)
Uterine leiomyoma	0	0	1 (0.1)	3 (0.4)	1 (0.1)	5 (0.2)
Patients with ≥ 1 adverse event leading to permanent discontinuation of study drug						
n (%)	0	0	10 (1.4)	11 (1.3)	9 (1.1)	30 (1.2)
Infections and infestations	0	0	3 (0.4)	0	2 (0.2)	5 (0.2)
Neoplasms (benign, malignant, and unspecified, including cysts and polyps)	0	0	1 (0.1)	4 (0.5)	2 (0.2)	7 (0.3)
Blood and lymphatic system disorders	0	0	1 (0.1)	0	0	1 (< 0.1)
Immune system disorders	0	0	0	1 (0.1)	0	1 (< 0.1)
Psychiatric disorders	0	0	0	1 (0.1)	2 (0.2)	3 (0.1)
Nervous system disorders	0	0	2 (0.3)	0	1 (0.1)	3 (0.1)
Eye disorders	0	0	2 (0.3)	0	0	2 (< 0.1)
Cardiac disorders	0	0	0	0	1 (0.1)	1 (< 0.1)
Respiratory, thoracic, and mediastinal disorders	0	0	0	0	1 (0.1)	1 (< 0.1)
Hepatobiliary disorders	0	0	0	1 (0.1)	0	1 (< 0.1)
Musculoskeletal and connective tissue disorders	0	0	1 (0.1)	9	9	1 (< 0.1)
Investigations (lab measures)	0	0	2 (0.3)	7 (0.8)	0	9 (0.4)
Injury, poisoning, and procedural complications	0	0	1 (0.1)	0	1 (0.1)	2 (< 0.1)
Adverse events leading to study withdrawal						
n (%)	0	0	10 (1.4)	11 (1.3)	8 (0.9)	29 (1.2)
Deaths						
n (%)	0	0	0	2 (0.2)	1 (0.1)	3 (< 0.1)
Cause of death, n (%)						
Multiple craniocerebral injuries	0	0	0	1 (0.1)	0	1 (< 0.1)
Pulmonary embolism	0	0	0	0	1 (0.1)	1 (< 0.1)
Not specified[c]	0	0	0	1 (0.1)	0	1 (< 0.1)
Averse events of special interest						
n (%)	3 (8.1)	0	9 (1.2)	12 (1.4)	10 (1.2)	34 (1.4)
Infections and Infestations						
Herpes zoster	0	0	1 (0.1)	3 (0.4)	2 (0.2)	6 (0.2)

	Pooled parent treatment groups					All patients (N = 2,494)
	Placebo → ozanimod 0.5 mg → ozanimod 1 mg (N = 37)	Placebo → ozanimod 1 mg → ozanimod 1 mg (N = 35)	Interferon beta-1a 30 mcg → ozanimod 1 mg (N = 736)	Ozanimod 0.5 mg → ozanimod 1 mg (N = 840)	Ozanimod 1 mg → ozanimod 1 mg (N = 846)	
Varicella-zoster virus infection	1 (2.7)	0	0	1 (0.1)	0	2 (< 0.1)
Oral herpes	1 (2.7)	0	0	0	0	1 (< 0.1)
Acute pyelonephritis	0	0	0	1 (0.1)	0	1 (< 0.1)
Varicella	0	0	1 (0.1)	0	0	1 (<0.1)
Neoplasms (benign, malignant, and unspecified, including cysts and polyps)						
Basal cell carcinoma	0	0	1 (0.1)	0	1 (0.1)	2 (< 0.1)
Breast cancer	0	0	0	1 (0.1)	0	1 (< 0.1)
Cervix carcinoma	0	0	0	1 (0.1)	0	1 (< 0.1)
Malignant melanoma	0	0	0	0	1 (0.1)	1 (< 0.1)
Metastasis	0	0	1 (0.1)	0	0	1 (< 0.1)
Papillary thyroid cancer	0	0	0	0	1 (0.1)	1 (< 0.1)
Squamous cell carcinoma	1 (2.7)	0	0	0	0	1 (<0.1)
Squamous cell carcinoma of skin	1 (2.7)	0	0	0	0	1 (<0.1)
Uterine cancer	0	0	0	1 (0.1)	0	1 (< 0.1)
Eye disorders						
Macular edema	0	0	3 (0.4)	1 (0.1)	1 (0.1)	5 (0.2)
Cardiac disorders						
Bundle branch block left	0	0	0	0	1 (0.1)	1 (< 0.1)
Investigations						
Increased alanine aminotransferase	0	0	2 (0.3)	2 (0.2)	1 (0.1)	5 (0.2)
Forced expiratory volume decrease	0	0	0	1 (0.1)	1 (0.1)	2 (< 0.1)
Increased aspartate aminotransferase	0	0	0	1 (0.1)	0	1 (< 0.1)
Forced vital capacity decreased	0	0	0	0	1 (0.1)	1 (< 0.1)
Increased transaminases	0	0	0	1 (0.1)	0	1 (< 0.1)

ITT = intention-to-treat; OLE = open-label extension.

[a] Frequency equal to or greater than 2% of patients.

[b] Frequency greater than 2 patients.

[c] A serious adverse event of pancreatic carcinoma metastatic was reported for patient prior to discontinuing study drug.

Source: Clinical Study Report for DAYBREAK.[44]

Critical Appraisal

Internal Validity

The OLE study had several limitations imposed by the overall design. The lack of a randomized comparison group to provide context and control for potential confounders and the open-label design may have influenced the perception of improvement by patients and clinicians. Specific limitations to the DAYBREAK study include the lack of a group that would have been maintained on interferon beta-1a, while another would have switched to ozanimod. This makes it difficult to obtain high-quality information on the benefits of switching from interferon beta-1a to ozanimod. As part of the eligibility criteria for the OLE study, patients had to complete 1 of the parent studies, potentially allowing for selection bias. [redacted] Additionally, there was potential for survival bias because any patients who discontinued the parent studies due to AEs were excluded. This could result in the enrolment of more patients who were better able to tolerate ozanimod and possibly fewer AEs being reported. Any lack of follow-up after discontinuing DAYBREAK could mean that important long-term safety data are also missing. Of the OLE ITT population, 89.1% had a confirmed diagnosis of RRMS, which is the population in which ozanimod is indicated. Data from MRI scans for 12 and 24 months from OLE baseline were reported, although the mean treatment exposure time was only 19.0 months (SD = 4.2; median = 19.5; range = 0.03 to 32.5). Although changes in EDSS, MSFC, and MSQOL-54 scores were listed as exploratory efficacy end points for DAYBREAK, no results were available, and consequently, information on long-term MS-related disability and quality-of-life outcomes are unknown.

External Validity

Because the patients who took part in the DAYBREAK OLE were originally from the parent studies and the eligibility criteria remained the same, it is reasonable to expect that the same limitations to generalizability are relevant to the OLE study. For example, although 99.2% of the OLE study population was White and 90.1% were from the Eastern European region, the clinical expert CADTH consulted for this review did not expect this to be a major concern. The clinical expert also noted that patients outside the eligibility criteria for the parent and OLE studies could be included for treatment with ozanimod in clinical practice. These patients include those who are older than 55 years of age, have an EDSS score greater than 5.0, have a contraindication to gadolinium, or have had MS for longer than 15 years with an EDSS score less than 2.0. In the DAYBREAK OLE study, ozanimod appears to have been used according to what is outlined in the product monograph and it is anticipated to be used in clinical practice. [redacted] The median times to first confirmed relapse and onset of disability progression could not be estimated for the phase III ITT populations due to low rates of disease progression and the limited time for data collection. Despite the absence of enrolled Canadians, the results from the DAYBREAK study may be generalizable to the Canadian population and should still be interpreted with caution.

Discussion

Summary of Available Evidence

The 2 pivotal trials for ozanimod, RADIANCE Part B (N = 1,320) and SUNBEAM (N = 1,346), were the only studies that met the criteria for inclusion in the CADTH systematic review. The RADIANCE Part B and SUNBEAM studies followed a randomized, double-blind, double-dummy, active comparator-controlled, parallel-group, multi-centre design. The main difference between the 2 phase III studies was the duration of treatment, which was 24 months for RADIANCE Part B, and up to approximately 22 months (mean of 13.6 months) for SUNBEAM, where treatment was continued until all patients received a minimum of 12 months of treatment. Patients included in the 2 studies were adults (18 to 55 years of age) with a diagnosis of RMS, an EDSS score of between 0 and 5.0 (inclusive), and had recent (1 to 2 years) documentation of disease activity based on relapses and/or imaging features. Patients were randomized 1:1:1 to receive ozanimod 1 mg once daily, ozanimod 0.5 mg once daily (beyond the scope of this review), or interferon beta-1a 30 mcg IM weekly in a double-dummy manner. The primary objective of both studies was to assess whether the clinical efficacy of ozanimod is superior to interferon beta-1a at reducing the rate of clinical relapses in patients with RMS. The key secondary objectives were to assess whether the efficacy of ozanimod is superior to interferon beta-1a in terms of various disability outcomes based on the EDSS, MSFC, and LCLA tests and MRI outcomes. In addition, HRQoL (MSQOL-54), mobility (T25FW and 9-HPT), cognitive function (SDMT and PASAT), as well as a composite outcome for disease activity (NEDA), were reported in both trials.

Overall, the RADIANCE Part B and SUNBEAM trials were fairly well conducted and consistent with the EMA guidance on clinical trials of treatments for MS. A double-blind, double-dummy study design was employed to maintain blinding in the studies; however, differential frequencies of AEs that are known risks of treatment with interferon beta-1a raised the potential for unblinding. Discontinuation rates were reasonable for an MS trial, but the differential discontinuation rate in both studies should be noted. Substantial missing data for the MRI outcomes created uncertainty for these results. In terms of generalizability of the results to patients living with RMS in Canada, the trials excluded patients over the age of 55, those with an EDSS score greater than 5, and pregnant/nursing women, which was considered a restrictive population by the clinical expert who was consulted for this review and who would not exclude those patients as candidates for ozanimod. Most of the outcomes included in the trials were seen as either useful to clinical practice or of interest to patients, although the trials may have been too short to obtain meaningful results as it can take up to 3 years to observe changes in mobility, cognitive function, and even disability.

The DAYBREAK study (an ongoing long-term extension phase III study) assessed long-term safety, tolerability, and efficacy of ozanimod 1 mg once daily in patients with RMS. Results available as of the interim analysis are also presented in this report.

In addition to the systematic review, a sponsor-submitted ITC and a published ITC were summarized and appraised for this review.

Interpretation of Results

Efficacy

The principal goal of treatment for MS is to delay or prevent the accumulation of disability by reducing the frequency of relapses and MRI lesions.[6] The primary end point in the 2 pivotal trials was the ARR. The use of the ARR as the primary end point is aligned with guidance from the EMA[10] and is a clinically relevant outcome to clinicians, according to the clinical expert consulted for this review. Treatment with ozanimod 1 mg demonstrated superiority over interferon beta-1a in terms of reducing the frequency of confirmed relapses based on the ARR in patients with RRMS in RADIANCE Part B and SUNBEAM, in which treatment with ozanimod 1 mg corresponded to 37.66% and 48.21% reductions in terms of the ARR compared to interferon beta-1a in RADIANCE Part B and SUNBEAM, respectively, as indicated by a statistically significant ARR ratio ($P < 0.001$) in both trials. This reduction was also considered clinically relevant by the clinical expert consulted by CADTH. These results from both RADIANCE Part B and SUNBEAM were supported by multiple pre-specified sensitivity analyses, including confirmed and unconfirmed relapses, assuming a negative binomial distribution. In both RADIANCE Part B and SUNBEAM the RRs and 95% CIs for the ARR were generally consistent across the subgroups (age, relapses in prior 12 months, baseline GdE lesions, baseline EDSS, and prior DMT). The use of the ARR as the primary end point is aligned with guidance from the EMA[10] and is a clinically relevant outcome to clinicians, as indicated by the clinical expert consulted for this review.

Imaging or MRI outcomes were considered important to clinicians. The number of new or enlarging hyperintense T2-weighted brain MRI lesions and the number of GdE brain MRI lesions were included in the pivotal trials as key secondary outcomes, and were also included in the statistical testing hierarchy. The proportion of patients who were GdE lesion-free, the proportion of patients who were new or enlarging T2 lesion-free, and percent change in normalized brain volume (atrophy) on MRI scans from baseline were other secondary outcomes that were not included in the statistical testing hierarchy. Lesions enhanced by gadolinium are useful for identifying active inflammation, whereas interpretation of the occurrence of T2 lesions requires a comparison with the number of T2 lesions observed in previous scans.[74] According to the 2020 treatment optimization recommendations,[6] the rate of brain atrophy may have prognostic value, but technical issues preclude routine use in clinical practice. The clinical expert for this review stated that new or enlarging T2 lesions are of most interest to clinical practice, in which gadolinium imaging is being used less frequently due to evidence that gadolinium accumulates in the brain with frequent use.[6]

Ozanimod 1 mg demonstrated superiority to interferon beta-1a in terms of the number of new or enlarging hyperintense T2-weighted brain MRI lesions with a reduction in new or enlarging hyperintense T2 lesions in favour of ozanimod 1.0 mg of 42.351% and 48.330% in RADIANCE Part B and SUNBEAM, respectively. Similarly, ozanimod 1 mg was superior to interferon beta-1a in terms of the number of GdE brain MRI lesions, with a 52.944% and 62.973% reduction in numbers of GdE brain MRI lesions in RADIANCE Part B and SUNBEAM, respectively. All of these comparisons were statistically significant ($P < 0.001$).

[redacted] The

imputation methodologies in 2 of the pre-specified sensitivity analyses relied on a potentially flawed methodology that allowed a patient who dropped out of the study early to have a lesion number value imputed as the average lesion number of the patients who had completed a longer duration of the study; that is, patients who remained in the trial for longer and therefore likely experienced greater cumulative treatment effects compared with the patients who were earlier dropouts, which would likely bias results conservatively against ozanimod. In summary, although ozanimod 1 mg achieved statistical significance in the reduction of lesion numbers over interferon beta-1a, there is potential for bias in the estimates of the lesion numbers.

The composite outcome of NEDA is defined as no relapses, no disability progression, no new or enlarging T2 lesions, and no new GdE lesions. The proportion of patients meeting the NEDA criteria was reported in the 2 trials as an "exploratory" outcome, and not included in the statistical hierarchy. After 1 year on study treatment, the proportions of patients meeting the criteria for NEDA in SUNBEAM were 26.8 (95% CI, 22.3 to 31.2), and 22.5 (95% CI, 18.3 to 26.8) for the ozanimod 1 mg treatment group and interferon beta-1a treatment group, respectively. After 2 years on study treatment, the proportions of patients meeting the criteria for NEDA in RADIANCE Part B were 24.2% (95% CI, 19.5 to 28.8), and 17.0% (95% CI, 13.0 to 21.0) for the ozanimod 1 mg treatment group and interferon beta-1a treatment group, respectively. This outcome was not controlled for multiplicity, despite statistical testing and a reported P value, limiting the ability to draw conclusions based on this outcome. An MID for this outcome was not identified during this review.

As noted in the patient group submission, "patients are looking for a treatment that would result in fewer relapses requiring hospitalization, decrease work absenteeism, and allowing them to remain active within their social networks." In the RADIANCE Part B and SUNBEAM studies, HRQoL was evaluated using the MSQOL-54 as a secondary outcome not included in the statistical testing hierarchy. The MSQOL-54 is a well-validated HRQoL outcome for patients with MS, with MIDs of 2.5 points and 1.5 points each from total scores of 100 for the mental and physical summary scores, respectively. In RADIANCE Part B, no treatment was favoured for [redacted] physical summary scores, while SUNBEAM ozanimod 1.0 mg was favoured when compared with the interferon beta-1a group for the physical health composite summary score of the MSQOL-54 at month 12, with a difference between the treatment groups of 1.642 (95% CI, 0.104 to 3.180; nominal P = 0.0364) which exceeds the estimated MID of 1.5, [redacted].

The MSFC, T25FW, and 9-HPT, which are well-validated and widely used outcomes that measure mobility in patients with MS, were included in the ozanimod trials as "other secondary" outcomes. There was no difference between treatment groups for any of the outcomes assessed in either study. The clinical expert on this review suggested that treatments like ozanimod are designed to reduce relapses and inflammatory activity, but a change in mobility is the result of physiotherapy and other paramedical services that patients are able to focus on when active disease is less of a barrier. As a result, the clinical expert acknowledged that changes in mobility may not be observed in the short-term and suggested that patients should be followed for more than 2 years to assess these outcomes.

In the RADIANCE Part B and SUNBEAM studies, cognitive function was assessed using different measures (SDMT in SUNBEAM and PASAT in RADIANCE Part B), but neither of these measures was included in the statistical testing hierarchy. Further, input from the

clinical expert consulted for this review indicated that the duration of the studies may not be adequate to observe any potential changes in cognitive function.

Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and again after 6 months was a key secondary end point in both SUNBEAM and RADIANCE Part B. In both studies, the risk of disability progression after 3 and 6 months was low in all groups and no statistically significantly reduction was demonstrated between ozanimod 1 mg and interferon beta-1a treatment groups. This could be explained by 2 key aspects of the study design in the pivotal trials. First, disability progression in patients with RRMS is due mainly to a lack of complete recovery from severe relapses. The included patient population had low disease activity with regard to number of relapses prior to inclusion in the study (mean number of 1.3 in the past year in both studies; a mean number of 1.7 in SUNBEAM and 1.8 in RADIANCE Part B in the past 2 years). Second, the study duration may not have been adequate, particularly for SUNBEAM, in which only patients who experienced a severe relapse without complete recovery (tentative disability progression) within the first 6 months could show CDP at 6 months by the end of the trial at 12 months. Considering the anticipated latency of therapeutic response and duration of studies, a low rate of progressors was expected in the pivotal studies. These aspects may explain the low rate of CDP at 3 months and at 6 months in the clinical trials.

Specific outcomes related to the symptoms of MS, such as fatigue and cognition, were included in the CADTH systematic review protocol but were not reported in any of the studies included in this review. Use of rescue medication was also included in the protocol, although it was not formally assessed.

Maintenance of therapeutic response continued for up to 5 years of treatment (an additional 30 months of exposure in the OLE as of the data cut-off date) in patients who remained on ozanimod 1 mg treatment from the parent studies and continued in the long-term OLE DAYBREAK study. Patients who were initially randomized to interferon beta-1a or ozanimod 0.5 mg in the parent studies and switched to ozanimod 1 mg in the OLE showed improvements in MS activity in terms of the ARR and lesion count similar to those seen in patients initially randomized to ozanimod 1 mg. However, due to the lack of a randomized comparison group, and the open-label design, the study results should be interpreted with caution.

Interferon beta-1a is a commonly used DMT for the treatment of RRMS in Canada. Based on input from the clinical expert consulted by CADTH, it is an appropriate comparator for a treatment such as ozanimod. However, comparative evidence of ozanimod versus other DMTs available in Canada is lacking. The sponsor-submitted ITC[13] reported that ozanimod was favoured in reducing ARRs compared to many first-line therapies, including interferons, glatiramer acetate, and teriflunomide. When compared with therapies reserved for more active or severe disease, (i.e., ocrelizumab, alemtuzumab, and natalizumab), ozanimod was found to be less efficacious at reducing ARRs. In sensitivity analyses, results were largely insensitive to the exclusion of studies with statistically significant heterogeneity for ARRs or short study duration. Critical appraisal points of the sponsor-submitted ITC[13] involve the lack of reporting specific items that would improve the certainty of the indirect evidence. The sponsor-submitted ITC[13] could have used more sensitivity and subgroup analysis to satisfy the assumptions of transitivity and homogeneity, and it could have conducted a meta-regression that would adjust for effect modifiers that could influence the results. Given that the sponsor-submitted NMA did not adjust for the ARR in the placebo

arm, there is uncertainty around the comparison between ozanimod and other therapies for RRMS. In addition, uncertainty remains around long-term efficacy and tolerability of the various treatments for RRMS.

The MAIC by Swallow et al.[14] reported that ozanimod was associated with statistically significantly lower risks of adverse outcomes over 1 and 2 years of follow-up compared with fingolimod, and that ozanimod and fingolimod were comparable in terms of reducing annualized relapse rates and the proportion of patients with CDP. However, the analyses by Swallow et al.[14] have a number of limitations that affect internal and external validity. There are concerns regarding the overlap between the ozanimod and fingolimod trial populations, and the availability of data to allow for matching. The small effective sample size of many analyses further suggests substantial differences between the patient populations in the ozanimod and fingolimod trials; the effective sample size was only 31% of RADIANCE Part B and SUNBEAM study patients after matching. Definitions for the outcomes included in the analyses were not provided. Data were pooled and results were combined in a manner that was not clearly specified and likely does not align with recommendations by the NICE Decision Support Unit. Given these issues, there is substantial uncertainty in the MAIC results, and firm conclusions cannot be drawn from them. In addition, this MAIC raises further limitations of the sponsor-submitted ITC as the network for the NMA contains the same studies included in the MAIC. The identified sources of heterogeneity between the studies included in the MAIC would also be of concern with respect to introducing bias in the NMA as NMAs are generally less robust to sources of heterogeneity compared to MAICs.

Harms

In the RADIANCE Part B study, the majority of patients reported at least 1 treatment-emergent AE, with 324 patients (74.7%) in the ozanimod 1 mg group and 365 patients (83.0%) in the interferon beta-1a group experiencing at least 1 treatment-emergent AE. In the SUNBEAM study, 268 patients (59.8%) in the ozanimod 1 mg group and 336 patients (75.5%) in the interferon beta-1a group experienced at least 1 treatment-emergent AE. The most commonly reported AEs overall were influenza-like illness (3.8% to 51.0%), nasopharyngitis (6.7% to 15.7%), headache (5.6% to 12.0%), upper respiratory tract infection (4.0% to 8.4%), increased ALT (1.8% to 6.0%), and pyrexia (1.1% to 6.4%). In both studies, influenza-like illness, upper respiratory tract infection, and pyrexia were reported in a greater proportion of patients in the interferon beta-1a group (influenza-like illness, 48.9% to 51.0%; upper respiratory tract infection, 4.4% to 8.4%; pyrexia, 6.3% to 6.4%) than in the ozanimod 1 mg group (influenza-like illness, 3.8% to 6.2%; upper respiratory tract infection, 4.0% to 7.8%; pyrexia, 1.1% to 2.5%). The overall higher incidence of AEs in the interferon beta-1a treatment group compared with the ozanimod treatment groups could be attributed to the predominance of influenza-like illness and pyrexia events.

Serious adverse events were reported by 2.5% to 6.5% of patients in the treatment groups of both studies, but the frequency of individual SAEs was low. The proportions of patients who stopped treatment due to AEs were also low, ranging from 2.9% and 4.1% of patients across the 2 pivotal trials, and were similar between treatment groups in each study.

No deaths were reported during the SUNBEAM study. In RADIANCE Part B study, 1 death due to chronic kidney failure in the ozanimod 1 mg group occurred 157 days after treatment discontinuation.

Adverse events of special interest were rare, and the only events that occurred in more than 1 patient in RADIANCE Part B were increased ALT (6 patients [1.4%] in the ozanimod 1 mg group, and 8 patients [1.8%] in the interferon beta-1a group), increased AST (5 patients [1.1%] in the interferon beta-1a group), increased transaminases (2 patients [0.5%] in the ozanimod 1 mg group), increased blood pressure (3 patients [0.7%] in the ozanimod 1 mg group), and macular edema (2 patients [0.5%] in the interferon beta-1a group). In SUNBEAM, events that occurred in more than 1 patient were increased ALT and increased blood pressure, which were reported in 3 patients (0.7%) and 4 patients (0.9%), respectively, in the ozanimod 1 mg group.

Of the 2,494 patients in the OLE study (DAYBREAK), 1,704 (68.3%) experienced an AE. The most frequently reported AEs included nasopharyngitis, headache, and upper respiratory tract infection, which was consistent with the most common AEs in the parent studies. Decreased lymphocyte count and lymphopenia were also frequently reported, consistent with ozanimod's mechanism of action. The incidence of SAEs was low, affecting approximately 6% of patients. Few patients (approximately 1%) permanently discontinued the study drug due to an AE. Two deaths were reported during the study. One patient died after being diagnosed with pulmonary embolism; the other died of a craniocerebral injury. No new safety concerns were raised with ozanimod therapy in either patients who continued long-term treatment or those who switched from interferon beta-1a.

The sponsor-submitted ITC[13] reported that, for treatment discontinuation, ozanimod was favoured when compared with many first-line injectable therapies, including most interferons. There was no difference in discontinuation between ozanimod and other oral first-line therapies, including teriflunomide and dimethyl fumarate, or between ozanimod and fingolimod, cladribine, ocrelizumab, and natalizumab. Only alemtuzumab was superior to ozanimod for treatment discontinuation. For SAEs, ozanimod was neither superior nor inferior to any other treatment. However, the analysis found ozanimod was associated with similar or lower odds of AEs compared with interferon beta-1a, glatiramer acetate, peginterferon beta-1a, dimethyl fumarate, and alemtuzumab. The MAIC by Swallow et al.[14] reported that ozanimod was associated with statistically significantly lower risks of adverse outcomes over 1 year and 2 years of follow-up compared with fingolimod.

There is uncertainty around the long-term risk of malignancies, cardiovascular morbidity, and withdrawal effects following ozanimod withdrawal.

Other Considerations

The FDA clinical review[39] of ozanimod indicated that the safety profile of ozanimod appears to be largely similar to that of the S1P modulator fingolimod, with the exceptions of milder, but not absent, cardiac effects, and the presence of intermediate metabolites that act as monoamine oxidase inhibitors. It was also stated that, as is the case with other S1P modulators, ozanimod can cause bradycardia and atrioventricular conduction delays and therefore should be titrated to its maintenance dose. However, ozanimod’s maximum cardiac effect is mild and observed at the end of its 7-day titration; therefore, unlike fingolimod and siponimod, first-dose monitoring with initiation of ozanimod is not needed for any patients.[39] In addition, the clinical trial population of ozanimod included patients with mild conduction delays, and these patients tolerated ozanimod without worsening of their underlying cardiac conduction abnormalities. Patients with a history of serious bradycardia or severe atrioventricular conduction delay would be expected to be at higher risk of experiencing an AE related to cardiac toxicity compared with patients without such histories

and should discuss the cardiac risks of ozanimod with a cardiologist before initiating treatment.[39]

The Health Canada product monograph for ozanimod indicates that the initiation of treatment with ozanimod causes a transient decrease in heart rate and atrioventricular conduction delays. Health Canada recommended that prescribers should:

- obtain an electrocardiogram for all patients to determine whether pre-existing conduction abnormalities are present
- determine whether patients are taking concomitant medications that reduce heart rate or atrioventricular conduction
- for patients with sinus bradycardia (heart rate < 55 beats per minute), first- or second-degree (Mobitz type I) atrioventricular block, or a history of myocardial infarction or heart failure, prepare to administer the first dose of ozanimod in a clinical setting where patients can be monitored for signs and symptoms of bradycardia, with hourly pulse and blood pressure measurements for at least 6 hours, and where symptomatic bradycardia can be managed
- for patients with certain other pre-existing cardiac conditions, seek an evaluation from a cardiologist prior to initiating treatment, to assess suitability of treatment and to determine the most appropriate strategy for monitoring cardiac effects.[9]

The Health Canada product monograph also indicates that ozanimod causes a reduction in circulating lymphocyte counts to approximately 43% to 47% of baseline values at the 0.92 mg ozanimod dose via reversible retention in lymphoid organs and may increase the risk of infections. In addition, the Health Canada product monograph recommends that patients with diabetes mellitus, uveitis or a history of retinal disorders undergo an ophthalmic evaluation prior to initiating ozanimod therapy and during treatment.[9]

Conclusions

The RADIANCE Part B and SUNBEAM studies demonstrated the superiority of ozanimod 1 mg to interferon beta-1a in adult patients with RRMS in terms of relapse and imaging outcomes. This includes a reduction in the ARR, and in the number of new or enlarging hyperintense T2-weighted brain MRI lesions and the number of GdE brain MRI lesions. Outcomes related to HRQoL were noted as important to patients, but the effect of ozanimod on HRQoL was uncertain due to a lack of control for multiplicity. In both studies, no difference between ozanimod 1 mg and interferon beta-1a was demonstrated for disability progression, mobility, or cognitive function, which could be due to the short duration of the trials.

Direct comparative evidence for ozanimod 1 mg with DMTs other than interferon beta-1a was not identified. One sponsor-submitted ITC comparing ozanimod 1 mg to other DMTs suggested that ozanimod was more effective in reducing the ARR compared to many first-line therapies, including interferons, glatiramer acetate, and teriflunomide.

[redacted]

[redacted] The value of the ITC results is uncertain due to the heterogeneity between studies.

There were no concerns regarding the safety of ozanimod in the pivotal trials, other than the potential cardiac effects known to be associated with S1P modulators. Serious adverse events were reported by 2.5% to 6.5% of patients in the treatment groups of both studies, but the frequency of individual SAEs was low. There is no evidence concerning the long-term risk of malignancies, cardiovascular morbidity, and withdrawal effects following ozanimod withdrawal.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 24, 2020
Alerts:	Weekly search updates until project completion
Study Types:	No filters used
Limits:	Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase);
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
.jw	Journal word title
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy	
#	**Searches**
1	(Zeposia* or ozanimod* or RPC1063 or RPC 1063 or Z80293URPV).ti,ab,kf,ot,hw,rn,nm.
2	1 use medall
3	*ozanimod/
4	(Zeposia* or ozanimod* or RPC1063 or RPC 1063).ti,ab,kw,dq.
5	3 or 4
6	(conference abstract or conference review).pt.
7	5 not 6
8	7 use oemezd
9	2 or 8
10	remove duplicates from 9

Clinical Trial Registries		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. [Search -- Studies with results | Zeposia* OR ozanimod* OR RPC1063 OR RPC 1063 OR RPC-1063]	
EU Clinical Trials Register	Interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA). Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.] [Search terms -- Zeposia* OR ozanimod* OR RPC1063 OR RPC 1063 OR RPC-1063	

Grey Literature

Search dates:	September 15, 2020 – September 21, 2020
Keywords:	Zeposia* OR ozanimod* OR RPC1063 OR RPC 1063 OR RPC-1063 OR multiple sclerosis
Limits:	Publication years: no date limit
Updated:	Search updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool For Searching Health-Related Grey Literature[35] were searched:

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

Appendix 2: Excluded Studies

Table 35: Excluded Studies

Reference	Reason for exclusion
Swallow E, Patterson-Lomba O, Yin L, et al. Comparative safety and efficacy of ozanimod versus fingolimod for relapsing multiple sclerosis. J. 2020;9(4):275-285.	Systematic review
Cohen JA, Comi G, Arnold DL, et al. Efficacy and safety of ozanimod in multiple sclerosis: Dose-blinded extension of a randomized phase II study. Mult Scler. 2019;25(9):1255-1262. Cohen JA, Arnold DL, Comi G, et al. Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2016;15(4):373-381.	Study design (phase II RCT)
Koscielny V. Phase III SUNBEAM and RADIANCE PART B trials for Ozanimod in relapsing multiple sclerosis demonstrate superiority versus interferon-beta-1a (Avonex ®) in reducing annualized relapse rates and MRI brain lesions. Neurodegener Dis Manag. 2018;8(3):141-142.	Review article

Appendix 3: Detailed Outcome Data

Table 36: Sensitivity Analysis for the Annualized Relapse Rate During the Treatment Period

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Sensitivity analysis: Summary of annualized relapse rate at the end of 24 months – including unconfirmed relapses (ITT Population)[a]				
Number of patients contributing to the analysis	433	441	447	448
Total number of relapses	151	250	106	190
Adjusted annualized relapse rate (95% CI)	0.191 (0.159 to 0.228)	0.308 (0.264 to 0.358)	0.211 (0.165 to 0.269)	0.386 (0.311 to 0.478)
Rate ratio (ozanimod/interferon beta-1a) (95% CI)	0.620 (0.506 to 0.759)	Reference	0.547 (0.431 to 0.695)	Reference
Percent reduction (95% CI)	38.039 (24.121, 49.404)	Reference	45.278 (30.527 to 56.898)	Reference
P value	< 0.0001[b]		< 0.0001[b]	
Sensitivity analysis: Summary of annualized relapse rate at the end of 24 months – using Negative Binomial Regression Model (ITT Population)[c]				
Number of patients contributing to the analysis	433	441	447	448
Total number of relapses	143	236	97	184
Adjusted annualized relapse rate (95% CI)	0.178 (0.141 to 0.225)	0.288 (0.233 to 0.355)	0.180 (0.134, 0.240)	0.346 (0.266 to 0.449)
Rate ratio (ozanimod/interferon beta-1a) (95% CI)	0.620 (0.477 to0.806)	Reference	0.520 (0.394 to 0.686)	Reference
Percent reduction (95% CI)	38.037 (19.443 to 52.339)	Reference	48.050 (31.419 to 60.648)	Reference
P value	0.0004[b]		< 0.0001[b]	
Sensitivity analysis: Summary of annualized relapse rate at the end of 24 months – including unconfirmed relapses using Negative Binomial Regression Model (ITT Population)[c]				
Number of patients contributing to the analysis	433	441	447	448
Total number of relapses	151	250	106	190
Adjusted annualized relapse rate (95% CI)	0.198 (0.159 to 0.248)	0.322 (0.263 to 0.394)	0.209 (0.158 to 0.276)	0.381 (0.296 to 0.491)
Rate ratio (ozanimod/interferon beta-1a) (95% CI)	0.617 (0.477 to 0.797)	Reference	0.549 (0.418, 0.721)	Reference
Percent reduction (95% CI)	38.331 (20.308 to 52.278)	Reference	45.110 (27.880 to 58.224)	Reference
P value	0.0002[b]		<0.0001[b]	
Sensitivity analysis: Summary of annualized relapse rate during the treatment period per protocol population[a]				
Number of patients contributing to the analysis	432	436	445	447
Total number of relapses	143	233	97	183

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Adjusted annualized relapse rate (95% CI)	0.172 (0.143 to 0.208)	0.274 (0.233 to 0.323)	0.178 (0.136 to 0.233)	0.342 (0.270 to 0.432)
Rate ratio (ozanimod/interferon beta-1a) (95% CI)	0.628 (0.510 to 0.774)	Reference	0.522 (0.408 to 0.668)	Reference
Percent reduction (95% CI)	37.176 (22.597 to 49.009)	Reference	47.811 (33.176 to 59.241)	Reference
P value	< 0.0001[b]		< 0.0001[b]	

CI = confidence interval; IFN = interferon; ITT = intention-to-treat.

[a] Based on the Poisson regression model, adjusted for region (Eastern Europe vs Rest of the World), age at baseline, and the baseline number of GdE lesions, and included the natural log transformation of time on study as an offset term.

[b] P value has not been adjusted for multiple testing.

[c] Based on the negative binomial regression model, adjusted for region (Eastern Europe versus rest of world), age at baseline, and the baseline number of GdE lesions, and included the natural log transformation of time on study as an offset term.

Source: Clinical study reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Table 37: Subgroup Analyses for the Annualized Relapse Rate During the Treatment Period – (ITT Population)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Subgroup analyses for the annualized relapse rate during the treatment period[a]				
Patients who are treatment-naive to DMT				
Number (%) of patients contributing to the analysis	310 (71.6)	315 (71.4)	319 (71.4)	297 (66.3)
Adjusted Relapse Rate (95% CI)	0.157 (0.124, 0.200)	0.246 (0.201, 0.302)	0.195 (0.143, 0.267)	0.338 (0.253, 0.451)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.639 (0.496, 0.823)	reference	0.578 (0.428, 0.781)	reference
Patients who were previously treated with DMT				
Number (%) of patients contributing to the analysis	123 (28.4)	126 (28.6)	128 (28.6)	151 (33.7)
Adjusted Relapse Rate (95% CI)	0.205 (0.149, 0.282)	0.357 (0.271, 0.469)	0.154 (0.095, 0.251)	0.365 (0.251, 0.531)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.574 (0.397, 0.831)	reference	0.422 (0.271, 0.658)	reference
Patients with baseline EDSS score ≤ 3.5				
Number (%) of patients contributing to the analysis	366 (84.5)	377 (85.5)	360 (80.5)	370 (82.6)
Adjusted Relapse Rate (95% CI)	0.146 (0.117, 0.182)	0.237 (0.197, 0.286)	0.170 (0.127, 0.227)	0.369 (0.290, 0.468)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.614 (0.482, 0.782)	reference	0.461 (0.344, 0.616)	reference

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Patients with baseline EDSS score > 3.5				
Number (%) of patients contributing to the analysis	67 (15.5)	64 (14.5)	87 (19.5)	78 (17.4)
Adjusted Relapse Rate (95% CI)	0.334 (0.229, 0.485)	0.531 (0.377, 0.747)	0.145 (0.052, 0.407)	0.215 (0.077, 0.599)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.629 (0.417, 0.949)	reference	0.674 (0.418, 1.086)	reference
Patients with Gd-enhancing lesions absent at baseline				
Number (%) of patients contributing to the analysis	255 (58.9)	245 (55.6)	233 (52.1)	232 (51.8)
Adjusted Relapse Rate (95% CI)	0.152 (0.117, 0.197)	0.242 (0.193, 0.303)	0.129 (0.083, 0.201)	0.206 (0.137, 0.308)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.629 (0.473, 0.835)	reference	0.628 (0.426, 0.924)	reference
Patients with Gd-enhancing lesions present at baseline				
Number (%) of patients contributing to the analysis	178 (41.1)	196 (44.4)	214 (47.9)	216 (48.2)
Adjusted Relapse Rate (95% CI)	0.206 (0.156, 0.271)	0.353 (0.280, 0.444)	0.249 (0.179, 0.345)	0.548 (0.416, 0.722)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.583 (0.429, 0.791)	reference	0.454 (0.329, 0.626)	reference
Patients with less than 2 relapses in the past 12 months				
Number (%) of patients contributing to the analysis	325 (75.1)	313 (71.0)	333 (74.5)	337 (75.2)
Adjusted Relapse Rate (95% CI)	0.148 (0.116, 0.188)	0.229 (0.184, 0.285)	0.151 (0.109, 0.209)	0.314 (0.238, 0.415)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.644 (0.496, 0.837)	reference	0.480 (0.352, 0.656)	reference
Patients with at least 2 relapses in the past 12 months				
Number (%) of patients contributing to the analysis	108 (24.9)	128 (29.0)	114 (25.5)	111 (24.8)
Adjusted Relapse Rate (95% CI)	0.236 (0.173, 0.322)	0.382 (0.300, 0.486)	0.263 (0.167, 0.414)	0.457 (0.305, 0.686)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.618 (0.437, 0.873)	reference	0.575 (0.383, 0.864)	reference
Patients who are ≤ 40 years of age				
Number (%) of patients contributing to the analysis	295 (68.1)	311 (70.5)	324 (72.5)	307 (68.5)
Adjusted Relapse Rate (95% CI)	0.190 (0.151, 0.238)	0.313 (0.260, 0.376)	0.219 (0.163, 0.294)	0.462 (0.352, 0.606)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.606 (0.475, 0.774)	reference	0.474 (0.354, 0.633)	reference
Patients who are older than 40 years of age				

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Number (%) of patients contributing to the analysis	138 (31.9)	130 (29.5)	123 (27.5)	141 (31.5)
Adjusted Relapse Rate (95% CI)	0.137 (0.097, 0.196)	0.201 (0.143, 0.283)	0.132 (0.077, 0.226)	0.212 (0.134, 0.333)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.682 (0.456, 1.021)	reference	0.623 (0.386, 1.006)	reference

CI, confidence interval; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; IFN = interferon; ITT = intention-to-treat.

[a] Based on the Poisson regression model, adjusted for region (Eastern Europe versus rest of world), age at baseline, and the baseline number of GdE lesions, and included the natural log transformation of time on study as an offset term. Covariates in the model for region, age at baseline and baseline number of GdE lesions were not included for the respective subgroups.

Source: Clinical study reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Table 38: Sensitivity Analysis for the number of new or enlarging hyperintense T2-weighted brain MRI lesions – (ITT Population)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Sensitivity analysis: Number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months in the RADIANCE Part B study and over 12 months in the SUNBEAM study — imputation using treatment group mean				
Number of patients contributing to the analysis[a]	433	441	447	448
Adjusted Mean (95% CI) per Scan[b]	2.758 (2.343, 3.245)	6.267 (5.361, 7.326)	3.169 (2.648, 3.792)	6.602 (5.522, 7.893)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)[b]	0.440 (0.364, 0.531)	reference	0.480 (0.403, 0.571)	reference
Percent Reduction (95% CI)[b]	55.998 (46.865, 63.561)	reference	52.002 (42.884, 59.665)	reference
P value[b]	< 0.0001[c]		< 0.0001[c]	
Sensitivity analysis: Number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months in the RADIANCE Part B study and over 12 months in the SUNBEAM study — LOCF for missing scans				
Number of patients contributing to the analysis[ad]	420	425	439	441
Adjusted Mean (95% CI) per Scan[b]	1.931 (1.626, 2.293)	3.839 (3.247, 4.538)	2.798 (2.316, 3.380)	5.424 (4.494, 6.546)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)[b]	0.503 (0.412, 0.614)	reference	0.516 (0.429, 0.620)	reference
Percent Reduction (95% CI)[b]	49.703 (38.565, 58.822)	reference	48.414 (38.031, 57.058)	reference
P value[b]	< 0.0001[c]		< 0.0001[c]	

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Sensitivity analysis: Number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months in the RADIANCE Part B study and over 12 months in the SUNBEAM study — patients with complete T2 data at both month 12 and 24 in RADIANCE Part B study, and with complete T2 data at both month 6 and 12 in the SUNBEAM study				
Number of patients contributing to the analysis[ae]	307	312	371	367
Adjusted Mean (95% CI) per Scan[b]	1.878 (1.548, 2.277)	3.154 (2.595, 3.834)	2.566 (2.088, 3.152)	4.845 (3.952, 5.939)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)[b]	0.595 (0.477, 0.743)	reference	0.530 (0.435, 0.644)	reference
Percent Reduction (95% CI)[b]	40.472 (25.704, 52.305)	reference	47.044 (35.559, 56.483)	reference
P value[b]	< 0.0001[c]		< 0.0001[c]	

CI, confidence interval; IFN = interferon; ITT = intention-to-treat; LOCF = last observation carried forward; MRI = magnetic resonance imaging.

[a] Number of New or Enlarging Hyperintense T2-weighted Brain MRI Lesions was based on cumulative number of new or enlarging T2 lesions since baseline over 24 months in the RADIANCE Part B study and over 12 months in the SUNBEAM study at a patient level.

[b] Based on the negative binomial regression model, adjusted for region (Eastern Europe vs Rest of World), age at baseline, and the baseline number of GdE lesions. The offset term in the model is the natural log transformation of exposure time on study.

[c] P value has not been adjusted for multiple testing.

[d] Only data from post-baseline MRI scans can be carried forward to the Month 24 timepoints in the RADIANCE Part B study and to the Month 12 timepoints in the SUNBEAM study for this analysis.

e The complete observed cases analysis was using only patients with complete T2 data at both Months 12 and 24 in the RADIANCE Part B study and at both Months 6 and 12 in the SUNBEAM study.

Source: Clinical study reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Table 39: Subgroup Analyses for the number of new or enlarging hyperintense T2-weighted brain MRI lesions – (ITT Population)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Subgroup analyses for the number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months in the RADIANCE Part B study and over 12 months in the SUNBEAM study[ab]				
Patients who are treatment-naive to DMT				
Number (%) of patients contributing to the analysis	244 (74.6)	245 (72.9)	273 (70.4)	255 (66.8)
Adjusted Mean (95% CI) per Scan	1.866 (1.497, 2.325)	3.237 (2.599, 4.032)	1.441 (1.133, 1.832)	2.626 (2.060, 3.348)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.576 (0.451, 0.737)	reference	0.549 (0.435, 0.692)	reference
Patients who were previously treated with DMT				
Number (%) of patients contributing to the analysis	83 (25.4)	91 (27.1)	115 (29.6)	127 (33.2)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Adjusted Mean (95% CI) per Scan	1.678 (1.176, 2.395)	2.958 (2.072, 4.223)	1.413 (0.994, 2.008)	3.186 (2.284, 4.445)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.567 (0.367, 0.876)	reference	0.444 (0.317, 0.621)	reference
Patients with baseline EDSS score ≤ 3.5				
Number (%) of patients contributing to the analysis	278 (85.0)	292 (86.9)	318 (82.0)	317 (83.0)
Adjusted Mean (95% CI) per Scan	1.821 (1.493, 2.219)	2.986 (2.449, 3.641)	1.459 (1.178, 1.807)	2.977 (2.412, 3.675)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.610 (0.485, 0.766)	reference	0.490 (0.397, 0.604)	reference
Patients with baseline EDSS score > 3.5				
Number (%) of patients contributing to the analysis	49 (15.0)	44 (13.1)	70 (18.0)	65 (17.0)
Adjusted Mean (95% CI) per Scan	1.867 (1.109, 3.142)	4.042 (2.362, 6.917)	1.398 (0.831, 2.350)	2.142 (1.218, 3.767)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.462 (0.253, 0.844)	reference	0.652 (0.411, 1.035)	reference
Patients with Gd-enhancing lesions absent at baseline				
Number (%) of patients contributing to the analysis	189 (57.8)	191 (56.8)	207 (53.4)	207 (54.2)
Adjusted Mean (95% CI) per Scan	1.150 (0.864, 1.531)	1.775 (1.342, 2.347)	0.620 (0.444, 0.865)	1.301 (0.948, 1.785)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.648 (0.466, 0.902)	reference	0.476 (0.341, 0.665)	reference
Patients with Gd-enhancing lesions present at baseline				
Number (%) of patients contributing to the analysis	138 (42.2)	145 (43.2)	181 (46.6)	175 (45.8)
Adjusted Mean (95% CI) per Scan	4.074 (3.171, 5.233)	7.995 (6.197, 10.315)	3.657 (2.874, 4.655)	5.979 (4.669, 7.658)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.510 (0.386, 0.672)	reference	0.612 (0.486, 0.770)	reference
Patients who are ≤ 40 years of age				
Number (%) of patients contributing to the analysis	216 (66.1)	231 (68.8)	285 (73.5)	259 (67.8)
Adjusted Mean (95% CI) per Scan	2.886 (2.301, 3.619)	5.095 (4.091, 6.345)	1.765 (1.393, 2.237)	3.119 (2.429, 4.006)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.566 (0.441, 0.727)	reference	0.566 (0.456, 0.703)	reference
Patients who are older than 40 years of age				
Number (%) of patients contributing to the analysis	111 (33.9)	105 (31.3)	103 (26.5)	123 (32.2)
Adjusted Mean (95% CI) per Scan	0.888	1.386	0.897	2.027

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
	(0.607, 1.299)	(0.911, 2.108)	(0.595, 1.351)	(1.416, 2.900)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.640 (0.399, 1.028)	reference	0.442 (0.288, 0.680)	reference

CI, confidence interval; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; IFN = interferon; ITT = intention-to-treat.

[a] For RADIANCE Part B study: based on the negative binomial regression model, adjusted for region (Eastern Europe vs Rest of World), age at baseline, and the baseline number of GdE lesions. The natural log transformation of the number of available MRI scans over 24 months is used as an offset term. Covariates in the model for region, age at baseline and baseline number of GdE lesions were not included for the respective subgroups.

[b] For SUNBEAM study: based on the negative binomial regression model, adjusted for region (Eastern Europe versus Rest of World), age at baseline, and the baseline number of GdE lesions. The offset term in the model is the log of the number of post-baseline scans over 12 months. Covariates in the model for region, age at baseline and baseline number of GdE lesions were not included for the respective subgroups.

Source: Clinical study reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Table 40: Sensitivity Analysis for the Number of GdE Brain Lesions on Magnetic Resonance Imaging – (ITT Population)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Sensitivity analysis: Number of GdE Brain MRI lesions at month 24 in the RADIANCE Part B study and at month 12 in SUNBEAM study — imputation using treatment group mean				
Number of patients contributing to the analysis	433	441	447	448
Adjusted Mean (95% CI)[a]	0.142 (0.110, 0.183)	0.377 (0.305, 0.467)	0.181 (0.132, 0.248)	0.492 (0.371, 0.653)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)[a]	0.377 (0.288, 0.492)	reference	0.368 (0.276, 0.489)	reference
Percent Reduction (95% CI)[a]	62.345 (50.805, 71.178)	reference	63.245 (51.074, 72.388)	reference
P value[a]	<0.0001[b]		<0.0001[b]	
Sensitivity analysis: Number of GdE brain MRI lesions at month 24 in the RADIANCE Part B study and at month 12 in the SUNBEAM study — LOCF for missing scans[c]				
Number of patients contributing to the analysis	420	425	439	441
Adjusted Mean (95% CI)[a]	0.101 (0.069, 0.147)	0.256 (0.182, 0.358)	0.169 (0.114, 0.250)	0.596 (0.412, 0.863)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)[a]	0.395 (0.262, 0.593)	reference	0.283 (0.196, 0.409)	reference
Percent Reduction (95% CI)[a]	60.549 (40.701, 73.753)	reference	71.659 (59.079, 80.372)	reference
P value[a]	<0.0001[b]		<0.0001[b]	

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Sensitivity analysis: Number of GdE brain MRI lesions at month 24 in the RADIANCE Part B study and at month 12 in the SUNBEAM study — patients with complete GdE data at month 24 in RADIANCE Part B study, and with complete GdE data at month 12 in the SUNBEAM study				
Number of patients contributing to the analysis	307	312	388	382
Adjusted Mean (95% CI)[a]	0.095 (0.062, 0.146)	0.187 (0.126, 0.277)	0.139 (0.092, 0.211)	0.371 (0.252, 0.546)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)[a]	0.510 (0.325, 0.799)	reference	0.375 (0.259, 0.545)	reference
Percent Reduction (95% CI)[a]	49.030 (20.150, 67.464)	reference	62.461 (45.542, 74.123)	reference
P value[a]	0.0033[b]		<0.0001[b]	

CI, confidence interval; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; IFN = interferon; ITT = intention-to-treat; LOCF = last observation carried forward.

[a] Based on the negative binomial regression model, adjusted for region (Eastern Europe versus rest of world), age at baseline, and the baseline number of GdE lesions. The offset term in the model is the natural log transformation of exposure time on study.

[b] P value has not been adjusted for multiple testing.

[c] Only data from post-baseline MRI scans can be carried forward to the month 12 time point for this analysis.

Source: Clinical study reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Table 41: Subgroup Analyses for the Number of GdE Brain Lesions on Magnetic Resonance Imaging– (ITT Population)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Subgroup analyses for the number of GDE brain MRI lesions at month 24 in the RADIANCE Part B study and at month 12 in the SUNBEAM study[ab]				
Patients who are treatment-naive to DMT				
Number (%) of patients contributing to the analysis	244 (74.6)	245 (72.9)	273 (70.4)	255 (66.8)
Adjusted Mean (95% CI) per Scan	0.167 (0.101, 0.275)	0.325 (0.202, 0.523)	0.181 (0.110, 0.296)	0.281 (0.171, 0.462)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.513 (0.310, 0.847)	reference	0.642 (0.410, 1.005)	reference
Patients who were previously treated with DMT				
Number (%) of patients contributing to the analysis	83 (25.4)	91 (27.1)	115 (29.6)	127 (33.2)
Adjusted Mean (95% CI) per Scan	0.177 (0.080, 0.391)	0.442 (0.231, 0.844)	0.110 (0.051, 0.238)	0.682 (0.370, 1.259)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.401 (0.169, 0.949)	reference	0.161 (0.083, 0.316)	reference
Patients with baseline EDSS score ≤ 3.5				
Number (%) of patients contributing to the analysis	278 (85.0)	292 (86.9)	318 (82.0)	317 (83.0)
Adjusted Mean (95% CI) per Scan	0.187 (0.121, 0.291)	0.360 (0.238, 0.544)	0.166 (0.107, 0.257)	0.476 (0.318, 0.712)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.520 (0.329, 0.822)	reference	0.348 (0.232, 0.522)	reference
Patients with baseline EDSS score > 3.5				
Number (%) of patients contributing to the analysis	49 (15.0)	44 (13.1)	70 (18.0)	65 (17.0)
Adjusted Mean (95% CI) per Scan	0.091 (0.025, 0.334)	0.497 (0.199, 1.245)	NE (NE, NE)	NE (NE, NE)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.183 (0.047, 0.707)	reference	NE (NE, NE)	reference
Patients with Gd-enhancing lesions absent at baseline				
Number (%) of patients contributing to the analysis	189 (57.8)	191 (56.8)	207 (53.4)	207 (54.2)
Adjusted Mean (95% CI) per Scan	0.083 (0.038, 0.182)	0.141 (0.069, 0.289)	0.047 (0.019, 0.117)	0.133 (0.060, 0.295)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.591 (0.269, 1.297)	reference	0.355 (0.164, 0.767)	reference
Patients with Gd-enhancing lesions present at baseline				
Number (%) of patients contributing to the analysis	138 (42.2)	145 (43.2)	181 (46.6)	175 (45.8)
Adjusted Mean (95% CI) per Scan	0.430	1.270	0.500	1.339

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
	(0.258, 0.715)	(0.788, 2.045)	(0.310, 0.806)	(0.830, 2.161)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.339 (0.200, 0.574)	reference	0.373 (0.240, 0.582)	reference
Patients who are ≤ 40 years of age				
Number (%) of patients contributing to the analysis	216 (66.1)	231 (68.8)	285 (73.5)	259 (67.8)
Adjusted Mean (95% CI) per Scan	0.251 (0.156, 0.405)	0.724 (0.478, 1.096)	0.198 (0.122, 0.323)	0.551 (0.342, 0.888)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	0.347 (0.215, 0.560)	reference	0.360 (0.236, 0.549)	reference
Patients who are older than 40 years of age				
Number (%) of patients contributing to the analysis	111 (33.9)	105 (31.3)	103 (26.5)	123 (32.2)
Adjusted Mean (95% CI) per Scan	0.087 (0.032, 0.237)	0.044 (0.012, 0.157)	0.128 (0.057, 0.287)	0.285 (0.147, 0.552)
Rate Ratio (ozanimod/interferon beta-1a) (95% CI)	2.001 (0.623, 6.431)	reference	0.451 (0.211, 0.962)	reference

CI, confidence interval; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; IFN = interferon; ITT = intention-to-treat; NE = not estimable.

[a] For RADIANCE Part B study: based on the negative binomial regression model, adjusted for region (Eastern Europe versus rest of world), age at baseline, and the baseline number of GdE lesions. The natural log transformation of the number of available MRI scans at 24 month (1 scan per patient) was used as an offset term. Covariates in the model for age at baseline and baseline number of GdE lesions were not included for the respective subgroups.

[b] For SUNBEAM study: based on the negative binomial regression model, adjusted for region (Eastern Europe versus rest of world), age at baseline, and the baseline number of GdE lesions. The natural log transformation of number of available MRI scans at 12 month (1 scan per patient) is used as an offset term. Covariates in the model for age at baseline and baseline number of GdE lesions were not included for the respective subgroups.

Source: Clinical Study Reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Table 42: Proportion of Patients Who Are New or Enlarging T2 Lesion-Free — Nonresponder Imputation (ITT Population)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Proportion of patients who are new or enlarging T2 lesion-free at month 24 in the RADIANCE Part B study and at month 12 in the SUNBEAM study				
Missing T2 Lesion Count Imputed as Not T2 Lesion-Free, n (%)	106 (24.5)	105 (23.8)	59 (13.2)	66 (14.7)
Proportion of T2 Lesion-Free at Month 24 (95% CI)	23.8 (19.8, 27.8)	18.4 (14.8, 22.0)	27.96 (23.80, 32.12)	23.44 (19.51, 27.36)
Difference in proportions versus interferon beta-1a (95% CI)[a]	5.4 (0.0, 10.8)	reference	4.53 (−1.19, 10.24)	reference
P value[b]	0.0466[c]		0.1180	

CI, confidence interval; EDSS = Expanded Disability Status Scale; IFN = interferon; ITT = intention-to-treat; IVRS = interactive voice response system.

[a] Based on Wald 95% CI.

[b] Based on the Cochran-Mantel-Haenszel test stratified by region (Eastern Europe vs Rest of the World) and EDSS category per IVRS.

[c] P value has not been adjusted for multiple testing.

Source: Clinical Study Reports of RADIANCE Part B and SUNBEAM trials.[11,12]\

Table 43: Proportion of Patients Who Were GdE Lesion-Free — Nonresponder Imputation (ITT Population)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Proportion of patients who were GDE lesion-free at month 24 in the RADIANCE Part B study and at month 12 in the SUNBEAM study				
Missing GdE Lesion Count Imputed as Not GdE Lesion-Free, n (%)	106 (24.5)	105 (23.8)	59 (13.2)	66 (14.7)
Proportion of GdE Lesion-Free at Month 24 (95% CI)	65.6 (61.1, 70.1)	56.2 (51.6, 60.9)	74.05 (69.99, 78.11)	63.17 (58.70, 67.64)
Difference in proportions versus interferon beta-1a (95% CI)[a]	9.4 (2.9, 15.8)	reference	10.88 (4.84, 16.92)	reference
P value[b]	0.0047[c]		0.0006[c]	

CI, confidence interval; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; IFN = interferon; ITT = intention-to-treat; IVRS = interactive voice response system.

[a] Based on Wald 95% CI.

[b] Based on the Cochran-Mantel-Haenszel test stratified by region (Eastern Europe vs Rest of the World) and EDSS category per IVRS.

[c] P value has not been adjusted for multiple testing.

Source: Clinical study reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Table 44: Normalized Brain Volume: Actual Value at Baseline and Percent Change – Observed Cases (ITT Population)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Normalized brain volume (cm^3)				
Actual value at baseline				
n	432	439	447	445
Mean (SD)	1,441.949 (79.228)	1,449.581 (77.156)	1,455.980 (77.941)	1,443.355 (78.731)
Median (range)	1,445.978 (1,190.494, 1660.718)	1,455.662 (1,208.191, 1667.703)	1,458.301 (1,190.84, 1662.99)	1,445.526 (1,222.70, 1635.16)
Percent change from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study				
n	271	279	338	334
Mean (SD)	−0.850 (0.928)	−1.092 (0.991)	−0.42 (0.654)	−0.64 (0.696)
Median (range)	−0.690 (−5.65, 0.85)	−0.940 (−5.33, 1.44)	−0.39 (−2.8, 2.1)	−0.57 (−3.7, 1.1)
P value[a]	<0.0001[b]		<0.0001[b]	

IFN = interferon; ITT = intention-to-treat; SD = standard deviation.

[a] P value for comparison between the ozanimod and interferon beta-1a 30 mcg treatment groups were based on the analysis of covariance model, adjusted for region (Eastern Europe vs Rest of the World), and Expanded Disability Status Scale category per interactive voice response system, with the dependent variable as the residual of the rank of brain volume at baseline.

[b] P value has not been adjusted for multiple testing.

Source: Clinical study reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Table 45: Change From Baseline in MSFC Score (Including the Low-Contrast Letter Acuity Test Measurement of Visual Function as a Component) – ITT Population

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Change in MSFC z score from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study				
n	432	441	447	448
Mean (SD)	−0.006 (0.779)	−0.067 (0.745)	0.006 (0.382)	−0.024 (0.366)
Difference in means (95% CI)[a]	0.060 (−0.029, 0.148)	reference	0.040 (−0.009, 0.090)	reference
P value[a]	0.1874		0.1091	
Change in MSFC z score [including LCLA] from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study				
n	428	437	447	447
Mean (SD)	−0.010 (0.622)	−0.052 (0.601)	0.003 (0.328)	−0.022 (0.334)
Difference in means (95% CI)[a]	0.043 (−0.030, 0.116)	reference	0.034 (−0.010, 0.077)	reference
P value[a]	0.2480		0.1290	
Change in MSFC component timed 25-foot walk z score from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study				
n	433	441	447	448
Mean (SD)	−0.187 (1.046)	−0.249 (1.902)	−0.045 (0.622)	−0.060 (0.704)
Difference in means (95% CI)[b]	0.053 (−0.124, 0.230)	reference	0.024 (−0.065, 0.113)	reference
P value[b]	0.5553		0.5981	
Change in MSFC component Timed 25-Foot Walk Actual Time (seconds) from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study				
n	390	381	428	426
Mean (SD)	0.474 (2.765)	0.386 (4.056)	0.128 (1.928)	0.187 (2.093)
Difference in means (95% CI)[b]	0.111 (−0.318, 0.540)	reference	−0.077 (−0.353, 0.199)	reference
P value[b]	0.6119		0.5863	
Change in MSFC component 9HPT z score from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study				
n	433	441	447	448
Mean (SD)	0.058 (1.964)	−0.062 (0.603)	−0.009 (0.545)	0.017 (0.473)
Difference in means (95% CI)[c]	0.119 (−0.040, 0.278)	reference	−0.004 (−0.068, 0.059)	reference
P value[c]	0.1435		0.8945	
Change in MSFC component 9-HPT actual time (seconds) from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study				
N	390	383	428	426
Mean (SD)	0.598 (7.953)	0.502 (5.064)	−0.033 (3.276)	−0.076 (3.571)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Difference in means (95% CI)[c]	0.125 (−0.755, 1.005)	reference	0.017 (−0.413, 0.447)	reference
P value[c]	0.7808		0.9380	
Change in MSFC component PASAT-3 z score from baseline to month 24 in the RADIANCE Part B study				
n	432	441	NA	NA
Mean (SD)	0.102 (0.586)	0.111 (0.616)	NA	NA
Difference in means (95% CI)[d]	−0.005 (−0.081, 0.070)	reference	NA	NA
P value[d]	0.8875		NA	
Change in MSFC component PASAT-3 total correct responses from baseline to month 24 in RADIANCE Part B study				
n	385	381	NA	NA
Mean (SD)	1.5 (6.90)	1.2 (6.70)	NA	NA
Difference in means (95% CI)[d]	0.2 (−0.7, 1.1)	reference	NA	NA
P value[d]	0.7263		NA	
Change in MSFC component SDMT z score from baseline to month 12 in the SUNBEAM study				
n	NA	NA	447	448
Mean (SD)	NA	NA	0.073 (0.653)	−0.029 (0.508)
Difference in means (95% CI)[e]	NA	NA	0.111 (0.039, 0.182)	reference
P value[e]	NA		0.0024[f]	
Change in MSFC component SDMT total correct responses from baseline to month 12 in the SUNBEAM study				
n	NA	NA	427	426
Mean (SD)	NA	NA	1.1 (8.58)	−0.4 (6.86)
Difference in means (95% CI)[e]	NA	NA	1.6 (0.6, 2.5)	reference
P value[e]	NA		0.0016[f]	
Change in z score of LCLA from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study				
n	428	437	447	447
Mean (SD)	−0.023 (0.745)	0.013 (0.742)	−0.007 (0.551)	−0.014 (0.569)
Difference in means (95% CI)[g]	-0.023 (−0.117, 0.070)	reference	0.022 (−0.049, 0.092)	reference
P value[g]	0.6254		0.5508	
Change in number of letters correct for low-contrast letter acuity for 100% chart from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study				
n	383	377	427	425
Mean (SD)	−0.19 (6.421)	0.31 (5.395)	−0.1 (5.00)	−0.2 (5.14)
Difference in means (95% CI)[g]	−0.48 (−1.30, 0.34)	reference	0.3 (−0.4, 0.9)	reference
P value[g]	0.2480		0.4398	

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Change in number of letters correct for low-contrast letter acuity for 2.5% chart from baseline to month 24 in the RADIANCE Part B study and to month 12 in the SUNBEAM study				
n	382	377	427	425
Mean (SD)	0.10 (8.893)	−0.47 (8.251)	0.6 (7.76)	0.1 (7.76)
Difference in means (95% CI)[g]	0.30 (−0.83, 1.43)	reference	0.5 (−0.4, 1.5)	reference
P value[g]	0.6048		0.2663	

9HPT = 9-hole peg test; CI = confidence interval; EDSS = Expanded Disability Status Scale; IFN = interferon; ITT = intention-to-treat; IVRS = interactive voice response system; LCLA = Low-Contrast Letter Acuity Test; MSFC = Multiple Sclerosis Functional Composite; PASAT-3 = Paced Auditory Serial Addition Test; SD = standard deviation; SDMT = Symbol Digit Modalities Test.

[a] Difference in means and P value for comparison between the ozanimod and interferon beta-1a 30 mcg treatment groups were based on the analysis of covariance model, adjusted for region (Eastern Europe vs Rest of the World), EDSS category per IVRS, and the baseline MSFC z score.

[b] Difference in means and P value for comparison between the ozanimod and IFN bet-1a 30 mcg treatment groups were based on the analysis of covariance model, adjusted for region (Eastern Europe vs. rest of the world), EDSS category per IVRS, and the baseline Timed 25-Foot Walk Test score.

[c] Difference in means and P value for comparison between ozanimod and IFN beta-1a 30 mcg treatment groups were based on the analysis of covariance model, adjusted for region (Eastern Europe vs. rest of the world), EDSS category per IVRS, and the baseline 9HPT score.

[d] Difference in means and P value for comparison between the ozanimod and IFN β -1a 30 mcg treatment groups were based on the analysis of covariance model, adjusted for region (Eastern Europe vs. rest of the world), EDSS category per IVRS, and the baseline PASAT-3 score.

[e] Difference in means and P value for comparison between the ozanimod and IFN β -1a 30 mcg treatment groups were based on the analysis of covariance model, adjusted for region (Eastern Europe vs Rest of World), EDSS category per IVRS, and the baseline SDMT score.

[f] P value has not been adjusted for multiple testing.

[g] Difference in means and P value for comparison between the ozanimod and IFN β -1a 30 mcg treatment groups were based on the analysis of covariance model, adjusted for region (Eastern Europe vs Rest of World), EDSS category per IVRS, and the baseline visual function test score.

Source: Clinical study reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Table 46: Time to Onset of Disability Progression – (ITT Population)

	RADIANCE Part B		SUNBEAM		Pooled RADIANCE Part B and SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)	Ozanimod 1 mg (N = 880)	Interferon beta-1a 30 mcg (N = N = 889)
Confirmation after 3 months						
Number (%) of patients with a confirmed progression	54 (12.5)	50 (11.3)	13 (2.9)	19 (4.2)	67 (7.6)	69 (7.8)
Number (%) of patients censored	379 (87.5)	391 (88.7)	434 (97.1)	429 (95.8)	NR	NR
Cox Proportional Hazards						
Hazard Ratio (ozanimod /interferon beta-1a) (95% CI)[a]	1.045 (0.711, 1.537)	reference	0.690 (0.340, 1.402)	reference	0.950 (0.679, 1.330)	reference
Percent Reduction (95% CI)[a]	−4.5 (−53.7, 28.9)	reference	30.954 (−40.222, 66.002)	reference	NR	reference
P value[a]	0.8224		0.3055		0.7651	

	RADIANCE Part B		SUNBEAM		Pooled RADIANCE Part B and SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)	Ozanimod 1 mg (N = 880)	Interferon beta-1a 30 mcg (N = N = 889)
Confirmation after 6 months						
Number (%) of patients with a confirmed progression	42 (9.7)	29 (6.6)	9 (2.0)	7 (1.6)	51 (5.8)	36 (4.0)
Number (%) of patients censored	391 (90.3)	412 (93.4)	438 (98.0)	441 (98.4)	NR	reference
Cox Proportional Hazards						
Hazard Ratio (ozanimod /interferon beta-1a) (95% CI)[a]	1.435 (0.893, 2.305)	reference	1.238 (0.460, 3.337)	reference	1.413 (0.922, 2.165)	reference
Percent Reduction (95% CI)[a]	−43.5 (−130.5, 10.7)	reference	−23.839 (−233.740, 54.048)	reference	NR	reference
P value[a]	0.1353		0.6725		0.1126	

CI = confidence interval; EDSS = Expanded Disability Status Scale; IFN = interferon; ITT = intention-to-treat.

[a] Based on the Cox proportional hazard model with factors for treatment group, adjusted for region (Eastern Europe vs Rest of the World), age at baseline, and baseline EDSS score.

Source: Clinical study reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Table 47: Sensitivity Analysis for the Time to Onset of Disability Progression – (ITT Population)

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Sensitivity analysis: Time to onset of disability progression considering an EDSS score increase of 1.5 as progression for patients with baseline EDSS of 0 – confirmation after 3 months				
Number (%) of patients with a confirmed progression	50 (11.5)	47 (10.7)	11 (2.5)	18 (4.0)
Cox Proportional Hazards				
Hazard Ratio (ozanimod /interferon beta-1a) (95% CI)[a]	1.014 (0.680, 1.510)	reference	0.614 (0.289, 1.303)	reference
Percent Reduction (95% CI)[a]	−1.4 (−51.0, 32.0)	reference	38.596 (−30.347, 71.074)	reference
P value[a]	0.9467		0.2041	
Sensitivity analysis: Time to onset of disability progression considering an EDSS score increase of 1.5 as progression for patients with baseline EDSS of 0 – confirmation after 6 months				
Number (%) of patients with a confirmed progression	38 (8.8)	25 (5.7)	8 (1.8)	6 (1.3)
Cox Proportional Hazards				
Hazard Ratio (ozanimod /interferon beta-1a) (95% CI)[a]	1.465 (0.884, 2.429)	reference	1.299 (0.449, 3.759)	reference
Percent Reduction (95% CI)[a]	−46.5	reference	−29.949	reference

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
	(−142.9, 11.6)		(−275.921, 55.079)	
P value[a]	0.1383		0.6288	
Sensitivity analysis: Time to onset of disability progression including unconfirmed progressions – confirmation after 3 months				
Number (%) of patients with a confirmed progression	110 (25.4)	132 (29.9)	68 (15.2)	102 (22.8)
Cox Proportional Hazards				
Hazard Ratio (ozanimod /interferon beta-1a) (95% CI)[a]	0.804 (0.624, 1.036)	reference	0.631 (0.464, 0.859)	reference
Percent Reduction (95% CI)[a]	19.6 (−3.6, 37.6)	reference	36.896 (14.127, 53.628)	reference
P value[a]	0.0913		0.0034[b]	
Sensitivity analysis: Time to onset of disability progression including unconfirmed progressions – confirmation after 6 months				
Number (%) of patients with a confirmed progression	110 (25.4)	132 (29.9)	68 (15.2)	102 (22.8)
Cox Proportional Hazards				
Hazard Ratio (ozanimod /interferon beta-1a) (95% CI)[a]	0.805 (0.625, 1.037)	reference	0.630 (0.463, 0.857)	reference
Percent Reduction (95% CI)[a]	19.5 (−3.7, 37.5)	reference	37.041 (14.325, 53.735)	reference
P value[a]	0.0931		0.0032[b]	
Sensitivity analysis: Time to onset of disability progression including study withdrawal as progression – confirmation after 3 months				
Number (%) of patients with a confirmed progression	95 (21.9)	108 (24.5)	42 (9.4)	52 (11.6)
Cox Proportional Hazards				
Hazard Ratio (ozanimod /interferon beta-1a) (95% CI)[a]	0.863 (0.655, 1.138)	reference	0.779 (0.518, 1.171)	reference
Percent Reduction (95% CI)[a]	13.7 (−13.8, 34.5)	reference	22.120 (−17.136, 48.220)	reference
P value[a]	0.2969		0.2300	
Sensitivity analysis: Time to onset of disability progression including study withdrawal as progression – confirmation after 6 months				
Number (%) of patients with a confirmed progression	84 (19.4)	90 (20.4)	38 (8.5)	43 (9.6)
Cox Proportional Hazards				
Hazard Ratio (ozanimod /interferon beta-1a) (95% CI)[a]	0.930 (0.691, 1.253)	reference	0.846 (0.546, 1.311)	reference
Percent Reduction (95% CI)[a]	7.0 (−25.3, 30.9)	reference	15.412 (-31.076, 45.412)	reference
P value[a]	0.6347		0.4539	

	RADIANCE Part B		SUNBEAM	
	Ozanimod 1 mg (N = 433)	Interferon beta-1a 30 mcg (N = 441)	Ozanimod 1 mg (N = 447)	Interferon beta-1a 30 mcg (N = 448)
Sensitivity analysis: Time to onset of disability progression including unconfirmed progressions and study withdrawal as progression – confirmation after 3 months				
Number (%) of patients with a confirmed progression	144 (33.3)	170 (38.5)	93 (20.8)	129 (28.8)
Cox Proportional Hazards				
Hazard Ratio (ozanimod /interferon beta-1a) (95% CI)[a]	0.823 (0.659, 1.028)	reference	0.674 (0.516, 0.881)	reference
Percent Reduction (95% CI)[a]	17.7 (−2.8, 34.1)	reference	32.585 (11.886, 48.421)	reference
P value[a]	0.0867		0.0039[b]	
Sensitivity analysis: Time to onset of disability progression including unconfirmed progressions and study withdrawal as progression – confirmation after 6 months				
Number (%) of patients with a confirmed progression	144 (33.3)	170 (38.5)	93 (20.8)	129 (28.8)
Cox Proportional Hazards				
Hazard Ratio (ozanimod /interferon beta-1a) (95% CI)[a]	0.824 (0.660, 1.029)	reference	0.672 (0.514, 0.879)	reference
Percent Reduction (95% CI)[a]	17.6 (-2.9, 34.0)	reference	32.755 (12.109, 48.552)	reference
P value[a]	0.0880		0.0037	

CI = confidence interval; EDSS = Expanded Disability Status Scale; IFN = interferon; ITT = intention-to-treat.

[a] Based on the Cox proportional hazard model with factors for treatment group, adjusted for region (Eastern Europe vs Rest of the World), age at baseline, and baseline EDSS score.

[b] P value has not been adjusted for multiple testing.

Source: Clinical study reports of RADIANCE Part B and SUNBEAM trials.[11,12]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- Expanded Disability Status Scale (EDSS)
- Low-Contrast Letter Acuity (LCLA)
- MRI outcomes
- Multiple Sclerosis Quality of Life-54 items (MSQOL-54)
- Multiple Sclerosis Functional Composite (MSFC)
  - 9-Hole Peg Test (9-HPT)
  - Timed 25-Foot Walk Test (T25FW)
  - Paced Auditory Serial Addition Test (PASAT)
- Symbol Digital Modalities Test (SDMT).

Findings

Table 48: Summary of Outcome Measures and their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
EDSS	An ordinal scale (0 to 10) composed of 8 functional systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation) used to measure disability in patients with MS. A lower score indicates a lower level of disability.	**Validity**: Valid in patients with MS. **Reliability**: Fair to substantial intra-rater reliability (EDSS kappa values between 0.32 to 0.76 and between 0.23 to 0.58 for the individual functional systems) has been reported. **Responsiveness**: No clear evidence was identified in patients with MS.	1.0-point change when the EDSS score was between 0 to 5.5; 0.5-point change when the EDSS score was between 5.5 to 8.5.
LCLA	Uses the Low-Contrast Sloan Letter Charts featuring grey letters of decreasing size on a white background to measure contrast letter acuity. Depending on the chart, each has a maximum score of 60 or 70 correct letters.	**Validity**: Tests at 1.25% contrast are valid in patients with MS; moderate correlation with EDSS (r = –0.43 to –0.45) and strong correlation with MSFC (r = 0.56 to 0.57). **Reliability**: Good inter-rater reliability (ICC = 0.86 to 0.95) at all contrast levels in patients with MS. **Responsiveness**: No clear evidence was identified, but a 7-letter increase over 12 weeks was considered improvement for patients receiving and responding to natalizumab.	Suggested that a ≥5 to 7-letter change in score is clinically meaningful in patients with MS.
MRI outcomes	MRI scans for T1, T2, and GdE lesions.	**Validity**: No clear evidence was identified in patients with MS. **Reliability**: Mixed evidence was identified in patients with MS.	Not identified.

Outcome measure	Type	Conclusions about measurement properties	MID
		Responsiveness: No clear evidence was identified in patients with MS.	
MSQOL-54	A self-reported 54-item tool with Likert scales and multiple-choice items. Two summary scores (physical and mental health) can be derived from a weighted combination of scale scores (ranging from 0 to 100) where a higher score indicates improved quality of life.	**Validity**: Statistically significant differences between patients with mild vs. moderate symptoms were found for physical function, health distress, and physical health composite. **Reliability**: Good internal consistency reliability (Cronbach alpha ranging from 0.75 to 0.96 and ICC from 0.67 to 0.96). **Responsiveness**: Sensitivity of 0.91 for both summary scores, and specificity of 0.43 and 0.45 for of the mental and physical summary scores, respectively, for being able to discriminate between improved and unimproved patients with MS.	MIDs of 2.5 points and 1.5 points each from total scores of 100 for the mental and physical summary scores, respectively, determined from 265 patients with MS who had undergone 4 to 6 weeks of physiotherapy.
MSFC	A 3-part test made up of the 9-HPT, T25FW, and PASAT used to assess different clinical dimensions (arm, leg, and cognition, respectively).	**Validity**: Scores were lower in more disabled patients (–0.4 in PPMS and –0.3 in SPMS vs. +0.42 in RRMS); moderate to strong correlation between EDSS and MSFC (r = –0.41 to –0.83); moderate correlation between MRI outcomes and MSFC (r < 0.5). **Reliability**: Inter-examiner reliability and ICCs have been reported at 0.98 and 0.96, respectively. **Responsiveness**: Suggested that MSFC results should be assessed individually over time rather than collectively as an overall score.	Not identified for the overall MSFC score.
9-HPT	The time needed to insert and remove 9 pegs from 9 holes on a board. Measures manual dexterity.	**Validity**: Moderate correlation with EDSS (r = 0.51). **Reliability**: Strong test-retest reliability over 1 week (ICC between 0.902 and 0.972). **Responsiveness**: Variable evidence demonstrating test's ability to detect disease progression.	20% change in score in patients with MS though it has been noted that results differ between dominant and non-dominant hands.
T25FW	The time needed to walk 25 feet in a straight line. Measures ambulatory function.	**Validity**: Good correlation with EDSS (r = 0.84). **Reliability**: Strong reliability over various time periods (ICC between 0.94 and 0.99). **Responsiveness**: Some evidence demonstrating ability to detect meaningful change in walk time after one month for patients treated with intravenous methylprednisolone.	20% change in score in patients with MS.
PASAT	A test in which a number is presented every 3 seconds to a total of 60 numbers where each new digit must be added to the last. Measures auditory	**Validity**: Weak correlation with EDSS (r = 0.31); moderately correlated with the BRBN (validity coefficients ranged from 0.30 to 0.63); strongly correlated with	0.5 SD change in patients with MS.

Outcome measure	Type	Conclusions about measurement properties	MID
	processing ability for the total number of correct additions.	SDMT (validity coefficients ranged from 0.54 to 0.62). **Reliability**: Good internal consistency for individual trials (correlations ranging from 0.76 to 0.95) and high test-retest reliability (range = 0.90 to 0.97). **Responsiveness**: No clear evidence was identified in patients with MS though there is evidence indicating a learning effect after the first test administration.	
SDMT	The patient must associate numbers with figures as a measure of cognition.	**Validity**: Moderate to weak correlation with other outcomes measures: PASAT (r = 0.54), 9-HPT (r = –0.47), T25FW (r = –0.42), EDSS (r = –0.34), and LCLA (r = 0.34). **Reliability**: Strong reliability demonstrated with repeated testing (ICC = 0.93). **Responsiveness**: Sensitivity of 74% and specificity of 76% have been reported for detecting cognitive impairment in patients with MS.	Suggested to be a 3 to 5-point decrease in patients experiencing relapses in MS or a 10% change in test magnitude.

9-HPT = 9-Hole Peg Test; BRBN = brief repeatable battery of neuropsychological; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; ICC = intraclass correlation coefficient; LCLA = Low-Contrast Letter Acuity; MID = minimal important difference; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = MS functional composite; MSQOL-54 = MS quality of life-54 items; PASAT = paced auditory serial addition test; PPMS = primary progressive MS; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SDMT = Symbol Digital Modalities Test; SPMS = secondary progressive multiple sclerosis; T25FW = Timed 25-Foot Walk Test.

Expanded Disability Status Scale

EDSS is an ordinal scale used to measure disability in MS and addresses disability in 8 functional systems.[61] These are pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. The score ranges from 0 to 10 (in increments of 0.5) that incorporate functional system grades as well as the degree of functional disability and ambulation (Table 49).[62] A score from 0 to 4.5 represents normal ambulation, while a score of at least 5 represents a progressive loss of ambulatory ability.

The distribution of EDSS scores among MS patients is typically bimodal, 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 EDSS, including the fact that it has moderate intra-rater reliability (kappa values between 0.32 to 0.76 and between 0.23 to 0.58 for the individual functional system have been reported),[62] it is a poor assessment of upper limb and cognitive function, and it lacks linearity between score difference and the clinical severity.[63-66] EDSS was also found to be poorly correlated with neuropsychological impairment and brain changes measured by MRI.[62] Other limitations include that it relies heavily on the evaluation of motor function and the ability to walk, as such, a patient who might not be able to walk but maintains full dexterity is classified toward the severe end of the scale.

Self-reported walk distance was found to be inaccurate in at least 2 different studies.[75,76] In one by Berger et al., 44% of patients incorrectly estimated their maximum walking distance resulting in an inaccurate estimated EDSS score.[75] Of the 66 patients studied, 30.3% overestimated their walking distance while 13.6% underestimated theirs resulting in higher and lower estimated EDSS scores, respectively. On the other hand, Skjerbæk et al. found that 78% of patients in a retrospective analysis of a Danish MS hospitals rehabilitation study (n = 273) underestimated their walking disease and furthermore, that the use of assistive walking devices increased the risk of inaccuracy.[76] Self-reported and actual EDSS scores differed by at least 0.5 point in 24% of MS patients and there was a greater discrepancy between these scores in patients with a lower actual EDSS score (4.0 to 5.5 vs. 6.0 to 7.5). To rectify this, it has been suggested that a separate walking test be administered rather than relying on patient self-reporting.

In published literature, the MID was estimated to be a 1.0-point change when the EDSS score was between 0.0 and 5.5, but decreased to a 0.5-point change when the EDSS score was between 5.5 and 8.5.[67]

Table 49: Scoring of EDSS Scale

	Normal Neurological Exam (All Grade 0 in Functional Systems; Cerebral Grade 1 Acceptable)
1	No disability, minimal signs in 1 FS (i.e., grade 1, excluding cerebral grade 1).
1.5	No disability, minimal signs in more than 1 FS (more than 1 grade 1, excluding cerebral grade 1).
2.0	Minimal disability in 1 FS (1 FS at grade 2; other 0 or 1).
2.5	Minimal disability in 2 FSs (2 FSs at grade 2, others 0 or 1).
3.0	Moderate disability in 1 FS (1 FS at grade 3, others 0 or 1), or mild disability in 3 or 4 FSs (3 or 4 FSs at grade 2, others 0 or 1), but fully ambulatory.
3.5	Fully ambulatory, but with moderate disability in 1 FS (one grade 3) and 1 or 2 FSs at grade 2; or 2 FSs at grade 3; or 5 FSs at grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about approx. 12 hours a day despite relatively severe disability consisting of one FS at grade 4 (others 0 or 1), or combinations of lesser grades exceeding the limits of previous steps. Able to walk without aid or rest for approx. 500 metres.
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 at grade 4 (others 0 or 1) or combinations of lesser grades exceeding the limits of previous steps. Able to walk without aid or rest for approx. 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 FSs at 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 2 FSs at 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 approx. 12 hours a day. (Usual FS equivalents are combinations with more than one FS at 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 at grade 4+.)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed 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: Kurtzke JF.[77]

Low-Contrast Letter Acuity

LCLA is conducted using the Sloan Letter Charts which display grey letters on a white background that progressively decrease in size.[59] Sitting 2 m away, and with any usual corrective lenses, patients read aloud from the charts and the number of correct letters is recorded to a maximum score of 60 or 70 letters, depending on the chart.[59,60] Charts with 100%, 2.5%, and 1.25% contrast are typically used in MS clinical trials.[60] This test is subject to both floor and ceiling effects with very low and high contrast levels, respectively, where patients can have scores of zero or near zero for low contrast or have perfect or near-perfect scores that do not change over time.

The Low-Contrast Sloan Letter Charts have been reported as both sensitive and reliable for measuring contrast letter acuity in patients with MS compared to healthy individuals.[59,60]

At 1.25% contrast, binocular LCLA scores had moderate correlation with EDSS scores at a 12-month visit ($r = –0.43$, $p = 0.001$).[59] Monocular scores had weak correlation with overall neurological function (better eye with $r = –0.17$, $p = 0.26$, and worse eye with $r = –0.29$, $p = 0.05$). LCLA scores at 5% and 1.25% contrast had greater correlation with MSFC (significant to $p < 0.05$, not including the PASAT) than with EDSS. Baier et al. assessed the test's construct validity and reported higher mean scores for the 5% and 1.25% contrast for patients with EDSS scores less than 6.5 compared to those with higher EDSS scores. For predictive validity, after adjusting for the MSFC, tests at the 5% and 1.25% contrast levels at baseline provided good information for predicting changes in the following year regarding neurological disability measured by the EDSS[59] and low-contrast vision was a good predictor of typical everyday visual tasks such as reading, recognizing faces, and driving.[60] Tests at 1.25% contrast have been validated in patients with MS demonstrating moderate and good correlation with EDSS and MSFC ($r = –0.43$ to $–0.45$ and $r = 0.56$ to 0.57, respectively), and it has been suggested that the LCLA would be a useful addition to these 2 instruments for capturing additional MS-related visual dysfunction.

At all contrast levels, the LCLA demonstrated very good inter-rater reliability (ICC = 0.86 to 0.95) when testing individuals with and without MS.[60] When evaluating test-retest variability in healthy patients, an average improvement of one letter was observed though there was also large variability of up to 2 lines, or 10 letters, in either direction in this measure. A total of 7 letters is thought to be equivalent to 2 standard deviations on inter-rater difference.

A worse LCLA score has also been associated with greater T1 and T2 brain MRI lesion volumes more so than a change in EDSS or MSFC scores.[60] Specifically, a score decrease of 1 to 2 letters at both 2.5% and 1.5% contrast levels was related to a 1% decrease in brain volume by MRI. Additionally, a 7-letter sustained improvement over 12 weeks was considered as a positive response in patients responding well to natalizumab treatment.

There are still differing opinions on what a clinically meaningful change is with the most commonly reported range being from greater than 5 to 7 letters.[60]

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.[78-80]

In RADIANCE Part B and SUNBEAM, the following MRI outcomes were measured between treatment groups: T1 lesions, GdE lesions, and T2 lesions. These are conventional MRI outcomes that are widely used to monitor treatment effects in clinical trials of MS. Their roles as a surrogate for clinical outcomes, such as relapses and disability progression in RRMS, have been investigated in previous research. Findings from systematic reviews and large RCTs reporting the correlations between the treatment effect on relapses and disability progression and the treatment effect on MRI lesions are presented Table 50. 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 50: Summary of Correlations between MRI Outcomes and Clinical Outcomes

Study	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
Sormani 2013[81]	• 31 RCTs of all available DMTs for RRMS; published from 2008-2012	• Number of MRI lesions • ARR • 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 2011[82]	• 3 RCTs enrolling RRMS patients (cladribine vs. placebo; fingolimod vs. placebo; fingolimod vs. interferon) • Follow-up: 12-24 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 resulted close to those predicted by MRI active lesions; from the regression lines provided in the article, 10 out of 12 observed effects on the clinical variables were very close to those predicted by the lines	MRI markers were able to predict treatment effects on clinical end points in RRMS patients treated with novel oral agents
Sormani 2010[83]	• The PRISMS study enrolling 560 RRMS patients: subcutaneous interferon vs. placebo	• 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 lower new T2 lesion	The study provides evidence that new T2 MRI lesion count is a surrogate for relapses in MS patients

Study	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
	• Follow-up: 2 years.		number by 60% over 2 years, and the number of relapses decreased by 30%. PTE on relapses accounted for by the effect of treatment on new T2 MRI lesions was 53% in RRMS patients A pooled PTE of 62% was found when meta-analysis was performed on data from PRISMS and 2 other trials of DMTs	treated with interferon or drugs with similar mechanism of action
Kappos 1999[84]	• Patients in natural-course studies or 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: 6-24 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 GdE lesions: RR 1.13, p = 0.023 The mean of GdE 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	GdE MRI was not a strong predictor of the development of cumulative impairment or disability

ARR = annual relapse rate; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhanced; MS = multiple sclerosis; OR = odds ratio; PTE = proportion of treatment effect; RCT = randomized controlled trial; RR = relative risk; RRMS = relapsing-remitting MS.

Multiple Sclerosis Quality of Life-54

The MSQOL-54 is a self-reported, generic and disease-specific, quality of life instrument made up of Likert scales and multiple-choice items.[44,45] It contains 12 subscales, 2 summary scores, and 2 additional single-item measures. The subscales include physical function, role limitations–physical, role limitations–emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function while the additional single-item measures are satisfaction with sexual function and change in health.[44] There is no single overall score for MSQOL-54 though the 2 summary scores, physical health and mental health, can be derived from a weighted combination of scale scores which range from 0 to 100 where a higher score indicating improved quality of life.[46] Further to that, the multiple-item scales of each of these scores can be analyzed individually to better understand the changes in the composite scores. The physical health composite score is computed from the individual scores of the following scales: physical function, health perceptions, energy/fatigue, role limitations – physical, pain, sexual function, social function, and health distress. The mental health composite score is computed from the individual scores of the following scales: health distress, overall quality of life, emotional well-being, role limitations–emotional, and cognitive function.[46]

In terms of construct validity, statistically significant differences between patients with mild vs. moderate symptoms were found for physical function, health distress and physical health composite.[46] The role limitations due to emotional problems and the cognitive function scales were the least sensitive to group differences. MSQOL-54 has good internal consistency reliability (Cronbach alpha 0.75 to 0.96 scale items) and ICCs ranging from 0.67 and 0.96.

In a study of 265 patients with MS (221 with RRMS) and a mean EDSS of 2.23, Taheri et al. attempted to assess the instrument's responsiveness and determine a MID after 4 to 6 weeks of physiotherapy.[85] The receiver operating characteristics method was used in which the area under the curve (AUC) ranging from 0.5 to 1.0 indicates no ability to perfect ability to discern between improved and unimproved patients. They determined the MSQOL mental and physical summary scores to have AUCs of 0.66 and 0.61, respectively, which did not meet their acceptable level of high responsiveness (AUC > 0.70). In terms of sensitivity, they determined this to be 0.91 (95% CI, 0.84, 0.95) for both mental and physical summary scores, as well as a specificity rating of 0.43 (95% CI, 0.35, 0.51) and 0.45 (95% CI, 0.37, 0.53) for the 2 summary scores, respectively. Using the 7-point global rating scale as an external measure to the MSQOL, they found there was fair correlation to the mental and physical summary scores (correlation coefficient = 0.33 and 0.28, respectively). Taheri et al. calculated MIDs of 2.5 points and 1.5 points each from total scores of 100 for the mental and physical summary scores.

Multiple Sclerosis Functional Composite

MSFC is an instrument for measuring MS disability that was developed in 1994 by a task force convened by the US National Multiple Sclerosis Society.[48,86] This instrument has 3 components and assesses different clinical dimensions: arm (9-HPT, the time needed to insert and remove 9 pegs), leg (T25FW, the time needed to walk 25 feet), and cognition (PASAT, the total number of correct additions). For 9HPT and T25FW, a higher test result means the patient worsened from baseline. For PASAT, a higher test result means that the patient improved from baseline. In order to ensure that all measures are in the same direction, a transformation is necessary.[47] The raw scores for each item are transformed into z scores to achieve a common metric in SD units (i.e., a mean of 0 and an SD of 1). A z score represents the number of SDs by which a patient's test result is higher (Z > 0) or lower (Z < 0) than the average test result (Z = 0) of the reference population. The mean and SD from test results at the baseline visit for all patients in each study were used as the reference population values to create the z scores for each component of the composite. The z score is calculated by subtracting the mean of the reference population from the test result and then dividing this by the SD of the reference population. In creating the composite outcome measure, it was decided that a higher test result would indicate improvement from baseline.[48] The z scores for each component are averaged to generate a single MSFC score.[49] However, MSFC has been criticized based on its expression as a z score that is not intuitive for interpretation, dependence on a reference population for z score calculation, and the weighting of the different MSFC components.[50-52].

For construct validity, scores were lower in more disabled patients (–0.4 in PPMS and –0.3 in SPMS vs. +0.42 in RRMS).[86] Convergent validity was assessed in a study (N = 38) by Ozakbas et al. where they had found a moderate to strong correlation between EDSS and MSFC. When looking at individual components, EDSS had the lowest correlation (r = 0.31) with PASAT. The

authors suggested that this might confirm the observation of poor assessment of cognitive function by EDSS. The strongest correlation was between EDSS and T25WT (r = 0.84), followed by 9-HPT (r = 0.51). Again, this was consistent with the criticism of the EDSS's poor assessment of upper limb function. A systematic review of MSFC found the correlation with EDSS to range from –0.41 to –0.83.[62] Moderate correlation was observed between MSFC scores and MRI findings (r < 0.50).[51]

In a small cohort of patients (n = 10), MSFC was administered to each patient twice over a 2-week period for a total of 6 assessments examining test-retest reliability. Inter-examiner reliability and ICCs were reported at 0.98 and 0.96, respectively.[49,62]

A MID of 20% change in scores on T25FW and 9-HPT, and a 0.5 SD change on PASAT-3, have been considered clinically meaningful, however, a clinically meaningful value for overall MSFC score has not been determined.[51,86,87]

The MSFC has not been accepted by regulators as a primary end point in clinical trials.[52]

9-hole peg test (9-HPT)

9-HPT is a component of MSFC that assesses a patient's manual dexterity by having them pick up and place 9 pegs into 9 holes on a board, then remove the pegs once more as quickly as possible.[54] The test is performed twice with each hand and the score is recorded as the mean time in seconds required to complete the task for each hand.

To assess discriminative validity, cut-off values have been put forth to differentiate normal from abnormal hand function.[88] Values of 1.0 SD to a more conservative >1.95 SDs of the age- and sex-related normative values have been suggested. Other studies have noted a difference of 18 to 33 seconds to differentiate between no manual dysfunction and severe dysfunction. Further validation with greater standardization and larger numbers of participants is needed. 9-HPT has also shown variably validity compared with other non-MS-specific tests for upper extremity dexterity such as the ABILHAND and the modified Jebsen Taylor hand function test (correlation coefficients ranging from –0.37 to 0.95) in different populations.

A study of 69 patients, 58 (84.1%) of whom had RRMS, with a median EDSS of 4.0, was conducted to examine the reliability, precision, and MID of 9-HPT.[89] Patients performed the test with the same administrator with a week between each trial. For test-retest reliability over the span of one week, ICCs ranged from 0.902 to 0.972 indicating strong reliability. Hervault et al.[89] reported a coefficient of variation between 2.6% and 4.6%. The researchers also found that there was a smaller MID with a patient's dominant hand compared to their non-dominant hand at 4.38 and 7.46 seconds, respectively. They suggested that a 19.4% change in time for the dominant hand and a 29.1% change in time for the non-dominant hand would be considered clinically important which supports the commonly accepted 20% change in score for this test.

With regards to test responsiveness, studies have calculated the areas under the receiver operating characteristic curves (AUC) and found 9-HPT detected disease progression with AUC from 0.58 to 0.97 for anchors from clinician perspective and 0.49 to 0.91 for anchors from patient perspective.[88]

Timed 25-foot walk test

T25FW is a measure of gait velocity.[53] A standardized protocol is used to reduce variability between raters and across administration sites and involves the patient safely walking a clearly marked 25-foot straight course as quickly as possible. Using a stopwatch, the time is measured from the initiation of the walk from a static start position to completion (when the patient's foot crosses the plane of the 25-foot mark). Patients are instructed to continue walking beyond the marked 25-foot line before slowing down. The task is administered again by having the patient walk back the same distance. The score for T25FW is the average of the 2 completed trials, reported in seconds. Patients may use assistive devices when completing the T25FW (e.g., canes, crutches, walkers).[52]

T25FW is not appropriate for patients who are unable to walk 25 feet,[53] and, in some studies, has shown statistically significant improvement in patient performance during repeat test sessions, likely due to the practice effect.[49,90] However, other studies did not demonstrate this and instead, the test showed good test-retest reliability.[91,92] T25FW has served as the primary outcome measure in a phase III clinical trial for MS of any course type[93] and in exercise therapy for MS.[94]

Summaries of studies supporting the validity, reliability, responsiveness, and clinical meaningfulness of T25FW in adult patients with MS were presented in the 2012 recommendations of the Multiple Sclerosis Outcomes Measures Taskforce[53] and updated in a 2017 invited review by the Multiple Sclerosis Outcomes Assessments Consortium.[52] Strong reliability over various time periods has been demonstrated with an ICC between 0.94 and 0.99 though it has shown variability depending on the patient's EDSS score. To test construct validity, studies examined if patients with mild, moderate, and severe levels of disability (based on EDSS score) could be differentiated. A statistically significant difference in the median T25FW scores was found, specifically 3.9, 4.5, and 5.8 seconds, for patients with mild (EDSS 0 to 2.0), moderate (EDSS 2.5 to 3.5), and severe (EDSS 4.0 to 5.5) disability. Similar results were found even when EDSS score ranges differed slightly: 4.8, 6.3, and 9.0 seconds for mild (EDSS 0 to 3.0), moderate (EDSS 4.0 to 5.5), and severe (EDSS 6.0 to 6.5) disability. A notable difference was also demonstrated between patients with MS and age- and sex-matched healthy controls with median scores of 4.4 and 3.7 seconds, respectively. To measure responsiveness, a study investigated the effect of treatment with intravenous methylprednisolone in patients with RRMS. It was found that T25FW could detect a significantly improved walk time from 6.8 seconds to 5.9 seconds after one month of treatment.

A change of at least 20% in T25FW has been cited as the MCID for mixed MS populations and has been supported by members of an FDA advisory committee.[45,95] Multiple studies have corroborated the MID or MCID as being at least 15% to 20% using a variety of approaches, including clinical anchors, patient-reported anchors, real-life anchors, and distribution-based methods.[52,91,96-103] One cross-sectional study of 159 MS patients (with relapsing and progressive forms) in the US identified three T25FW score thresholds (< 6 seconds, 6 to 8 seconds, and ≥ 8 seconds) associated with real-world changes in patient employment status, instrumental activities of daily living, and the use of walking assistive devices.[98] These benchmarks warrant further investigation.

Paced Auditory Serial Addition Test

PASAT is a neuropsychological test and a measure of cognitive function, auditory processing ability, and verbal communication.[54] It was first developed to monitor the recovery of patients who had sustained mild head injuries, later adapted for use in patients with MS by Rao et al. in 1989 and is now widely used in MS studies.[49,55] During the test, a number is presented every 3 seconds to a total of 60 numbers. Each new digit must be added to the last and sum is spoken aloud by the patient. The total number of correct additions is then recorded. Many have criticized PASAT for its association with psychological stress and agitation, high reports of patient dropouts, its necessity for the patient to have a minimum level of mathematical ability, and the potential for practice effects.[56]

Studies have shown PASAT has good internal consistency with correlations among individual trial scores ranging from 0.76 to 0.95 and a Cronbach alpha of 0.90 from another study of 4 test trials.[104] PASAT was found to be moderately correlated with the brief repeatable battery of neuropsychological (BRBN) tests, global cognitive function of z score (validity coefficients ranged from 0.30 to 0.63), and strongly correlated with SDMT (validity coefficients ranged from 0.54 to 0.62).[56] Strong test-retest reliability over different time periods has also been demonstrated in some studies with coefficients in the 0.90 to 0.97 range. As with other repeated performance tests, there is evidence indicating a learning effect with PASAT. It has been shown that the greatest effect is seen between the first and second administration though scores are more consistent afterwards and are also independent of the time interval between tests. Since patient performance tends to improve after the first trial, 2 points should be considered: (1) the accuracy of the first attempt, and (2) the impact the learning effect may have on subsequent results (i.e., the test's ability to accurately track a patient's cognitive improvement or decline over time). A 0.5 SD change on PASAT has been considered clinically meaningful.[51,86,87]

Symbol digital modalities test

SDMT is a commonly used neuropsychological test that screens for cognitive impairment and takes little time to administer and score.[57] Similar to PASAT, SDMT measures processing speed along with visual working memory rather than auditory processing, all of which tend to decline with MS progression.[30] Additionally, SDMT and PASAT are alike in terms of practice effect and reliability when performed at 1-week intervals in patients with MS; however, SDMT is superior in its sensitivity when discriminating between healthy controls and patients with MS. It has been suggested that it would be an acceptable complementary test when examining cognitive impairment in patients with MS.

The patient is given a test sheet that includes a row of single digits, 1 to 9, corresponding to 9 unique symbols at the top and an array of symbols paired with empty spaces below.[57,58] They must choose the correct matching number as rapidly as possible in 90 seconds.[56] At the end of the test, the total number of correct responses, from 0 to 110, is recorded.

Magnin et al. conducted a study of 62 patients with MS and 19 non-MS matched controls to evaluate the reproducibility and test-retest reliability of SDMT after one week.[105] Results for both groups demonstrated strong reliability (ICC = 0.93 for the population with MS and ICC = 0.92 for those without) and significant ($p < 0.05$) improvement from one test to the next with an 8.94% increase in score for the patient group and 9.30% increase for the control group. A possible learning effect should be considered when conducting multiple tests over time. The researchers suggested that a true improvement in cognition at the individual level would be a performance increase of at least 35% on SDMT but do not propose a specific MID. Conducting the test multiples times and taking the mean of the scores may be necessary to ensure better reliability.

A study of 485 patients with MS (308 of whom had RRMS) was conducted to test PASAT and SDMT over repeated visits.[56] Sonder et al. found that there was a greater rate of missing values for PASAT mostly due to inability to understand or unwillingness to complete the test. Furthermore, SDMT showed no ceiling effect and minimal learning effect compared to PASAT. When compared to BRBN, an instrument used to identify cognitive disturbances in patients with MS, the data showed that BRBN had greater correlation with SDMT than PASAT at 0.586 vs. 0.296, respectively. Both PASAT and SDMT demonstrated very good test-retest reliability over time with slightly higher coefficients calculated for the latter (range = 0.700 to 0.865 and range = 0.809 to 0.882, respectively).

A review of pooled study results found that SDMT had the strongest correlation with PASAT (r = 0.54), moderate correlation with 9-HPT (r = -0.47) and T25FW (r = -0.42), and weaker correlation with EDSS (r = -0.34) and LCLA (r = 0.34).[106] Further to these pooled results, SDMT demonstrated good test-retest reliability (ICC = 0.85). After conducting known-group analyses, it was suggested that SDMT score is more closely correlated to disease severity rather than disease duration. An average of an 8.60-point difference was calculated for individuals with an EDSS score greater than 4.0 whereas only an average a 3.31-point difference was calculated for those with longer disease duration (≥10 years). To evaluate the concordance between SDMT and EDSS, kappa coefficients were calculated (for different definitions of SDMT worsening) ranging from –0.02 to 0.03 demonstrating poor correspondence between the 2 measures and that the 2 instruments measure decline in patients with MS differently. A sensitivity of 74% and specificity of 76% have been reported for detecting cognitive impairment in patients with MS.[105]

SDMT was used to screen cognitive impairment in 359 patients with MS. At a specificity of 0.60, a high sensitivity (0.91) was obtained indicating the potential of SDMT as a sentinel test for cognitive impairment.[58,107] In another study of 34 patients with MS, the test-retest reliability coefficient was 0.97 when tested over 2 weeks, and the reliability was maintained at 1-month and 2-year intervals.[58,107] Validity (construct, predictive, discriminative and criterion) was demonstrated in patients with MS, showing that SDMT is a good measure of processing speed or efficiency. In addition, SDMT was found to be strongly correlated to various MRI measures, such as atrophy, lesion burden and microstructural pathology.[58]

Studies have suggested a decrease in 3 to 5 points as being a notable difference in patients who experienced relapses[58] while a 10% change in magnitude was considered as an MID in SDMT.[58]

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