CADTH

CADTH Common Drug Review

Clinical Review Report

OFATUMUMAB (KESIMPTA)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Multiple sclerosis, relapsing-remitting

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Abbreviations

3mCDP	3-month confirmed disability progression
3mCDW	3-month confirmed disability worsening
6mCDW	6-month confirmed disability worsening
6mCDI	6-month confirmed disability improvement
6mCDP	6-month confirmed disability progression
9-HPT	9-hole peg test
ARR	annual relapse ratio
CDP	confirmed disability progression
CI	confidence interval
CIS	clinically isolated syndrome
CMSWG	Canadian Multiple Sclerosis Working Group
CNS	central nervous system
CRD	Centre for Reviews and Dissemination
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions questionnaire
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
FS	functional system
HR	hazard ratio
HRQoL	health-related quality of life
IFN	interferon
ITC	indirect treatment comparison
MID	minimal important difference
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSIS-29	29-item Multiple Sclerosis Impact Scale
MSWS-12	12-item Multiple Sclerosis Walking Scale
NEDA-4	4-parameter no evidence of disease activity

NfL	neurofilament light chain
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	odds ratio
PDDS	Patient Determined Disease Steps
PPMS	primary progressive multiple sclerosis
RCT	randomized controlled trial
RMS	relapsing forms of multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SPMS	secondary progressive multiple sclerosis
T25W	Timed 25-Foot Walk
VAS	Visual Analogue Scale
WPAI:MS	Work Productivity and Activity Impairment questionnaire for Multiple Sclerosis

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	Ofatumumab (Kesimpta), 20 mg/0.4 mL solution for injection, subcutaneous injection
Indication	For the treatment of adult patients with RRMS with active disease defined by clinical and imaging features
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	January 22, 2021
Sponsor	Novartis Pharmaceuticals Canada Inc.

NOC = Notice of Compliance; RRMS = relapsing-remitting multiple sclerosis.

Introduction

Multiple Sclerosis (MS) is an 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 of 28 years to 31 years.[2] The Public Health Agency of Canada reports that more than 77,000 Canadians live with MS and approximately 60% of newly diagnosed adults are between 20 and 49 years of age.[3] Cases of MS are 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]

Relapsing forms of multiple sclerosis (RMS) include clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), and active secondary progressive multiple sclerosis (SPMS).[5] The term CIS refers to the first clinical presentation of disease that is compatible with MS exhibiting characteristics of inflammatory demyelination, although the MS diagnostic criteria have not yet been fulfilled.[1,6] Cases of RRMS are 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.[7] Most patients who initially present with RRMS go on to develop SPMS, which is a progressive phase of the disease.[1,4] Patients with RRMS and SPMS can be further defined by an “active” phenotype of the disease diagnosed by clinical relapses and/or magnetic resonance imaging (MRI) that reveals contrast-enhanced lesions and new and unequivocally enlarging T2 lesions.

There is currently no curative treatment for MS. The principal goal of treatment for MS is to delay or prevent the accumulation of disability by reducing the frequency of relapses and the number of lesions visible in MRI.[8] The clinical expert consulted by CADTH identified the following goals of disease-modifying therapy (DMT): to delay disease progression; decrease the burden of disability or symptoms; decrease the number and severity of relapses; and preserve mobility, cognition, independence, and employment. It is recommended that all patients with RMS should begin treatment with a DMT as soon as possible following diagnosis to reduce the risk of disability worsening and improve long-

term outcomes.[8,9] Several DMTs for MS are currently available in Canada, allowing for a personalized approach to treatment. Because 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 drug safety profiles.[8,10] Treatment optimization by switching DMTs is typically carried out due to lack of efficacy or poor tolerability.

The current drug under review, ofatumumab (20 mg/0.4 mL), is indicated for the treatment of adult patients with RRMS with active disease defined by clinical and imaging features. Ofatumumab is a human monoclonal antibody (immunoglobulin G1) that is available as a solution for subcutaneous injection.[11] The recommended dose is 20 mg, to be initially administered weekly at weeks 0 (beginning of treatment), 1, and 2, followed by monthly dosing starting at week 4.[11] The sponsor has requested reimbursement of ofatumumab as per the indication under review.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient group in response 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 a 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 MS Society of Canada collected patient input through an online survey posted on its website (www.mssociety.ca) and Facebook page between August 4, 2020, and September 4, 2020, in both English and French. A total of 69 people between the ages of 31 and 60 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.

Depending on the type and severity of the symptom, the impact on an individual's quality of life can be great. Living with MS creates issues with employment due to relapses, symptoms, medication side effects, and disability progression. It also creates 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.

There is a growing number of high-efficacy DMTs, with varied forms of administration, dosing schedules, and decreased monitoring requirements — factors that are consistently identified by patients as priorities when selecting a DMT. Patients are looking for a treatment that would result in fewer relapses requiring hospitalization, decrease work absenteeism, and allow them to remain active within their social networks. The MS Society did not receive feedback from patients with current or previous experience with ofatumumab.

Clinician Input

The expert reported that additional treatment options for RMS are required as not all patients respond to the same mechanism of action of a DMT. The clinical expert also noted that lifestyle factors need to be considered, as do comorbidities and 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 ofatumumab, but noted that ofatumumab would be an option for all persons with RMS who require a DMT.

The clinical expert stated that ofatumumab should not be used in combination with any other DMT. In the expert's opinion, ofatumumab would be ideal as an option for both first-line treatment, as well as a switch due to lack of efficacy with a different DMT, following a personalized treatment or medicine. The expert also felt that it would not be appropriate to recommend that patients try other treatments before initiating treatment with ofatumumab, and if started early ofatumumab could contribute to improving the patient's health-related quality of life (HRQoL). Further, the expert indicated that ofatumumab would be suitable for any person with RMS who requires a DMT, and that patients should be identified by clinicians with consideration of the involvement of an MS expert (from a specialty practice, with an MS fellowship, or within an MS clinic). Patients who would be least suitable for treatment with ofatumumab were not identified.

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 they be monitored clinically and radiologically. The clinical expert described a clinically meaningful response as the relative stabilization of MS. When deciding 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 (e.g., community setting, hospital or outpatient clinic, or specialty clinic) would be appropriate for treatment with ofatumumab. The expert added that it would be ideal to have a specialist diagnose, treat, and monitor patients who might receive ofatumumab.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two identically designed pivotal trials for ofatumumab, ASCLEPIOS I and II, met the criteria for the CADTH systematic review. The ASCLEPIOS studies were conducted between 2016 and 2019 and followed a randomized, double-blind, double-dummy, active comparator-controlled, parallel-group, multi-centre design, with adaptive design features (flexible duration). Patients enrolled in the 2 studies had a diagnosis of RMS (representing 95% in RRMS or 5% SPMS with disease activity as defined by Lublin et al.[6]) with mild to moderate disease (a mean EDSS score of 2.9 to 3.0), were more than half-free of gadolinium-enhanced T1 lesions, and were neurologically stable within 1 month prior to randomization. ASCLEPIOS I and II randomized 927 and 955 patients with RMS, respectively, at a 1:1 ratio to either of 2 treatment groups: an ofatumumab group or a teriflunomide group. The ofatumumab group received subcutaneous injections of ofatumumab (20 mg) administered

on study days 1, 7, and 14, and month 1, then every 4 weeks until the end of study, plus a teriflunomide-matched placebo capsule orally once daily. Patients in the teriflunomide group were treated with oral teriflunomide (14 mg) once daily as well as subcutaneous placebo injections administered according to the ofatumumab treatment regimen. The primary objective of both studies was to demonstrate the superiority of ofatumumab 20 mg to teriflunomide 14 mg in terms of reducing the frequency of confirmed relapses based on the annualized relapse rate (ARR) in patients with RMS. The key secondary objectives were to demonstrate the superiority of ofatumumab to teriflunomide in terms of various disability outcomes based on the EDSS and MRI. Outcomes related to disability progression or improvement were evaluated with a pre-planned analysis using a pooled dataset of ASCLEPIOS I and II and included as key secondary end points in the statistical testing hierarchy. In addition, HRQoL (as measured by the 29-item Multiple Sclerosis Impact Scale [MSIS-29] and EuroQol 5-Dimensions questionnaire [EQ-5D]), mobility (Timed 25-Foot Walk [T25FW] and 9-hole peg test [9-HPT]), cognitive function (Symbol Digit Modalities Test [SDMT]), and the ability to work (Work Productivity and Activity Impairment questionnaire for Multiple Sclerosis [WPAI:MS]), as well as a composite outcome for disease activity (4-item no evidence of disease activity [NEDA-4]), were assessed in the 2 trials.

Overall, baseline characteristics were well balanced between treatment arms in each of the trials, and were similar between the ASCLEPIOS I and II studies. The mean (standard deviation [SD]) age of patients ranged from 37.8 (9.0) to 38.9 (8.8) years, and the majority were female (66.3% to 68.6%) and White (88.0% to 89.2%). At baseline, the mean (SD) number of relapses in the 12 months prior to screening ranged from 1.2 (0.6) to 1.3 (0.7). Most patients had RRMS at study entry (93.9% to 94.9%) and the remainder had SPMS (5.1% to 6.1%). Patients had a mean (SD) EDSS score of 2.9 (1.3) to 3.0 (1.4), indicating moderate disability in 1 functional system (FS) or mild disability in 3 to 4 FSs, and no impairment to walking,[12] and between 56.1% and 63.4% of patients were free of gadolinium-enhanced T1 lesions.

Efficacy Results

A summary of key efficacy results from the 2 pivotal trials, ASCLEPIOS I and II, is provided in Table 2.

The primary analysis in ASCLEPIOS I and II was ARR, defined as the number of confirmed MS relapses in a year. The primary end point was met in both trials. Patients in the ofatumumab treatment group experienced a lower ARR than did patients in the teriflunomide treatment group. Treatment with ofatumumab resulted in a rate reduction of 50.5% based on an ARR ratio of 0.50 (95% confidence interval [CI], 0.37 to 0.65; $P < 0.001$) in ASCLEPIOS I. Similarly, the comparison of ofatumumab to teriflunomide in ASCLEPIOS II demonstrated a rate reduction of 58.5% based on an ARR ratio of 0.42 (95% CI, 0.31 to 0.56; $P < 0.001$) in favour of ofatumumab. The results of a sensitivity analysis that included all relapses (rather than only confirmed relapses) supported the primary efficacy analysis.

The following imaging outcomes were key secondary outcomes in the 2 trials: number of gadolinium-enhanced T1 lesions per scan, number of new or enlarging T2 lesions per year relative to baseline, and percent brain volume loss. Ofatumumab demonstrated superiority to teriflunomide for the measures of T1 and T2 lesions. In other words, patients in the ofatumumab groups exhibited fewer gadolinium-enhanced T1 lesions per scan and fewer new or enlarging T2 lesions per year relative to baseline, compared with patients in the

teriflunomide treatment groups in the 2 trials. More specifically, the number of gadolinium-enhanced lesions per scan corresponded to a rate reduction of 97.5% (rate ratio = 0.03; 95% CI, 0.01 to 0.05) and 93.8% (rate ratio = 0.06; 95% CI, 0.04 to 0.10) in ASCLEPIOS I and II, respectively, for the comparison of ofatumumab to teriflunomide in both studies (P < 0.001). The difference between ofatumumab and teriflunomide in terms of the mean rate of new or enlarging T2 lesions per year was 0.18 lesions (95% CI, 0.15 to 0.22; P < 0.001) in ASCLEPIOS I and 0.15 lesions (95% CI, 0.13 to 0.19; P < 0.001) in ASCLEPIOS II, both in favour of ofatumumab. No between-groups difference was found for percent brain volume loss based on the adjusted mean difference of 0.07% (95% CI, −0.02 to 0.15; P = 0.116) in ASCLEPIOS I and 0.07% (95% CI, −0.02 to 0.15; P = 0.129) in ASCLEPIOS II. As noted by the clinical expert on this review, the duration of the trials may not have been sufficient to measure changes in brain volume loss.

The MSIS-29 was 1 of the scales used in the ofatumumab trials to evaluate HRQoL, and more specifically the ability to remain active within social networks. Both were noted as outcomes of importance to patients. The MSIS-29 was included as a secondary outcome and measured [redacted]. In ASCLEPIOS I, the [redacted] corresponded to a between-group difference of [redacted]

In ASCLEPIOS II, this between-groups difference [redacted] Of note, a decrease in an MSIS-29 score suggests an improvement in HRQoL, and an increase in score indicates a decrease in HRQoL. The psychological impact score of the MSIS-29 was evaluated in the same way as the physical impact score. The results of the psychological impact score were [redacted] The minimal important difference (MID) for the MSIS-29 was identified as a difference of 8 points for patients with an EDSS score between 5.5 and 8.0, and a difference of 7 when the EDSS score ranged between 0 and 5.0.[13] [redacted] of the results of the MSIS-29 were considered [redacted] Further, none of these measures were included in the statistical testing hierarchy, which adds to the uncertainty about the treatment effect of ofatumumab compared to teriflunomide in terms of HRQoL.

The results of confirmed disability worsening at 3 and 6 months (3mCDW and 6mCDW, respectively), and confirmed disability improvement at 6 months (6mCDI) from the pooled analysis of ASCLEPIOS I and II are provided in Table 2. The between-treatment comparison of ofatumumab to teriflunomide (pooled analysis) in time to 3mCDW corresponded to a risk reduction of 34.4% or a hazard ratio (HR) of 0.66 (95% CI, 0.50 to 0.86; P = 0.002), in favour of ofatumumab. This was consistent with the results in the individual studies. Similarly, time to 6mCDW corresponded to a risk reduction of 32.5% or an HR of 0.68 (95% CI, 0.50 to 0.92; P = 0.012) in favour of ofatumumab in the pooled analysis; however, for the individual studies, the difference in ASCLEPIOS I was statistically significant, but not in ASCLEPIOS II (0.76; 95% CI, 0.49 to 1.17), possibly due to a relatively smaller effect size (24% reduction) and lack of precision as a result of a high proportion of earlier discontinuations (17%) in this trial. The between-groups comparison for 6mCDI resulted in no difference between groups (pooled analysis HR = 1.35; 95% CI, 0.95 to 1.92; P = 0.094), which was consistent with the results of the individual trials.

Subgroup analyses were conducted in the 2 pivotal studies with respect to age (≤ 40 or > 40 years), number of relapses in the previous 2 years (< 2 or ≥ 2), prior treatment experience (treatment experience versus naive), RMS subtype (RRMS versus SPMS), and

disease severity (EDSS score > 3.5 or ≤ 3.5). The effect on ARR was generally consistent across all the subgroups but it remains unknown if the effect could be different between highly active and non-active RMS disease as no subgroup results were available. For the effect on 3mCDW and 6mCDW, the subgroup results revealed that the treatment effect was potentially more evident in younger patients (≤ 40 years old) or those free of gadolinium-enhanced T1 lesions at baseline. It appeared the treatment effects on 3mCDW and 6mCDW were similar regardless of disease severity, number of relapses in the previous 2 year (< 2 or ≥ 2) or prior treatment experience, but unknown by disease activity as no subgroup results were available.

Harms Results

A summary of key safety results from the 2 pivotal trials is provided in Table 2.

No deaths were reported during the treatment period in either of the pivotal trials. The majority of patients reported at least 1 treatment-emergent adverse event (82.2% versus 82.3% in ASCLEPIOS I and 85.0% versus 86.1% in ASCLEPIOS II, for the ofatumumab versus teriflunomide treatment groups, respectively). The most commonly reported adverse events were injection-related reactions, nasopharyngitis, headaches, and upper respiratory tract infections. In both studies, injection-site reactions and a decrease in blood immunoglobulin M were reported in a greater proportion of patients in the ofatumumab treatment groups than in the teriflunomide groups. Alopecia and diarrhea were more common in patients in the teriflunomide group than in the ofatumumab groups. Additionally, injection-related reactions were reported by a greater proportion of patients in the ofatumumab treatment group than in the teriflunomide group in ASCLEPIOS II, as well as upper respiratory tract infections in ASCLEPIOS I.

Serious adverse events were reported by 7.6% to 10.3% of patients in the treatment groups of both studies, but the frequency of individual serious adverse events was low. The proportion of patients who stopped treatment due to adverse events was low, ranging from 5.2% to 5.8% of patients across the 2 pivotal trials. The most common adverse events leading to treatment discontinuation was a decrease in blood immunoglobulin M, which occurred in 2.2% and 1.9% of patients in the ofatumumab groups and 0.6% and 0.6% in the teriflunomide groups of ASCLEPIOS I and II, respectively.

Regarding notable harms for this review, injection-related reactions were reported among 13.9% to 24.7% of patients, and reductions in serum immunoglobulins (specifically, decreases in blood immunoglobulin M) were reported in 1.7% to 6.2% of patients across ASCLEPIOS I and II. Both of these events were more common among patients in the ofatumumab treatment groups than in the teriflunomide treatment groups. Other notable harms (as per the CADTH systematic review protocol) reported in the 2 studies included malignancies, neutropenia, decreased blood immunoglobulin G, and lymphopenia. Each of these events was reported in no more than 2.4% of patients in any treatment group, with no major differences between treatment groups. There were no cases of opportunistic infections such as cryptococcal meningitis and serious infections, such as progressive multifocal leukoencephalopathy, reported in ASCLEPIOS I or II.

Table 2: Summary of Key Results from ASCLEPIOS I and II

	ASCLEPIOS I		ASCLEPIOS II		ASCLEPIOS I and II (pooled)	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg	TER 14 mg
ARR (confirmed relapses)[a]						
N′	454	452	469	469	NA	
Adjusted ARR (95% CI)	0.11 (0.09 to 0.14)	0.22 (0.18 to 0.26)	0.10 (0.08 to 0.13)	0.25 (0.21 to 0.30)		
OMB vs. TER						
Rate reduction (%)	50.5		58.5			
Treatment-group difference versus control, ARR ratio (95% CI)	0.50 (0.37 to 0.65)		0.42 (0.31 to 0.56)			
P value	< 0.001		< 0.001			
Number of Gd-enhanced T1 lesions per scan[b]						
N′	432	422	439	434	NA	
Adjusted mean number of Gd-enhanced lesions per scan (95% CI)	0.01 (0.01 to 0.02)	0.45 (0.36 to 0.58)	0.03 (0.02 to 0.05)	0.51 (0.40 to 0.66)		
OMB vs. TER						
Rate reduction (%)	97.5		93.8			
Treatment-group difference versus control, rate ratio (95% CI)	0.03 (0.01 to 0.05)		0.06 (0.04 to 0.10)			
P value	< 0.001		< 0.001			
Number of new or enlarging T2 lesions per year relative to baseline[b]						
N′	440	431	448	443	NA	
Adjusted annualized mean rate at end of study (last scan in the DBT epoch) (95% CI)	0.72 (0.61 to 0.85)	4.00 (3.47 to 4.61)	0.64 (0.55 to 0.75)	4.15 (3.64 to 4.74)		
OMB vs. TER						
Rate reduction (%)	82.0		84.5			
Treatment-group difference versus control, rate ratio (95% CI)	0.18 (0.15 to 0.22)		0.15 (0.13 to 0.19)			
P value	< 0.001		< 0.001			
Percent brain volume loss (annual rate of change from baseline)[c]						
N′	418	409	437	434	NA	
Adjusted mean annual rate of change from baseline (95% CI)	–0.28 (–0.34 to 0.22)	–0.35 (–0.41 to 0.29)	–0.29 (–0.35 to –0.23)	–0.35 (–0.42 to –0.29)		
OMB vs. TER						
Adjusted mean difference (95% CI)	0.07 (–0.02 to 0.15)		0.07 (–0.02 to 0.15)			
P value[d]	0.116		0.129			

	ASCLEPIOS I		ASCLEPIOS II		ASCLEPIOS I and II (pooled)	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg	TER 14 mg
MSIS-29 physical impact score at month 30[c]						
N′	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]		
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]		
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]			
P value[e]	[redacted]		[redacted]			
MSIS-29 psychological impact score at month 30[c]						
N′	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]		
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]		
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]			
P value[e]	[redacted]		[redacted]			
Time to 3-month confirmed disability worsening during the treatment epoch[f]						
N′	465	459	479	472	944	931
Proportion of patients with 3mCDW (%)	9.7	13.7	9.0	13.1	9.3	13.4
OMB vs. TER						
Risk reduction (%)	34.8		34.0		34.4	
Hazard ratio (95% CI)	0.65 (0.45 to 0.96)		0.66 (0.45 to 0.97)		0.66 (0.50 to 0.86)	
P value	0.029		0.036		0.002	
Time to 6-month confirmed disability worsening during the treatment epoch[d]						
N′	465	459	479	472	944	931
Proportion of patients with 6mCDW (%)	7.5	11.5	7.5	9.7	7.5	10.6
OMB vs. TER						
Risk reduction (%)	39.3		24.4		32.5	
Hazard ratio (95% CI)	0.61 (0.40 to 0.93)		0.76 (0.49 to 1.17)		0.68 (0.50 to 0.92)	
P value	0.022		0.209		0.012	
Time to 6-month confirmed disability improvement during the treatment epoch[d]						
N'	375	363	374	360	749	723
Proportion of patients with 6mCDI (%)	8.8	7.2	11.0	7.2	9.9	7.3
OMB vs. TER						
Risk reduction (%)	–18.6		–51.6		–35.2	

	ASCLEPIOS I		ASCLEPIOS II		ASCLEPIOS I and II (pooled)	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg	TER 14 mg
Hazard ratio (95% CI)	1.19 (0.71 to 1.98)		1.52 (0.93 to 2.47)		1.35 (0.95 to 1.92)	
P value	0.515		0.094		0.094	
Harms, n (%) (safety set)						
AEs	382 (82.2)	380 (82.3)	409 (85.0)	408 (86.1)	NA	
SAEs	48 (10.3)	38 (8.2)	38 (7.9)	36 (7.6)		
WDAE (from study treatment)	27 (5.8)	24 (5.2)	27 (5.6)	25 (5.3)		
Deaths	0	0	0	0		
Notable harms[h]						
Injection-related reactions	76 (16.3)	77 (16.7)	119 (24.7)	66 (13.9)	NA	
Lymphopenia	1 (0.2)	0	2 (0.4)	2 (0.4)		
Neutropenia	1 (0.2)	8 (1.7)	1 (0.2)	3 (0.6)		
Malignancies[i]	11 (2.4)	11 (2.4)	0	1 (0.2)		
Reduction in serum immunoglobulins						
Blood IgG decreased	2 (0.4)	4 (0.9)	0	0		
Blood IgM decreased	26 (5.6)	13 (2.8)	30 (6.2)	8 (1.7)		

3mCDW = 3-month confirmed disability worsening; 6mCDW = 6-month confirmed disability worsening; AE = adverse event; ARR = annualized relapse rate; CI = confidence interval; DBT = double-blind treatment; EDSS = Expanded Disability Status Scale; Gd = gadolinium; IgG = immunoglobulin G; IgM = immunoglobulin M; MSIS-29 = 29-item Multiple Sclerosis Impact Scale; N′ = number of patients contributing to analysis; NA = not available; NR = not reported; OMB = ofatumumab; SAE = serious adverse event; SD = standard deviation; TER = teriflunomide; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Analyzed using a negative binomial regression model with log-link, treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of T1 Gd-enhanced lesions and the patient's age at baseline as covariates.

[b] Analyzed using a negative binomial model with adjustments for treatment and region (factors), and age, and corresponding baseline values (number of Gd-enhanced lesions or volume of T2 lesions) as continuous covariates.

[c] Analyzed using a random coefficients model with treatment and region as fixed effects; and time, baseline number of Gd-enhanced lesions, baseline T2 volume, and baseline normalized brain volume as continuous covariates.

[d] Statistical testing on this key secondary outcome was conducted after the statistical testing hierarchy was violated.

[redacted]

[f] Cox regression adjusted for study as stratum, treatment, and region as factors and baseline EDSS as a continuous covariate.

[g] The P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[h] Notable harms with no events reported: opportunistic infections (e.g., cryptococcal meningitis), serious infections (e.g., progressive multifocal leukoencephalopathy).

[i] Neoplasms benign, malignant, and unspecified (including cysts and polyps).

Note: All efficacy analyses reported in this table were analyzed using the full analysis set, and NA indicates analyses that were not conducted in the pooled dataset.

Source: Clinical Study Reports for ASCLEPIOS I,[14] ASCLEPIOS II,[15] and ASCLEPIOS I and II meta-analysis.[16]

Critical Appraisal

The ASCLEPIOS studies used an adequate method of randomization, resulting in a roughly balanced comparison between treatment arms regarding the baseline demographic and disease characteristics. Allocation concealment (double-dummy) was implemented for the 2 studies; however, differential incidence of adverse events, such as alopecia (13.9% and 15.6% versus 5.8% and 5.8%, respectively) and diarrhea (13.4% and 10.3% versus 4.5% and 5.8%, respectively) in the teriflunomide group versus the ofatumumab group, and injection-site or injection-related reactions in the ofatumumab group, had the potential to

reveal treatment assignment to physicians and patients, which may have compromised the assessment of subjective outcomes, including disability worsening and MSIS-29. Although the studies were adequately powered for the primary and key secondary outcomes, the duration of the 2 studies limits the ability to reliably evaluate the treatment effect of ofatumumab on outcomes such as HRQoL, mobility, cognitive function, and disability. Further, HRQoL outcomes and the WPAI:MS were important to patients, but interpretation of the results is limited due to relatively large amounts of missing data. Pre-specified subgroup analysis showed a consistent effect on the reduction of ARR. It also revealed that younger patients (≤ 40 years) or patients with no gadolinium-enhanced T1 lesions (0) may have been more likely to benefit from a delayed disability worsening compared with patients who were older or those with gadolinium-enhanced T1 lesions; however, due to various limitations, this needs to be further explored. High concomitant use of systemic corticosteroids was reported in ASCLEPIOS I and II; however, subgroup analyses by steroid use was not available and therefore the impact of steroid use on the efficacy and safety of the treatment is unknown.

In terms of external validity, the characteristics of patients included in the 2 studies were generally representative of Canadian patients living with RMS, subject to certain limitations. Based on expert input, key limitations to the generalizability include the exclusion of subsets of patients who would be suitable for treatment with ofatumumab, such as those with various comorbidities, those older than 55 years of age, and those with an EDSS score of up to 6.5. The duration of the trials may have been too short to obtain meaningful results in changes in mobility, cognitive function, and even disability, as well as long-term safety, as the treatment of MS is life-long.

Indirect Comparisons

Description of Studies

One sponsor-submitted indirect treatment comparison (ITC) was included in this review. The ITC consisted of a systematic review and network meta-analysis (NMA) of ofatumumab and other DMTs for the treatment of adult patients (at least 18 years old) with RMS. The following outcomes were included: ARR, 3-month confirmed disability progression (3mCDP) and 6-month confirmed disability progression (6mCDP). The NMA approach used by the authors of the ITC was based on evidence synthesis techniques described by the National Institute for Health and Care Excellence (NICE) Decision Support Unit Technical Support Document 2.

Efficacy Results

In this systematic review of ofatumumab against placebo and other DMTs, the evidence from direct comparisons (from the ASCLEPIOS I and II trials) shows that the use of ofatumumab results in a clinical improvement in the ARR, and in a moderate improvement in 3mCDP and 6mCDP when compared to teriflunomide. The results from the indirect comparisons show that ofatumumab, administered subcutaneously, is likely to be as effective as the other monoclonal antibody DMTs (i.e., alemtuzumab, natalizumab, cladribine, and ocrelizumab) for ARRs. For this same outcome, when compared to all other DMTs (interferon [IFN] beta, teriflunomide, glatiramer, dimethyl fumarate, fingolimod) and placebo, ofatumumab results in an improvement.

For the time to clinical disability progression, ofatumumab is likely as effective as ocrelizumab, alemtuzumab, natalizumab, IFN beta, dimethyl fumarate, cladribine for 3mCDP, and superior to teriflunomide, IFN beta, glatiramer acetate, fingolimod, and

placebo. For 6mCDP, ofatumumab is likely as effective as ocrelizumab, alemtuzumab, natalizumab, IFN beta, dimethyl fumarate, cladribine, and fingolimod, and superior only to teriflunomide and placebo.

Critical Appraisal

Limitations of the ITC and NMA stemmed from the heterogeneity in trial designs, including the varying definitions of relapse, time to confirmed disability worsening or progression, different study duration, and the relatively sparse network compared to the total number of included treatments. As with any Bayesian NMA using non-informative priors, the effect estimates may be less precise, particularly for between-study heterogeneity in a sparse network for each of the 3 study outcomes, and when considering the node for ofatumumab, which was compared only against teriflunomide in the ASCLEPIOS trials. Although sensitivity analyses alleviate concerns of bias in this area, some older trials were included and may have elevated placebo-arm relapse rates (i.e., elevated baseline risk), which also creates issues in the heterogeneity and applicability of the results. The safety of the different interventions was assessed narratively and the rationale for this appears to be appropriate, although the authors present numerical data in the appendices.

Conclusions

ASCLEPIOS I and II demonstrated superiority of ofatumumab to teriflunomide in adult patients with RRMS in terms of relapse, disability-related, and imaging outcomes. This includes a reduction in ARR, time to confirmed disability of worsening, the number of gadolinium-enhanced T1 lesions per MRI scan, and the number of new or enlarging T2 lesions per year (relative to baseline). The ability to work and HRQoL outcomes were also noted as important to patients, [redacted]

Direct comparative evidence for ofatumumab with other DMTs, including available monoclonal antibodies, is absent. One sponsor-submitted ITC comparing ofatumumab to other DMTs showed that ofatumumab is likely as effective as other monoclonal antibodies (alemtuzumab, natalizumab, cladribine, and ocrelizumab) in terms of ARR and confirmed disability progression (CDP). However, these findings may have suffered from a sparse network along with methodology heterogeneity, which resulted in a wide 95% credible interval and lack of precision in the effect estimates.

Last, there was no significant signal of concerns regarding the safety of ofatumumab in the pivotal trials, other than the anticipated injection-related reactions due to the subcutaneous route of administration. Serious adverse events were reported by 7.6% to 10.3% of patients in the treatment groups of both studies, but the frequency of individual serious adverse events was low. However, considering the anticipated long-term use of ofatumumab as a chronic therapy for RRMS, evidence beyond the 1- to 2-year duration of the ASCLEPIOS trials is required to reliably assess the safety of ofatumumab.

Introduction

Disease Background

Multiple sclerosis is an 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 years to 31 years.[2] The Public Health Agency of Canada reports that more than 77,000 Canadians live with MS and approximately 60% of newly diagnosed adults are between the 20 and 49 years of age.[3] While the etiology of MS remains unknown, it is commonly accepted that autoreactive lymphocytes are implicated.[2] The disease is characterized by focal demyelinated plaques in the CNS, and 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, most recently updated in 2017, are used in diagnosing MS.[17] Clinical evidence can be sufficient to meet the diagnostic criteria, although MRI can be used in conjunction with clinical evidence to make a diagnosis.[17,18] More specifically, the criteria for diagnosis are based on the occurrence of 1 or more attacks (relapse, exacerbation, and/or CIS) and objective clinical evidence of 1 or more lesions.[17,18] Depending on the number of attacks or lesions present, additional data may be required to make a diagnosis. This may include dissemination in time, demonstrated by evidence of an additional lesion, and/or dissemination in space, demonstrated by evidence of lesions in at least 2 CNS regions.[17]

Relapsing forms of MS (RMS) include CIS, RRMS, and active SPMS.[5] The term CIS refers to the first clinical presentation of disease that is compatible with MS exhibiting characteristics of inflammatory demyelination, although the MS diagnostic criteria have not yet been fulfilled.[1,6] Approximately 85% of patients with MS experience the RRMS phenotype at disease onset.[1,4] Cases of RRMS are 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.[7] 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, approximately 50% of patients with RRMS develop SPMS within 10 years of their diagnosis of RRMS.[19] Active SPMS is defined by clinical relapses and/or MRI evidence (contrast-enhanced lesions and new and unequivocally enlarging T2 lesions).

Standards of Therapy

There is currently no curative treatment for MS. 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.[8] The clinical expert consulted by CADTH noted that ideally, the goals of treatment with DMTs are to delay disease progression, decrease the burden of disability or symptoms, decrease the number and severity of relapses, and preserve mobility, cognition, independence, and employment. The expert also noted that all of these factors would then contribute to a better HRQoL as well as decrease 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.[8,9] The clinical expert consulted by CADTH for this review described the current

treatment paradigm as the same for persons with all forms of MS, whether CIS, RMS, or active SPMS; what may differ is which DMT is chosen in terms of safety (for example, pregnancy in a younger female patient, type 2 diabetes in an older patient, or hypertension). The clinical expert added that it is important to weigh the benefit against potential harm; the lower the harm, the more ideal the DMT.

The availability of several DMTs for MS in Canada allows for a personalized approach to treatment. According to Canadian MS Working Group (CMSWG) recommendations for treatment optimization in MS, 5 injectable agents (glatiramer acetate, IFN beta-1b, and 3 formulation of IFN beta-1a) and 2 oral agents (teriflunomide and dimethyl fumarate) are used as starting treatments for RMS.[8] Additionally, natalizumab, alemtuzumab, and ocrelizumab (all IV 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.[10] 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. As 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 drug safety profiles;[8,10] these were also highlighted by the clinical expert consulted for this review. Although not the most common or conservative approach, a higher-efficacy therapy may also be used as an initial therapy for patients with high disease activity or aggressive or rapidly evolving MS at onset.[8] 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. For example, a patient 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 a suboptimal response to a first-line drug.[8] However, as per feedback from the clinical expert, the main approach would be to switch to a DMT that has a different mechanism of action compared with the therapy that lacked efficacy. Of note, 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. Additionally, siponimod is available for patients with active SPMS as evidenced by relapses or imaging features characteristic of MS. Ozanimod was also recently approved in Canada with an indication for the treatment of patients with RRMS to decrease the frequency of clinical exacerbations.[20]

Clinical criteria to identify patients who should discontinue treatment have not been established because there are limited data about the long-term safety of chronic immunosuppression.[8] The CMSWG noted that treatment discontinuation may be considered for patients who have been clinically stable for more than 5 years, but added 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.[8]

Aside from DMTs, patients with MS may receive medications or non-pharmacological interventions for management of MS-related complications and symptoms. These include medications for bladder dysfunction, bowel dysfunction, depression, fatigue, pain, paroxysmal attacks, seizures, and spasticity.[21] However, some MS symptoms and treatments can exacerbate other symptoms and potential underlying causes should also be addressed. There are several non-pharmacological approaches to managing complications and symptoms, such as behavioural modification, physical therapy, mobility aids, feeding tubes, and non-invasive ventilation.[21] 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.[22]

Drug

Ofatumumab is a fully human monoclonal antibody (immunoglobulin G1), which binds to the CD20 molecule on B lymphocytes and induces lysis (cell death). Because B lymphocytes contribute to the production of pro-inflammatory cytokines, the release of autoreactive antibodies, and activation of pathogenic T cells, they play an important role in the pathogenesis of MS.[11] Ofatumumab (20 mg/0.4 mL) is indicated for the treatment of adult patients with RRMS with active disease defined by clinical and imaging features and is available as a solution for subcutaneous injection.[11] Ofatumumab is intended to be self-administered and is available as a pre-filled SensoReady pen, which contains 20 mg of ofatumumab solution for injection (0.4 mL of a 50 mg/mL solution). The recommended dose is 20 mg, to be administered weekly at weeks 0 (beginning of treatment), 1, and 2, followed by monthly dosing beginning at week 4.[11]

The sponsor has requested reimbursement of ofatumumab as per the indication under review. At the time of this review, ofatumumab is currently under review in Europe and the UK. The FDA has reviewed and approved ofatumumab for “the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.”[23]

Table 3: Key Characteristics of DMTs for Relapsing forms of Multiple Sclerosis

	Mechanism of action	Indication[a]	Route of administration	Recommended dose	Serious side effects or safety issues
Ofatumumab (Kesimpta)	B-cell depletion via CD20	RRMS with active disease defined by clinical and imaging features	SC injection	20 mg (0.4 mL of 50 mg/mL solution): • initial dosing at weeks 0, 1 and 2, followed by • subsequent monthly dosing, starting at week 4	Injection-related reactions, vaccinations, infections (PML, HBV reactivation) Contraindicated in patients who are hypersensitive to this drug, or any ingredient in the formulation
Teriflunomide (Aubagio)[24]	Not completely understood; may reduce numbers of activated lymphocytes available for migration into the CNS	RRMS[b]	Oral tablet	14 mg once daily	Hepatotoxicity and risk of teratogenicity Contraindicated in patients who are hypersensitive to this drug or to leflunomide; patients currently treated with leflunomide; severe hepatic impairment; 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 thromobocytopenia
Dimethyl fumarate (Tecfidera)[25]	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

	Mechanism of action	Indication[a]	Route of administration	Recommended dose	Serious side effects or safety issues
Interferon beta-1a (Avonex; Rebif)[26,27]	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	RMS (RRMS, SPMS with relapses); and patients with a single demyelinating event, accompanied by abnormal MRI scans, with lesions typical of MS	IM injection (Avonex) SC injection (Rebif)	IM: 30 mcg/ week (increase up to 60 mcg/week if needed) SC: 22 mcg or 44 mcg 3 times/week	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection-site reactions, depression or suicide Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease (Rebif only), pregnant women (Rebif only)
Interferon beta-1b (Betaseron; Extavia)[28,29]	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 (Betaseron, Extavia)	0.25 mg every other day	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection-site reactions, depression or suicidal ideation Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, pregnant women, and patients with current severe depression and/or suicidal ideation (Extavia only)
Pegylated IFN beta-1a (Plegridy)[30]	Its effects in MS not completely understood; it exerts its biological effects by binding to type I IFN receptors on the surface of human cells	RRMS	SC injection	125 mcg every 2 weeks	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection-site reactions, depression/suicidal ideation Contraindicated in patients with a history of

	Mechanism of action	Indication[a]	Route of administration	Recommended dose	Serious side effects or safety issues
					hypersensitivity to natural or recombinant IFN beta or pegylated IFN or any other component of the formulation or the container, pregnant patients, patients with current severe depression and/or suicidal ideation
Glatiramer acetate (Copaxone)[31]	Likely modifies the immune processes responsible for pathogenesis of MS	RRMS; single demyelinating event, accompanied by abnormal MRI scans and considered to be at risk of developing CDMS	SC injection	20 mg/day	Contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol
Ocrelizumab (Ocrevus)[32]	Reduction in CD20	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)[33]	Inhibits lymphocyte proliferation	monotherapy for the treatment of adult patients with RRMS	Oral	3.5mg/kg over 2 years	Lymphopenia, infections (herpes zoster, tuberculosis or latent tuberculosis reactivation, PML), malignancies, teratogenic
Siponimod (Mayzent)[34]	A S1P receptor modulator that binds selectively to 2 out of 5 GPCRs for S1P (S1P1 and S1P5); acts as a functional antagonist on S1P1 receptors on lymphocytes, preventing egress from lymph nodes and consequently reducing recirculation of T cells into the CNS to limit central inflammation	For the treatment of patients with SPMS with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability	Oral tablet	2 mg daily with 5-day titration period Note: A 1 mg daily maintenance dose is recommended for patients with CYP2C9*2*3 or *1*3 genotype	Bradyarrhythmia, atrioventricular conduction, liver function, infections (cryptococcal meningitis and herpes), macular edema, fetal harm. Contraindicated in patients with known hypersensitivity, homozygous for CYP2C9*3*3 genotype

	Mechanism of action	Indication[a]	Route of administration	Recommended dose	Serious side effects or safety issues
Fingolimod (Gilenya)[35]	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)[36]	Binds to the alpha-4 subunit of human integrin; blocks interaction of alpha-4 beta-1 integrin with VCAM-1; and blocks the interaction of alpha-4 beta-7 integrin with MadCAM-1	RRMS[b]; generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, other therapies for MS	IV infusion	300 mg every 4 weeks	PML, herpes Contraindicated in patients who have or have had PML or are at risk for PML; hypersensitive to this drug or to any ingredient in the formulation or any component of the drug; immunocompromized, including those immunocompromized due to immunosuppressant or antineoplastic therapies, or immunodeficiencies
Alemtuzumab (Lemtrada)[37]	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 ≥ 2 other DMTs	IV infusion	Initial treatment cycle: 12 mg/day for 5 consecutive days Second treatment cycle: 12 mg/day for 3 consecutive days administered 12	Autoimmune and immune-mediated conditions, infections, infusion reactions, stroke, malignancies Contraindicated in patients who are hypersensitive to alemtuzumab or to any

	Mechanism of action	Indication[a]	Route of administration	Recommended dose	Serious side effects or safety issues
				months after the initial treatment course	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; GPCR = G-protein-coupled receptor; HBV = hepatitis B virus; IFN = interferon; IM = intramuscular; MadCAM-1 = mucosal addressin cell adhesion molecule-1; MRI = magnetic resonance imaging; MS = multiple sclerosis; Nfr2 = nuclear factor (erythroid-derived)-like-2; PML = progressive multifocal leukoencephalopathy; RMS = relapsing forms of multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; S1P = sphingosine-1-phosphate; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; VCAM-1 = vascular cell adhesion molecule-1; VSV = varicella zoster virus.

[a] Health Canada–approved indication.

[b] Indicated as monotherapy.

Source: Product monographs for siponimod,[34] cladribine,[33] ocrelizumab,[32] Plegridy,[30] alemtuzumab,[37] dimethyl fumarate,[25] fingolimod,[35] glatiramer acetate,[31] Avonex,[26] Rebif,[27] Betaseron,[28] Extavia,[29] natalizumab,[36] and teriflunomide.[24]

Stakeholder Engagement

Patient Group Input

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

About the Patient Groups and Information Gathered

One patient group responded to the call from CADTH to provide input on the topic, the MS 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 MS Society of Canada works toward an MS-free world by funding research into the cause of 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 patient input related to MS from an online survey posted on its website (www.mssociety.ca) and Facebook page. The survey was displayed from August 4, 2020, to 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 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 symptom, the impact on an individual's quality of life can be severe. Living with MS creates employment issues such as the inability to maintain stable employment 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 lives. Caregivers are also greatly affected by MS as they play instrumental roles in the overall care and management plan of people living with the disease.

Experience with Treatment

There is a growing number of high-efficacy DMTs, with varied forms of administration, 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 having a choice in the selection of the administration, dosing schedule, side-effect profile, and level of medication monitoring that best fits their lifestyle and personal preferences. Without 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 did not receive feedback from patients with current or previous experience with ofatumumab. More than 70% (48 of 69) of all respondents had not been informed by their neurologist about ofatumumab as a new treatment for relapsing MS. Information related to mechanism of action, administration, and dosing of ofatumumab was provided in the introduction of the survey. When informed about the possible and common side effects of ofatumumab obtained from clinical trial data (symptoms of upper respiratory tract

infection such as sore throat and runny nose; local and generalized injection reactions, and decrease in immunoglobulin M blood levels), 24 of 69 (35%) did not know if they were willing to trade the risks of adverse effects for the perceived benefits, 17 (25%) said they would not take the risk, and 21 (30%) said they would be willing to take the risk.

As with other DMTs, ofatumumab administration requires pre-treatment laboratory tests or post-treatment monitoring that may present a burden (e.g., complete blood counts, liver enzyme, thyroid function, and screening for infections such as hepatitis C and B, HIV, and tuberculosis, among others). However, patients did not indicate that pre-treatment or monitoring tests were challenges for them to fulfill, other than the time away from work and waiting times required for blood collection.

Improved Outcomes

According to the patient input, ofatumumab is expected to fill a significant gap in MS treatment for patients who are recommended to use a high-efficacy monoclonal antibody, as ofatumumab offers a new method of administration; i.e., a monthly, subcutaneous, self-injection, as opposed to IV infusions that require specialized clinics. In addition, high-efficacy medications can reduce the financial burden to health and social systems through fewer relapses requiring hospitalization and loss of employment. Patients stated that ofatumumab has the potential to reduce this burden further as there is no requirement for a clinic visit or missing work to receive an infusion.

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. Patient comments included:

- *"Accessibility is a very important issue. The cost and inability to travel for treatment are challenges that should be address by our government."*
- *"We must continue pushing for affordable access to MS treatments for everyone afflicted by this disease."*

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 (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of multiple sclerosis. The input from the clinician consulted for this review and summarized below was provided prior to the receipt of the Notice of Compliance and revised indication for ofatumumab; however, patients with RRMS represent a subset of patients with RMS.

Unmet Needs

As indicated by the clinical expert, the ideal goal for patients with RMS is a cure. The expert indicated 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 pose a higher risk. The clinical expert also noted that lifestyle factors need to be taken into account, such as whether the patient lives in a remote area that does not have access to an infusion site or MRI to monitor risks of progressive multifocal

leukoencephalopathy, or if the patient is of child-bearing age. Also, some DMTs may be contraindicated due to comorbidities or severe side effects that interfere with compliance. According to the clinical expert, 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 ofatumumab, but noted that ofatumumab would be an option for all persons with RMS who require a DMT.

Place in Therapy

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

Patient Population

As previously noted, the expert believes ofatumumab would be suitable for any person with RMS who requires a DMT, and that patients should be identified by a clinician with consideration for the involvement of an MS expert (a physician from a specialty practice, with an MS fellowship, or from within an MS clinic). The expert did not identify patients who would be least suitable for treatment with ofatumumab. The expert also stated that it is not possible to identify patients who would be most likely to exhibit a response to treatment with ofatumumab; however, there is growing evidence suggesting that starting a DMT earlier will help improve disease-related outcomes in all persons with MS.

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. They also noted that there are no clear markers to indicate a medication is not working for 1 person with MS, and that the 2020 treatment optimization recommendations[8] criteria details switching criteria for patients. 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 acknowledged that this is not a realistic goal and again referred to 2020 treatment optimization recommendations.[8]

Discontinuing Treatment

When making a decision to discontinue treatment, the clinical expert recommended taking into account factors such as safety (for example, in those over the age of 65) and significant disability (an EDSS score of 8.0).

Prescribing Conditions

When asked about which settings would be appropriate for treatment with ofatumumab, the clinical expert stated that any community setting, hospital or outpatient clinic, or specialty clinic would be appropriate. The expert indicated that it would be ideal to have a specialist diagnose, treat, and monitor patients who receive ofatumumab, but acknowledged that this may be difficult to achieve in some areas of the country.

Clinical Evidence

The clinical evidence included in the review of ofatumumab 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 that were 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 ofatumumab (20 mg/0.4 mL) solution for subcutaneous injection for the treatment of adult patients with RMS.

Methods

Studies selected for inclusion in the systematic review include 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.

The CADTH Systematic Review protocol was developed prior to the granting of a Notice of Compliance for ofatumumab by Health Canada.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adults with RMS Subgroups: • Prior treatment experience • RMS subtype • Disease severity • Disease activity (e.g., highly active or not) • Age
Intervention	Ofatumumab 20 mg, administered by SC injection Ofatumumab administration: • Initial dosing at weeks 0, 1, and 2, followed by • Subsequent monthly dosing, starting at week 4
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)

	• Siponimod (Mayzent) • Fingolimod (Gilenya) • Alemtuzumab (Lemtrada)
Outcomes	**Efficacy outcomes** • Relapse (e.g., relapse rate and relapse-free rate)[a] • Imaging outcomes (e.g., MRI brain lesions, MRI brain volume) • Health-related quality of life[a] • Mobility • Cognitive function • Symptoms of MS (e.g., fatigue, cognition, and visual disturbance) • Ability to work or attend school[a] • Use of rescue medication • Disability progression or improvement **Harms outcomes** • AEs • SAEs • WDAEs • Mortality • Notable harms: injection-related reactions, opportunistic infections (e.g., cryptococcal meningitis), serious infections (e.g., progressive multifocal leukoencephalopathy), lymphopenia, neutropenia, reduction in serum immunoglobulins, malignancies
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; DMT = disease-modifying therapy; MRI = magnetic resonance imaging; MS = multiple sclerosis; RCT = randomized controlled trial; RMS = relapsing multiple sclerosis; SAE = serious adverse event; SC = subcutaneous; WDAE = withdrawal due to adverse event.

[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 *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[38]

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 concepts were ofatumumab and multiple sclerosis. Clinical trial registries were searched: 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 1 for detailed search strategies.

The initial search was completed on September 21, 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):[39] 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. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for 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

A total of 2 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

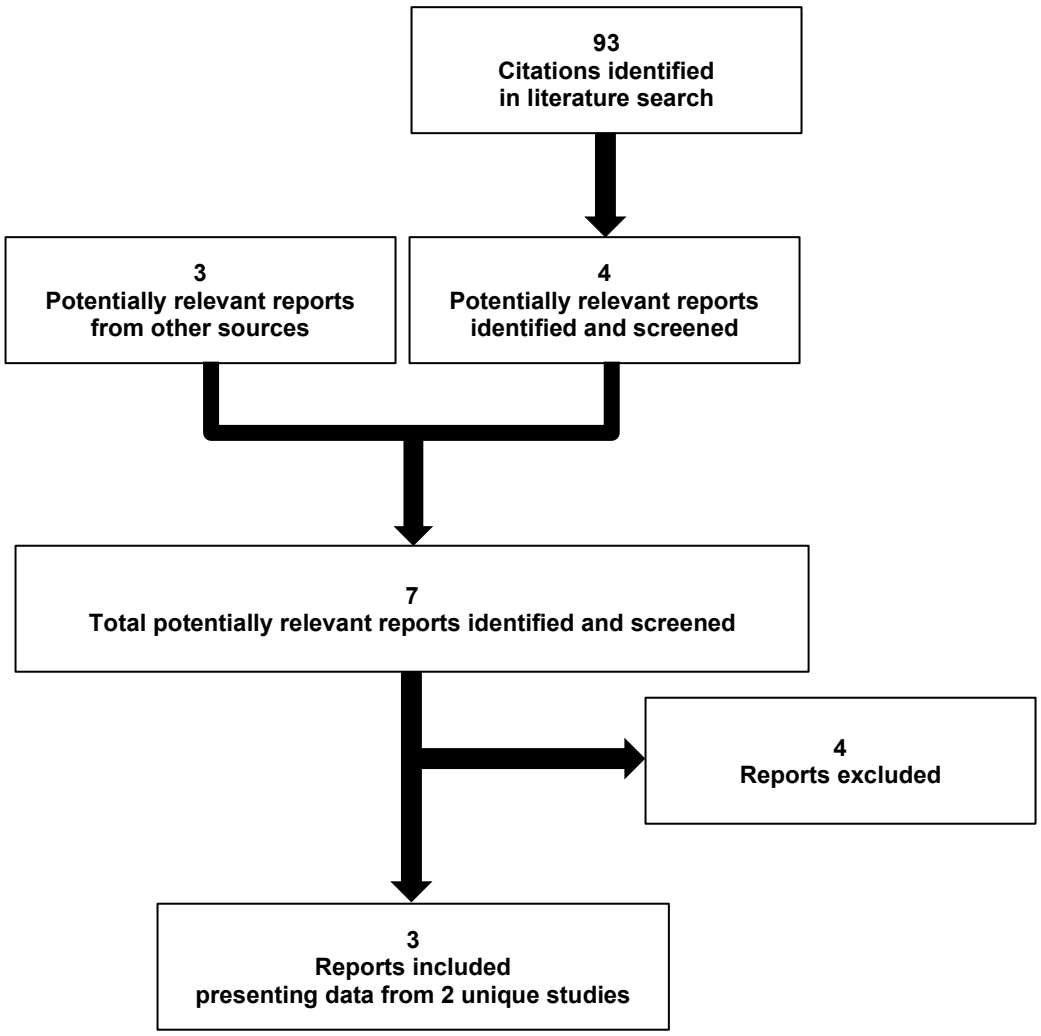


Table 5: Details of Included Studies

		ASCLEPIOS I	ASCLEPIOS II
Designs and Populations	**Study design**	Phase III, double-blind, double-dummy, active comparator-controlled, parallel-group, multi-centre, RCT	
	Locations	170 centres in 28 countries (Canada, US, UK, Argentina, Australia, India, Mexico, Thailand, Europe)	180 centres in 30 countries (Canada, US, UK, Argentina, Australia, India, Mexico, Peru, South Africa, Taiwan, Europe)
	Randomized (N)	927	955
	Inclusion criteria	• 18 to 55 years old (inclusive) at screening • Diagnosis of MS according to the 2010 Revised McDonald criteria • Relapsing MS: relapsing-remitting course (RRMS), or secondary progressive (SPMS) course with disease activity as defined by Lublin et al. (2014) • Disability status at screening with an EDSS score of 0 to 5.5 (inclusive) • Documentation of at least: 1 relapse during the previous 1 year OR 2 relapses during the previous 2 years prior to screening OR a positive Gd-enhanced MRI scan during the year prior to randomization (screening of MRI scans could have been used if no positive Gd-enhanced scan existed from the prior year) • Neurologically stable within 1 month prior to randomization	
	Exclusion criteria	• Patients with PPMS or SPMS without disease activity • Patients meeting criteria for neuromyelitis optica • Disease duration of more than 10 years in patients with an EDSS score of 2 or less • Pregnant or nursing (lactating) women • Patients with an active chronic disease of the immune system other than MS or with immunodeficiency syndrome • Patients with neurological findings consistent with PML or confirmed PML • Patients at risk of developing or having reactivation of hepatitis (A, B, C, and E), syphilis, or tuberculosis • Patients with active systemic infections or known to have AIDS or to test positive for HIV antibodies at screening • Have received any live or live-attenuated vaccines within 2 months prior to randomization • Have been treated with medications as specified or within timeframes specified (e.g., corticosteroids, ofatumumab, rituximab, ocrelizumab, alemtuzumab, natalizumab, cyclophosphamide, teriflunomide, or leflunomide) • Patients with neurologic or psychiatric disorders prior to randomization, including suicidal ideation or behaviour as indicated by the C-SSRS, ongoing substance abuse that may interfere with the study, or a history of clinically significant CNS disease or neurological disorders that may mimic MS	
Drugs	**Intervention**	Ofatumumab 20 mg, SC injection • Initial dosing at days 1, 7, and 14, followed by • Subsequent monthly dosing, starting at week 4, plus teriflunomide-matching placebo capsule orally	
	Comparator(s)	Teriflunomide 14 mg, oral capsule, administered once daily, plus ofatumumab-matching placebo injections on days 1, 7, and 14, and week 4 (study month 1) and every 4 weeks thereafter	
Duration	**Phase**		
	Run-in	"Screening epoch" (screening phase and baseline phase), 45 days	
	Double-blind	"Treatment epoch," variable (event-driven) up to a maximum of 30 months	
	Follow-up	"Safety follow-up epoch," variable, at least 9 months following end of treatment	

		ASCLEPIOS I	ASCLEPIOS II
Outcomes	**Primary end point**	ARR, defined as the number of confirmed MS relapses in a year	
	Secondary and exploratory end points	**Key secondary** • Time to 3mCDW, 6mCDW on the EDSS • Time to 6-month CDI on the EDSS • Number of T1 Gd-enhanced lesions per MRI scan • Annualized rate of new or enlarging T2 lesions • NfL concentration in serum • Change from baseline in brain volume **Secondary** • Time to 6-month CCD[a] (4-point worsening on SDMT); time to 6mCDW or 6-month CCD (whichever came first) • Change from baseline in cognitive performance (SDMT)[a] • Time to 6-month confirmed worsening of at least 20% in T25FW[a], 9-HPT[a] • Time to 6-month CDI[a] sustained until the end of study (EDSS) • MS relapse characteristics: proportion of patients hospitalized for relapse; proportion of patients with severe relapses • Number of new or enlarging T2 lesions between month 12 and EOS • Change in T2 lesion volume relative to baseline • Proportion of patients with 4-parameter NEDA at year 1 and 2 • MSIS-29 • Change from baseline in EDSS,[a] T25FW,[a] 9-HPT[a] **Exploratory** • Volume of cortical grey matter, hemispheric white matter, and thalamus • EQ-5D-5L • WPAI:MS	
Notes	**Publications**	Hauser et al. (2020)[40]	

3mCDW = 3-month confirmed disability worsening; 6mCDW = 6-month confirmed disability worsening; 9-HPT = 9-hole peg test; ARR = annualized relapse rate; CCD = confirmed cognitive decline; CDI = confirmed disability improvement; CNS = central nervous system; C-SSRS = Columbia Suicide Severity Rating Scale; EDSS = Expanded Disability Status Scale; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; Gd = gadolinium; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = 29-item Multiple Sclerosis Impact Scale; NEDA = no evidence of disease activity; NfL = neurofilament light chain; PML = progressive multifocal leukoencephalopathy; PPMS = primary progressive multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SDMT = Symbol Digit Modalities Test; SPMS = secondary progressive multiple sclerosis; T25FW = Timed 25-Foot Walk; WPAI:MS = Work Productivity and Activity Impairment for Multiple Sclerosis questionnaire.

[a] Outcome analyzed in pooled dataset (ASCLEPIOS I and II).

Note: One additional report was included: Hauser et al. (2020).[40]

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Description of Studies

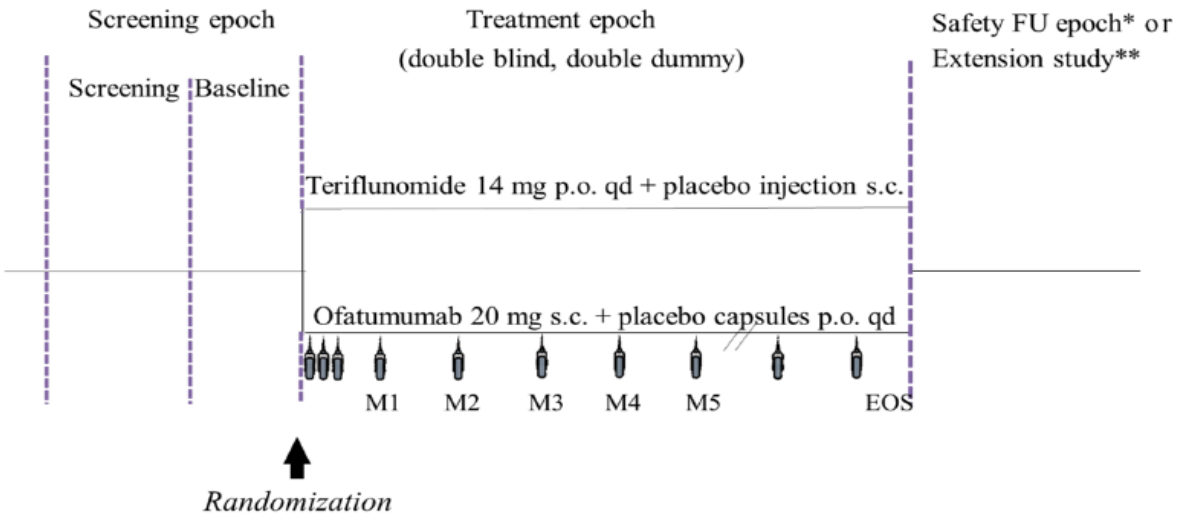
Two identical pivotal studies, ASCLEPIOS I and ASCLEPIOS II, were submitted by the sponsor and were the only studies that met the inclusion criteria for the CADTH systematic review. Details of the included studies and their study designs are provided in Table 5 and Figure 2.

The ASCLEPIOS studies were conducted between 2016 and 2019 and followed a randomized, double-blind, double-dummy, active comparator-controlled, parallel-group, multi-centre design, with adaptive design features (flexible duration). The primary objective of both studies was to demonstrate the superiority of ofatumumab 20 mg administered subcutaneously every 4 weeks to teriflunomide 14 mg administered orally once daily in terms of reducing the frequency of confirmed relapses based on the ARR in adult patients with RMS. The key secondary objectives were to demonstrate the superiority of

ofatumumab to teriflunomide in terms of various disability outcomes based on the EDSS, MRI, and serum neurofilament light chain (NfL), an exploratory biomarker for axonal damage and neurodegeneration.[8] An NfL concentration in serum was not included in the CADTH systematic review protocol as the clinical expert consulted for this review stated that the use of NfL results in clinical practice is exploratory at this time. In addition, disability outcomes were analyzed in a pre-planned pooled analysis that included patients from both ASCLEPIOS I and II. ASCLEPIOS I and II randomized 927 and 955 patients with RMS, respectively, and each of the studies included patients from 4 sites in Canada. Patients were randomized using interactive response technology at a 1:1 ratio to either of 2 treatment groups, the ofatumumab group or teriflunomide group, and randomization was stratified by geographical region and by subtype of RMS (RRMS and SPMS). Patients in the ofatumumab group received subcutaneous injections of ofatumumab (20 mg) administered on study days 1, 7, and 14, and month 1, then every 4 weeks until the end of study. Patients in the teriflunomide group were treated with oral teriflunomide (14 mg) once daily.

The ASCLEPIOS studies included a 45-day screening period that was used to determine patient eligibility and conduct baseline assessments. The treatment period followed, varying in duration for each patient; patients were treated until the end of study or for a maximum of 30 months, whichever occurred first. Patients who discontinued from the study drug had an end-of-treatment visit and associated study assessments and were asked to remain in the study until the end-of-study visit. Patients were permitted to initiate an alternative therapy for MS following study drug discontinuation, if clinically indicated. Upon completion of the double-blind treatment period, patients had the option of entering an open-label extension study (Study OMB157G2399). Patients who prematurely discontinued the study drug or completed the treatment period on the study drug but did not continue to the extension study entered a safety follow-up period of at least 9 months.

Figure 2: ASCLEPIOS I and II Study Design



EOS = end of study; FU = follow-up; M = month; po = by mouth; qd = once daily; sc = subcutaneous.

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Populations

Inclusion and Exclusion Criteria

Patients included in the ASCLEPIOS studies were between the age of 18 and 55 years at screening, had a diagnosis of MS according to the 2010 Revised McDonald criteria,[18] and a diagnosis of RMS (RRMS or SPMS with disease activity as defined by Lublin et al.,[6] i.e., evidenced by clinical relapses and/or MRI activity). Patients were required to be neurologically stable within 1 month prior to randomization, have an EDSS score of between 0 and 5.5 (inclusive) at screening, and have documentation of at least 1 of the following: 1 relapse during the previous year, 2 relapses during the previous 2 years, or a positive gadolinium-enhanced MRI scan during the year prior to randomization.

Key exclusion criteria for the ASCLEPIOS studies included a diagnosis of primary progressive MS or SPMS without disease activity, meeting the criteria for neuromyelitis optica, a duration of MS of greater than 10 years with an EDSS score of 2 or less, and various comorbidities as described in Table 6. Patients were excluded if they were treated with any medications listed in Table 6 within the specified time frame.

Table 6: Exclusionary Medications and Associated Washout Period Required

Medication	Minimum time required for washout
Systemic corticosteroids, adrenocorticotropic hormone	30 days prior to MRI scan at screening
Dimethyl fumarate	1 month prior to randomization
IV immunoglobulin, fingolimod, natalizumab	2 months prior to randomization
Daclizumab	4 months prior to randomization
Teriflunomide	3.5 months prior to randomization or 1 month prior to randomization if the patient undergoes acute eosinophilic pneumonia and has a documented teriflunomide plasma level below 0.02 mg/L before randomization
Mildly to moderately immunosuppressive or chemotherapeutic medications (e.g., azathioprine, methotrexate)	6 months prior to randomization
Highly immunosuppressive or chemotherapeutic medications (mitoxantrone, cyclophosphamide, cladribine) B-cell targeted therapies (e.g., rituximab, ocrelizumab) Laquinimod	2 years prior to randomization
Mitoxantrone Alemtuzumab Lymphoid irradiation; bone marrow transplantation Other strongly immunosuppressive treatments (with effects potentially lasting over 6 months) Ofatumumab Teriflunomide (if discontinued for reasons related to safety or lack of efficacy)	Any time

MRI = magnetic resonance imaging.

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Baseline Characteristics

Baseline demographic and disease characteristics of patients in the ASCLEPIOS studies are summarized in Table 7. The mean (SD) age ranged from 37.8 (9.0) years to 38.9 (8.8) years, and the majority of patients were female (66.3% to 68.6%) and White (88.0% to 89.2%). At baseline, patients reported experiencing a mean (SD) number of relapses

ranging from 1.2 (0.6) to 1.3 (0.7) in the 12 months prior to screening, and the mean (SD) time since onset of the most recent relapse ranged from 7.1 (10.5) months to 7.9 (16.1) months. Most patients were diagnosed with RRMS at study entry (93.9% to 94.9%) and the remainder had a diagnosis of SPMS (5.1% to 6.1%). Patients had a mean (SD) score on the EDSS of 2.9 (1.3) to 3.0 (1.4), indicating moderate disability in 1 FS or mild disability in 3 to 4 FSs, and no impairment to walking.[12] Between 56.1% and 63.4% of patients were free of gadolinium-enhanced T1 lesions. There were no major differences of note between the ofatumumab and teriflunomide treatment groups in either of the ASCLEPIOS studies. The baseline characteristics of the 2 studies were similar as well.

Table 7: Summary of Baseline Characteristics (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Demographic and baseline characteristics				
Age (years)				
mean (SD)	38.9 (8.8)	37.8 (9.0)	38.0 (9.3)	38.2 (9.5)
median (range)	40.0 (19 to 56)	38.0 (18 to 55)	38.0 (18 to 56)	38.0 (18 to 56)
Sex, n (%)				
Female	318 (68.4)	317 (68.6)	319 (66.3)	319 (67.3)
Male	147 (31.6)	145 (31.4)	162 (33.7)	155 (32.7)
Race, n (%)				
Asian	15 (3.2)	16 (3.5)	21 (4.4)	19 (4.0)
Black or African-American	15 (3.2)	20 (4.3)	13 (2.7)	18 (3.8)
White	411 (88.4)	412 (89.2)	418 (86.9)	417 (88.0)
Other	22 (4.7)	14 (13.0)	20 (4.2)	14 (3.0)
Unknown	2 (0.4)	0	9 (1.9)	6 (1.3)
Weight (kg), mean (SD)	74.8 (19.9)	75.5 (20.0)	73.6 (19.0)	74.0 (17.9)
MS disease history				
Duration of MS since diagnosis (years)				
mean (SD)	5.8 (6.0)	5.6 (6.2)	5.6 (6.4)	5.5 (6.0)
median (range)	3.9 (0.1 to 29.0)	3.5 (0.1 to 35.8)	3.2 (0.1 to 31.8)	3.1 (0.1 to 33.5)
Duration of MS since first symptom (years)				
mean (SD)	8.4 (6.8)	8.2 (7.2)	8.2 (7.4)	8.2 (7.4)
median (range)	6.4 (0.1 to 38.7)	6.7 (0.2 to 35.8)	5.7 (0.1 to 34.5)	6.3 (0.2 to 36.1)
Number of relapses in the last 12 months prior to screening (years), mean (SD)	1.2 (0.6)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)
Number of relapses in the last 12 to 24 months prior to screening (years), mean (SD)	0.9 (1.0)	0.9 (1.2)	0.7 (1.0)	0.8 (1.0)
Time since onset of most recent relapse (months)				
mean (SD)	7.1 (10.5)	7.9 (16.1)	7.8 (15.0)	7.7 (11.1)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
median (range)	4.9 (1.2 to 119.2)	5.3 (1.2 to 264.8)	5.2 (1.3 to 261.5)	5.2 (1.2 to 150.3)
Type of MS at study entry, n (%)				
RRMS	438 (94.2)	434 (93.9)	452 (94.0)	450 (94.9)
SPMS	27 (5.8)	28 (6.1)	29 (6.0)	24 (5.1)
MS disease characteristics at baseline				
EDSS				
mean (SD)	3.0 (1.4)	2.9 (1.4)	2.9 (1.3)	2.9 (1.4)
median (range)	3.0 (0 to 6.0)	3.0 (0 to 6.5)	3.0 (0 to 6.0)	2.5 (0 to 6.0)
9-HPT (seconds)				
mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
median (range)	[redacted]	[redacted]	[redacted]	[redacted]
T25FW (seconds)				
mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
median (range)	[redacted]	[redacted]	[redacted]	[redacted]
SDMT (correct answers in 90 seconds)				
mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Gd-enhanced T1 lesions				
mean (SD)	1.7 (4.9)	1.2 (2.6)	1.6 (4.1)	1.5 (4.1)
median (range)	0 (0 to 47)	0 (0 to 18)	0 (0 to 58)	0 (0 to 63)
Proportion of patients free of Gd-enhanced T1 lesions, n (%)	291 (62.6)	293 (63.4)	270 (56.1)	291 (61.4)
Total volume of T2 lesions (cc)				
mean (SD)	13.2 (13.3)	13.1 (14.6)	14.3 (14.2)	12.0 (13.0)
median (range)	8.8 (0.1 to 85.9)	7.7 (0.1 to 93.5)	9.0 (0.1 to 81.9)	7.7 (0.0 to 112.3)
Normalized[a] brain volume (cc)				
mean (SD)	1,439.0 (80.7)	1,442.2 (79.1)	1,440.5 (77.3)	1,445.7 (76.7)
median (range)	1,440.9 (1,184.8 to 1,709.4)	1,445.7 (1,184.4 to 1,675.3)	1,440.0 (1,193.3 to 1,659.3)	1,449.9 (1,195.1 to 1,671.0)

9-HPT = 9-hole peg test; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MS = multiple sclerosis; OMB = ofatumumab; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SPMS = secondary progressive multiple sclerosis; T25FW = Timed 25-Foot Walk Test; TER = teriflunomide.

[a] Normalized for skull size.

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

A summary of the DMTs for MS previously used by patients is provided in Table 8. Between 58.9% and 61.8% of patients in the 2 studies had prior experience with any DMT for MS at baseline. The most commonly used DMT was IFN beta (37.6% to 39.2% of patients), followed by glatiramer acetate (22.9% to 31.4%), and fingolimod (5.8% to 9.5%). Prior use of glatiramer acetate was higher among members of the ofatumumab group in ASCLEPIOS I (26.7% versus 22.9%) and higher in the teriflunomide group in ASCLEPIOS II (31.4%

versus 24.5%). There was also differential experience with fingolimod in ASCLEPIOS I, which was used by 9.5% of patients and 5.8% of patients in the ofatumumab and teriflunomide treatment groups, respectively.

Table 8: Use of Disease-Modifying Therapies for MS Prior to Study Entry (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
PRIOR MEDICATIONS				
Any MS disease-modifying therapy, n (%)	274 (58.9)	280 (60.6)	286 (59.5)	293 (61.8)
Any interferon beta	175 (37.6)	181 (39.2)	182 (37.8)	180 (38.3)
Interferon beta	6 (1.3)	10 (2.2)	10 (2.1)	9 (1.9)
Interferon beta-1a	121 (26.0)	117 (25.3)	126 (26.2)	131 (27.6)
Interferon beta-1b	62 (13.3)	66 (14.3)	61 (12.7)	53 (11.2)
Glatiramer acetate	124 (26.7)	106 (22.9)	118 (24.5)	149 (31.4)
Dimethyl fumarate	36 (7.7)	37 (8.0)	36 (7.5)	44 (9.3)
Teriflunomide	8 (1.7)	6 (1.3)	13 (2.7)	9 (1.9)
Daclizumab	5 (1.1)	12 (2.6)	8 (1.7)	7 (1.5)
Fingolimod	27 (5.8)	44 (9.5)	39 (8.1)	43 (9.1)
Natalizumab	31 (6.7)	36 (7.8)	26 (5.4)	20 (4.2)
Any B-cell therapy	2 (0.4)	3 (0.6)	NR[a]	NR[a]
Rituximab	0	1 (0.2)	NR[a]	NR[a]
Ocrelizumab	2 (0.4)	2 (0.4)	NR[a]	NR[a]
Laquinimod	5 (1.1)	4 (0.9)	2 (0.4)	7 (1.5)
Other DMT[b]	31 (6.7)	36 (7.8)	41 (8.5)	46 (9.7)

DMT = disease-modifying therapy; MS = multiple sclerosis; OMB = ofatumumab; TER = teriflunomide.

[a] It is unknown whether the data were not reported or did not apply to any patients.

[b] Includes all medications that were labelled by the investigator as a DMT for MS but are not part of the listed medications.

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Interventions

The interventions used in the ASCLEPIOS I and II studies were identical. Two treatment groups were included in each trial, the ofatumumab group and teriflunomide group. Patients in the ofatumumab groups received subcutaneous injections of ofatumumab 20 mg administered on days 1, 7, and 14, and week 4 (month 1), then once every 4 weeks thereafter. Ofatumumab was self-administered under supervision by study staff until month 1, followed by self-administration at home after demonstrating the ability to self-administer treatment at prior visits. Patients in the teriflunomide groups received teriflunomide 14 mg as an oral capsule once daily. Double-dummy controls were employed in both treatment groups; the ofatumumab groups received teriflunomide-matching placebo as an oral capsule once daily and the teriflunomide groups received ofatumumab-matching placebo for subcutaneous injection, which was administered following the same dosing regimen as the ofatumumab groups.

In terms of concomitant treatment, patients receiving dalfampridine were permitted to continue use on a stable dose throughout the study. Additionally, the use of acetaminophen and/or antihistamines were recommended for use prior to subcutaneous injection.

Dose adjustments were not permitted during the trials. Study drug discontinuation was considered for patients that met 6mCDW on the EDSS after a reassessment of the benefits and risks of continuing treatment. Study drug discontinuation was also considered when the benefit-risk ratio of continuing the study drug was unfavourable or if the patient did not wish to continue. Rescue medication was permitted for the treatment of MS relapses. The decision to use rescue medication was based on the investigator's judgment or local clinical practice. The recommended rescue medication consisted of 3 to 5 days of up to 1,000 mg of methylprednisolone (a corticosteroid) per day or equivalent, alongside standard of care during treatment. Plasmapheresis could be considered for patients who did not respond to standard corticosteroid treatment.

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 9. These end points are further summarized below. A detailed discussion and critical appraisal of the outcome measures are provided in Appendix 4.

Table 9: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	ASCLEPIOS I	ASCLEPIOS II
Relapse – annualized relapse rate	Primary	Primary
EDSS – through 3mCDW and 6mCDW, 6mCDI	Key secondary[a]	Key secondary[a]
T1 lesions per MRI	Key secondary	Key secondary
T2 lesions per MRI	Key secondary	Key secondary
Brain volume loss	Key secondary	Key secondary
EQ-5D-5L	Exploratory	Exploratory
MSIS-29	Secondary	Secondary
T25FW test	Secondary	Secondary
9-HPT	Secondary	Secondary
SDMT	Secondary	Secondary
WPAI:MS	Exploratory	Exploratory
NEDA-4	Secondary	Secondary

3mCDW = 3-month confirmed disability worsening; 6mCDI = 6-month confirmed disability improvement; 6mCDW = 6-month confirmed disability worsening; 9-HPT = 9-hole peg test; EDSS = Expanded Disability Status Scale; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; MRI = magnetic resonance imaging; MSIS-29 = 29-item Multiple Sclerosis Impact Scale; NEDA-4 = 4-parameter no evidence of disease activity; SDMT = Symbol Digit Modalities Test; T25FW = Times 25-Foot Walk; WPAI:MS = Work Productivity and Activity Impairment questionnaire for Multiple Sclerosis.

[a] Included as a pooled analysis in the combined data report for ASCLEPIOS I and II.

Relapses (Relapse Rate and Relapse-Free Rate)

Annualized Relapse Rate

The primary outcome in both ASCLEPIOS studies was ARR, defined as the number of confirmed MS relapses in a year. An MS relapse was defined as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated from the onset of a preceding clinical demyelinating

event by at least 30 days. The abnormality must have been present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or known infection. A confirmed relapse is one that is accompanied by a clinically relevant change in the EDSS (an increase of ≥ 0.5 points on the EDSS score, or an increase of 1 point on 2 FSs, or 2 points on a single FS, excluding changes involving a bowel and/or bladder or cerebral FS compared to the previous available rating). 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. Confirmation of MS relapse and severity grading was done centrally and based on the EDSS score (provided by an independent EDSS rater). Last, an MID for the ARR has not been identified.

During the 2 studies, the diagnosis of MS relapses began with patients reporting symptoms indicative of a relapse either at a scheduled study visit or at any other time. Patients were asked about related symptoms at each phone interview (occurring monthly). If new or worsening neurological symptoms were reported, an unscheduled study visit was arranged to determine if the neurological abnormalities were consistent with the definition of a MS relapse. If so, an EDSS assessment was performed to confirm the MS relapse.

Imaging Outcomes (MRI-Indicated Brain Lesions and Brain Volume)

Number of Gadolinium-Enhanced T1 Lesions per Scan, Number of New or Enlarging T2 Lesions per Year Relative to Baseline, and Percent Brain Volume Loss

Data obtained from MRI brain scans were included as various outcomes in the ASCLEPIOS I and II studies. The number of gadolinium-enhanced T1 lesions per scan, number of new or enlarging T2 lesions per year relative to baseline, and percent brain volume loss (as an annual rate of change from baseline) were included in the CADTH systematic review. Briefly, the MRI scans are used as a secondary end point measurement and as a surrogate for clinical disease activity. Gadolinium-enhanced lesions are useful for identifying active inflammation, whereas the occurrence of T2 lesions requires interpretation based on a comparison with the number of T2 lesions observed in previous scans.[41] Changes in brain volume provide a cumulative measure of disease activity. The MRI criteria to predict treatment response has been reported to have a sensitivity ranging from 24% to 71% and a specificity of 71% to 97%.[42] 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 of blinding of the outcome assessors in both studies. An MID has not been identified for these outcomes.

In the ASCLEPIOS studies, patients underwent MRI scans of the brain at screening, 12 months, and 24 months; T1 hypointense images (with and without gadolinium-based contrast agent), T2-weighted images, and brain volume were included. Scans were read by a blinded central reading centre and previewed by a local neurologist or radiologist. The percentage change from baseline in brain volume was estimated using all scans up to the last available MRI scan and compared to baseline.

Health-Related Quality of Life

The MSIS-29 and EQ-5D were used in both of the included studies to evaluate HRQoL.

Multiple Sclerosis Impact Scale

The MSIS-29 (version 2) is also a patient-reported outcome that uses a self-administered questionnaire to assess HRQoL in terms of the patient's views about the impact of MS on day-to-day life. The MSIS-29 uses a standardized psychometric approach.[43] It is a measure

of the perceived physical and psychological impact of MS from the patient's perspective, structured in 2 subscales: a 20-item scale for the physical impact and a 9-item scale for the psychological impact of the disease. The items are answered based on a 2-week recall period using a 4-point Likert scale ranging from 1 ("not at all") to 4 ("extremely"). A final score ranging from 0 to 100 is generated by summing all the individual items, with higher scores indicating a worse outcome and disease burden. The physical subscale is associated with an MID of 8, and the MID for the psychological subscale is 6.25.[13,44] The MSIS-29 has demonstrated excellent reliability, and convergent and discriminant validity. In the ASCLEPIOS studies, the MSIS-29 scores were reported as a change from baseline.

EuroQol 5-Dimensions Questionnaire

The EQ-5D is a commonly used, generic, preference-based assessment of health status consisting of a Visual Analogue Scale (VAS) and composite index score that includes 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The 5-level version of the EQ-5D (EQ-5D-5L) was used in the ASCLEPIOS studies, meaning patients respond to each of the 5 dimensions according to 1 of 5 statements increasing in level of severity: no problems (1), slight problems (2), moderate problems (3), severe problems (4), and unable to do/extreme problems (5). Acceptable test-retest reliability and validity of the EQ-5D-5L has been established in patients with MS and the MID for EQ-5D-5L index score ranging from 0.050 and 0.084.[45,46] In the ASCLEPIOS studies, the EQ-5D-5L utility score was summarized by treatment group and the VAS scores were reported as a mean change in VAS.

Mobility

The Timed 25-Foot Walk Test (T25FW) and the 9-HPT were used to inform mobility-related outcomes included in the ASCLEPIOS I and II studies.

Timed 25-Foot Walk Test

The T25FW is an objective and quantitative continuous tool that assesses the leg function and ambulation of the patient (with a T25FW). It is performed by asking patients to walk to the end of a 25-foot mark as quickly as possible and back, with assistive device if needed.[47] A final score is reported in seconds with the average of 2 completed studies.[48] A higher test result represents a worse outcome for the T25FW and 9-HPT.[49] The T25FW test has a strong correlation (convergent validity) with the EDSS ($r = 0.84$).[50] Test-retest reliability has been verified in small studies with values of intra-class coefficients of 0.96 (almost perfect agreement).[50,51] A 20% change in scores in T25FW trials is considered clinically meaningful.[50]

9-Hole Peg Test

The 9-HPT is an objective, quantitative test of neurological function that is used to assess upper extremity function. The manual dexterity of the patient is evaluated as they move 9 pegs into 9 holes on a board then back into a box; this test is done twice with each hand and the times averaged for each one separately.[52] A higher test result represents a worse outcome. The inter-rater and test-retest reliability ranges from $r = 0.86$ to 0.98, indicating almost perfect agreement.[51] Intra-class correlation coefficients demonstrated substantial to almost perfect agreement based on a range of 0.69 to 0.96.[53] The validity of the 9-HPT was good but variation was wide, with moderate to strong correlation coefficients between the 9-HPT and other outcome measures (range of $r = -0.37$ to -0.79).[53] A 20% change in score on the 9-HPT is considered clinically meaningful.[50]

In both of the pivotal studies for ofatumumab, the T25FW and 9-HPT were assessed as the time to 6-month confirmed worsening of at least 20% in either outcome. The T25FW and 9-HPT were administered in 2 trials during assessments following standardized instructions. The last assessment prior to the first dose of the study treatment was considered the baseline assessment, and the 20% worsening was defined relative to baseline.

Cognitive Function

Symbol Digit Modalities Test

The SDMT is a symbol-substitution neuropsychological test that examines the attention and speed of processing in patients with MS. The score is the number of correct substitutions completed within the time limit, with a maximum score of 110. Higher scores indicate better outcomes. Obtaining a score of less than 33 is considered an indicator of a cognitive disorder. In patients with MS, the intra-class correlation coefficient for the SDMT ranges from 0.74 to 0.96. In other studies, a similar intra-class correlation coefficient is reported at 0.86 (almost perfect agreement[51]) with improvements over time likely due to practice effects.[54] The SDMT has good construct validity, although with modest association with other measures of physical disability (i.e., EDSS, 9-HPT, and T25FW) with correlation coefficient values ranging from 0.34 to 0.47. A raw score of 4 points has been considered a clinically meaningful threshold for improvement in patients with MS.[52,55] The SDMT was evaluated in the pooled analysis of the ASCLEPIOS I and II studies as a change from baseline.

Symptoms of Multiple Sclerosis (Fatigue, Cognition, and Visual Disturbance)

Outcomes specific to symptoms of MS as an efficacy end point were not reported in the ASCLEPIOS I and II studies.

Ability to Work or Attend School

Work Productivity and Activity Impairment Questionnaire for Multiple Sclerosis

The WPAI:MS outcome was included in both ASCLEPIOS studies. In both studies, patients were asked to complete the WPAI:MS questionnaire before other clinical assessments to avoid influence from the investigators. The WPAI:MS is a patient-reported outcome that measures impairments in both paid and unpaid work. It consists of 6 questions[56,57] that measure absenteeism and presenteeism, as well as impairments in unpaid activity. In addition, 2 outcomes are calculated based on questions 2 through 6.

> Outcome 1: Percent work time missed due to health = Q2/(Q2 + Q4)
>
> Outcome 2: Percent overall work impairment due to health = Q2/(Q2 + Q4) + (1 – Q2/(Q2 + Q4) × (Q5/10)
>
> where Q2 = hours missed from work due to health problems; Q4 = hours actually worked; and Q5 = degree health-affected productivity while working (0 to 10).

Outcomes 1 and 2 were reported in this review as outcomes related to the ability to work or attend school. High scores indicate prolonged sick leave or impairment and decreased productivity. The WPAI:MS has been validated as a general instrument and in numerous clinical conditions.[57-59] Spearman correlations of the WPAI with other instruments for global assessment of health status measures in terms of functional disability, pain, fatigue, and disease activity, ranged from 0.34 to 0.77 (moderate to strong[60]), but this was not specific to patients with MS.[59] The WPAI:MS also demonstrated good reliability and internal

consistency, with intra-class correlation coefficients ranging from 0.78 to 0.90 and values for Cronbach alpha of 0.80 to 0.90.[61] No MID for this outcome specific for patients with MS was identified.

Use of Rescue Medication

Characteristics of MS relapses were reported as supportive analyses of the primary end point, which included MS relapses that required steroid treatment. This outcome was reported descriptively for confirmed relapses and all relapses.

Disability Progression or Improvement

Expanded Disability Status Scale

The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. The Kurtze functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other) and ambulation are rated in the context of a standard neurological examination, and then these ratings (FS scores) are used in conjunction with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign an EDSS score. The validity of the EDSS has been established and it is regarded as the gold standard for evaluating new scales.[50] Reliability of the scale has low to moderate values, with inter-rater kappa values of between 0.32 and 0.76 for the EDSS and between 0.23 and 0.58 for the individual FSs. For scores below 3.5, reliability is regarded as good.[50] A clinically meaningful change of at least 1.0 for patients with MS has been proposed if the EDSS score at baseline was 0 to 5.5, and at least 0.5 for higher-baseline EDSS scores.[47] This was similar to the clinically meaningful increase in 2 other studies: an increase of at least 1.5 when the baseline was 0; an increase of at least 1 point from a baseline of 1 to 5.5; and an increase of at least 0.5 points from a baseline score of 6 or greater.[62,63]

The EDSS was used to inform 3 of the outcomes included in both ASCLEPIOS studies: 3mCDW, 6mCDW, and 6mCDI. The disability worsening outcomes were defined as an increase from baseline in EDSS for at least 3 months or 6 months. Criteria for disability worsening were based on total EDSS scores at baseline. An EDSS score of 0, 1 to 5, or 5.5 or greater at baseline needed to increase by at least 1.5, 1, or 0.5, respectively, to be considered evidence of disability worsening.[14,15] Similarly, the 6mCDI outcome was defined as a decrease from baseline EDSS that was sustained for at least 6 months. An EDSS score of at least 2 to 6, and at least 6.5 to 9.5 at baseline, required a decrease in an EDSS score of no more than 1 and 0.5 or lower, respectively, to be considered disability improvement. It was not possible to improve from a total EDSS baseline score of 0 to 1.5.[14,15]

Composite Outcomes: NEDA-4 (Relapses and Imaging)

No Evidence of Disease Activity

No evidence of disease activity is a composite outcome defined by not having 3mCDW, no confirmed MS relapse, no new or enlarging T2 lesions on any MRI scan compared to baseline, and a decrease in brain volume of no more than 0.4% per year on all MRI scans (> −0.4%). The information identified regarding the measurement properties of NEDA-4, which is based on a 3-item version that does not include the fourth criterion regarding brain atrophy, is summarized in Appendix 4. Evidence of an MID was not identified. In the ASCLEPIOS studies, the proportion of patients meeting the criteria for NEDA-4 was reported at year 1 and year 2.

Harms Outcomes

Adverse events were reported through non-directive patient questioning at each study visit. Adverse events were also detected when voluntarily reported by a patient during or between study visits or based on findings of a physical examination, laboratory test, or other assessments.

Statistical Analysis

The statistical analysis plans for ASCLEPIOS I and II were identical (see Table 11). The primary outcome was ARR, defined as the number of confirmed MS relapses in a year. Using the full analysis set, the primary analysis evaluated the superiority of ofatumumab 20 mg over teriflunomide 14 mg. Superiority was claimed if the observed ARR was lower in the ofatumumab group compared to teriflunomide, and the null hypothesis was rejected at a 2-sided significance level of 0.05.

Power Calculation

Both ASCLEPIOS I and II were independently powered to address the primary end point and all key secondary end points. This was based on a sample size of 900 patients for each study, which was deemed sufficient to achieve 90% power for the primary analysis. The power for the key secondary outcomes was dependent on the rejection of the null hypothesis for the primary outcome. The disability-related outcomes, namely 3mCDW, 6mCDW, and 6mCDI, required a sample size of 1,800 patients across the 2 studies to provide at least 90% power (3mCDW) or at least 80% power (6mCDW and 6mCDI). A sample size of 900 patients in each study was required to provide at least 80% power for the analyses of MRI-related outcomes.

Data from the pivotal trials for ocrelizumab (OPERA I and OPERA II), from an unpublished phase II trial of ofatumumab, and from the phase III program for fingolimod were used to inform the power calculation for the primary end point in both ASCLEPIOS I and II. As it was anticipated that patients would be exposed to a study treatment for 1 to 2 years, a follow-up time of 1.5 years and discontinuation rate of 20% of randomized patients were assumed. Similar assumptions were used for power calculations of the key secondary outcomes.

Statistical Test or Model

The primary analysis of ARR used a negative binomial regression model with log-link, treatment, and region as factors, and number of relapses in the previous year, baseline EDSS, baseline number of T1 gadolinium-enhanced lesions, and the patient's age at baseline as covariates. The number of confirmed relapses and the patient's time in study were used as an offset variable to adjust for the varying length of time in the study among patients.

Outcomes related to MRI were analyzed using a negative binomial regression model with log-link, similar to the primary analysis. For disability-related outcomes, a stratified Cox proportional hazards model was used with study as stratum, treatment and region as factors, and baseline EDSS as a continuous covariate. Mobility outcomes (time to 6-month confirmed worsening of at least 20% in T25FW and 9-HPT) were analyzed using a Cox proportional hazards model with study as stratum, treatment and region as factors, and the baseline result as a continuous covariate. The proportion of patients free of clinical and MRI disease activity (NEDA-4) outcome was analyzed using a logistic regression model with

treatment and region as factor, and age, baseline EDSS, and number of gadolinium-enhanced lesions at baseline as covariates. Missing values were considered not free of disease activity. Last, the MSIS-29 was evaluated as a change from baseline using a repeated measures mixed-effects analysis.

A hierarchical testing order was implemented to control for the type I error rate. The multiple-testing procedure included hypotheses from both ASCLEPIOS I and II, as well as the combined pooled analysis, as illustrated in

Figure 3. To summarize, rejection of the primary hypothesis was required to proceed with statistical testing of the following hypotheses related to MRI and NfL outcomes. This applied to both ASCLEPIOS I and ASCLEPIOS II independently. In order to test the disability-related hypotheses (3mCDW, 6mCDW, and 6mCDI) within the pooled analysis set, the primary hypotheses of both ASCLEPIOS I and II needed to be rejected first. At the study level, the primary hypotheses regarding ARR were tested at a 2-sided significance level of 0.05 or less. Testing of disability end points in the pooled dataset was done at a 2-sided significance level of 0.04875 or less. Under the "global null hypothesis," which considers the individual trials as well as the pooled analysis, the type I error rate is controlled at a 1-sided level of 0.025 and a submission level of no more than 0.000625 (= 0.025^2). These procedures were pre-planned and the sponsor noted that the use of pooled data was approved by the FDA and European Medicines Agency (EMA) during protocol development. Data from the 2 trials were combined to provide sufficient power for end points related to MS disability.

Pooled Analyses

The appropriateness of using a pooled dataset of ASCLEPIOS I and II and corresponding analyses was determined a priori based on the identical study design and simultaneous global conduct of both studies.

Data Imputation Methods

Missing data were adjusted using a negative binomial model with an offset for the time in study, following an assumption of non-informative dropout, information that is missing at random, and a constant relapse rate over time. All data collected in the double-blind treatment period were included in the primary analysis. Beyond this, missing data were not imputed for the primary or any key secondary outcomes.

Subgroup Analyses

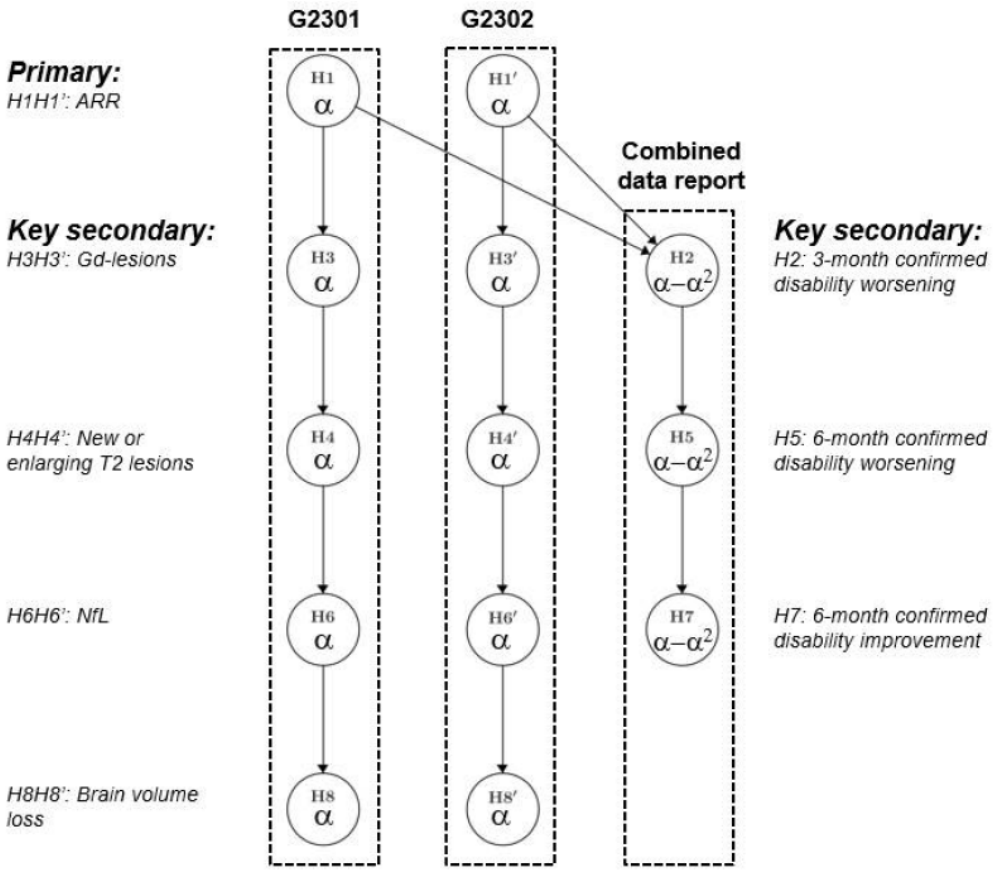
A subgroup of newly diagnosed, treatment-naive patients were analyzed in terms of NfL concentration at baseline. This was not relevant to the CADTH systematic review protocol and therefore not included in this review. In addition, subgroup analyses by age, MS type, baseline EDSS score, number of relapses in the previous 2 years, gadolinium-enhanced T1 lesions at baseline, and prior DMTs for MS were reported in the sponsor's submission. Subgroup analyses were conducted for ARR and for all key secondary end points using the pooled dataset for ASLCEPIOS I and II. Details of the methodology for these subgroup analyses were limited. The common technical document notes that subgroup analyses were performed based on a simplified statistical model with fewer adjustments than the primary analysis to avoid convergence problems.[5] The subgroup analyses were also not controlled for type I or type II errors.

Sensitivity Analyses

A series of pre-planned sensitivity analyses of the primary analysis were conducted. This included analyses with the use of:

- all reported MS relapses (as opposed to only confirmed relapses)
- the per-protocol set, to evaluate on-treatment data from patients without any major protocol violations
- relapse rates during the first 8 weeks on-treatment and relapse rates thereafter (> 56 days) to evaluate the treatment effect during the "onset of action" period and longer-term efficacy
- time to first relapse in a Cox proportional hazards model, which, unlike the primary analysis, does not assume constant relapse rates.

Figure 3: Statistical Testing Hierarchy



ARR = annualized relapse rate; G2301 = ASCLEPIOS I trial; G2302 = ASCLEPIOS II trial; H = hypothesis; NfL = neurofilament light chain.

Note: The significance level at which the hypotheses were tested are indicated by α or α – α^2.

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Table 10: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Sensitivity analyses
ASCLEPIOS I and ASCLEPIOS II			
ARR	Negative binomial regression model with log-link	Treatment and region	• All reported MS relapses • Per-protocol set • Relapse rates during the first 8 weeks on-treatment and relapse rates thereafter (> 56 days) • Time to first relapse in a Cox proportional hazards model, which does not assume constant relapse rates
Number of Gd-enhanced T1 lesions per scan	Negative binomial regression model with log-link	Treatment and region	None
Number of new or enlarging T2 lesions per year relative to baseline	Negative binomial regression model with log-link	Treatment and region	None
Brain volume loss	Random coefficients model	Treatment and region	None
MSIS-29	Repeated measures mixed-effects analysis	Treatment, region, baseline measurement of outcome	None
Time to first 6-month confirmed worsening of ≥ 20% in the T25FW	Cox proportional hazards model	Treatment and region	None
Time to first 6-month confirmed worsening of ≥ 20% in the 9-HPT	Cox proportional hazards model	Treatment and region	None
NEDA-4	Logistic regression analysis	Treatment and region	None
WPAI:MS	Repeated measures model	Treatment, region, visit-windows, baseline measurement of outcome	None
EQ-5D-5L	Repeated measures mixed-effects analysis	Treatment, region, visit-windows, baseline measurement of outcome	None
Pooled analysis (ASCLEPIOS I and II)			
SDMT	Repeated measures mixed-effects analysis		None
Time to 3-month confirmed disease worsening during the treatment epoch	Cox proportional hazards model	Study as stratum, treatment, and region	Considering all patients who discontinue from the study due to “lack of efficacy” as patients with a confirmed event
Time to 6-month confirmed disease worsening during the treatment epoch	Cox proportional hazards model	Study as stratum, treatment, and region	Considering all patients who discontinue from the study due to “lack of efficacy” as patients with a confirmed event

End point	Statistical model	Adjustment factors	Sensitivity analyses
Time to 6-month confirmed disease improvement during the treatment epoch	Cox proportional hazards model	Study as stratum, treatment, and region	None

9-HPT = 9-hole peg test; ARR = annualized relapse rate; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; Gd = gadolinium; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = 29-item Multiple Sclerosis Impact Scale; NEDA-4 = 4-item no evidence of disease activity; SDMT = Symbol Digit Modalities Test; T25FW = Timed 25-Foot Walk; WPAI:MS = Work Productivity and Activity Impairment questionnaire for Multiple Sclerosis.

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Analysis Populations

The full analysis set included all randomized patients with assigned treatments and follows the intention-to-treat principle, i.e., patients were analyzed according to randomized treatment assignment regardless of whether it was received. The full analysis set was used for the summary of demographic and baseline characteristics as well as all efficacy analyses.

The per-protocol set included all randomized patients who took at least 1 dose of the study treatment and had no major protocol deviations. Analyses using the per-protocol set included only assessments that occurred during the on-treatment period.

The safety set included all patients who received at least 1 dose of study treatment. Patients were analyzed by the actual treatment that was received. The safety set was used for all safety analyses.

Results

Patient Disposition

A summary of the patient disposition in ASCLEPIOS I and II is provided in Table 11. Totals of 1,277 and 1,280 patients were screened in ASCLEPIOS I and II, respectively, and 927 (72.6%) and 955 (74.6%) were randomized in the 2 studies, respectively. A differential dropout rate (discontinuation from study) was reported for ASCLEPIOS I, with 10.3% of patients in the ofatumumab treatment group discontinuing compared to 17.5% of patients in the teriflunomide group. This difference was driven by the proportion of patients who discontinued due to a patient or guardian decision (3.4% versus 9.1% for ofatumumab versus teriflunomide, respectively) and lack of efficacy (0.2% for ofatumumab versus 2.6% for teriflunomide). Discontinuation rates in ASCLEPIOS II were similar between treatment groups, with 17.3% to 17.7% of patients discontinuing from the study. The most common reasons for discontinuation in ASCLEPIOS II included a patient or guardian decision (6.7% to 8.6%), adverse events (2.7% to 3.3%) and physician decision (2.3% to 2.9%).

Table 11: Patient Disposition (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg	TER 14 mg	OMB 20 mg	TER 14 mg
Screened, N	1,277		1,280	
Randomized, N (%)	465	462	481	474
Completed treatment period,[a] N (%)	416 (89.5)	376 (81.4)	397 (82.5)	389 (82.1)
On study drug	400 (86.0)	359 (77.7)	383 (79.6)	370 (78.1)
Off study drug	16 (3.4)	17 (3.7)	14 (2.9)	19 (4.0)
Discontinued from study, N (%)	48 (10.3)	81 (17.5)	83 (17.3)	84 (17.7)
Reason for discontinuation, N (%)				
Adverse events	14 (3.0)	14 (3.0)	16 (3.3)	13 (2.7)
Lack of efficacy	1 (0.2)	12 (2.6)	7 (1.5)	9 (1.9)
Lost to follow-up	10 (2.2)	5 (1.1)	9 (1.9)	5 (1.1)
New therapy for study indication	0	1 (0.2)	0	0
Non-compliance with study treatment	0	1 (0.2)	2 (0.4)	1 (0.2)
Patient or guardian decision	16 (3.4)	42 (9.1)	32 (6.7)	41 (8.6)
Physician decision	3 (0.6)	4 (0.9)	14 (2.9)	11 (2.3)
Pregnancy	1 (0.2)	0	1 (0.2)	3 (0.6)
Protocol deviation	3 (0.6)	2 (0.4)	2 (0.4)	0
Technical problems	0	0	0	1 (0.2)
FAS, N	465	462	481	474
PP, N	441	426	449	444
Safety, N	465	462	481	474

FAS = full analysis set; OMB = ofatumumab; PP = per protocol; TER = teriflunomide.

[a] Six patients were considered "ongoing" as the study completion date was greater than the treatment cut-off date.

Note: Patient disposition for the treatment epoch only. Patient disposition was not reported for the pooled analysis.

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Exposure to Study Treatments

A summary of exposure to study treatments is provided in Table 12. The duration of study in ASCLEPIOS I and II was event-driven and therefore varied between patients. In ASCLEPIOS I, exposure to study treatment was greater in patients in the ofatumumab group than the teriflunomide group (mean [SD] days of exposure of 585.9 [180.0] and 550.0 [180.0], respectively). Relative exposure was similar in ASCLEPIOS II, in which patients in the ofatumumab group were exposed to treatment for a mean (SD) of 562.5 (191.5) days compared to 541.0 (181.7) days in the teriflunomide group. Most patients were exposed to study treatments for at least 1 year, with exposure for 1 to 2 years ranging from 53.6% to 64.8% of patients in the 2 studies. Between 21.5% and 34.0% of patients were exposed for longer than 2 years.

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

Table 12: Exposure to Study Treatment (Safety Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mcg N = 462	OMB 20 mg N = 481	TER 14 mcg N = 474
Exposure (days)				
Mean (SD)	585.9 (180.0)	550.0 (180.0)	562.5 (191.5)	541.0 (181.7)
Median (range)	613.0 (31 to 873)	580.0 (13 to 848)	589.0 (31 to 873)	573.5 (14 to 847)
Any exposure				
< 48 weeks (1 year)	45 (9.7)	56 (12.1)	69 (14.3)	65 (13.7)
48 weeks to 96 weeks (1 to 2 years)	262 (56.3)	291 (63.0)	258 (53.6)	307 (64.8)
> 96 weeks (2 years)	158 (34.0)	115 (24.9)	154 (32.0)	102 (21.5)

OMB = ofatumumab; SD = standard deviation; TER = teriflunomide.

Note: Exposure was not reported for the pooled analysis.

Source: Clinical Study Reports for ASCLEPIOS I[14] and II.[15]

Concomitant medication use was high in the 2 trials (Table 13). Between 94.4% and 97.3% of patients reported concomitant medication use during the ASCLEPIOS studies. There were no major differences between treatment groups or across the 2 trials in terms of concomitant medication use. Briefly, systemic corticosteroids were used by 71.1% to 74.5% of patients, systemic antihistamines by 60.9% to 63.0%, systemic anti-infectives by 38.7% to 41.1%, Nonsteroidal anti-inflammatory drugs by 31.2% to 38.0%, hormonal contraceptives by 28.2% to 31.2%, and fampridine by 1.9% to 4.5% of patients in the 2 studies.

Table 13: Concomitant Medication Use (Safety Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Medication				
Any concomitant medication	439 (94.4)	439 (95.0)	464 (96.5)	461 (97.3)
Systemic corticosteroids	341 (73.3)	344 (74.5)	342 (71.1)	352 (74.3)
Methylprednisolone sodium succinate	176 (37.8)	192 (41.6)	211 (43.9)	207 (43.7)
Methylprednisolone	143 (30.8)	159 (34.4)	108 (22.5)	128 (27.0)
Prednisone	32 (6.9)	26 (5.6)	30 (6.2)	32 (6.8)
Systemic antihistamines	293 (63.0)	287 (62.1)	293 (60.9)	289 (61.0)
Systemic anti-infectives	180 (38.7)	179 (38.7)	188 (39.1)	195 (41.1)
NSAID	152 (32.7)	144 (31.2)	183 (38.0)	161 (34.0)
Hormonal contraceptive	131 (28.2)	143 (31.0)	145 (30.1)	148 (31.2)
fampridine	12 (2.6)	21 (4.5)	16 (3.3)	9 (1.9)

NSAID = nonsteroidal anti-inflammatory drug; OMB = ofatumumab; TER = teriflunomide.

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below.

Relapses

Results pertaining to ARR are presented in Table 14. In ASCLEPIOS I, the adjusted ARR in patients in the ofatumumab treatment group and teriflunomide treatment group was 0.11 (95% CI, 0.09 to 0.14) and 0.22 (95% CI, 0.18 to 0.26), respectively. This corresponded to a rate reduction of 50.5% based on an ARR ratio of 0.50 (95% CI, 0.37 to 0.65; P < 0.001) in favour of ofatumumab. Similarly, in ASCLEPIOS II, the adjusted ARR in patients in the ofatumumab treatment group and teriflunomide treatment group was 0.10 (95% CI, 0.08 to 0.13) and 0.25 (95% CI, 0.21 to 0.30), respectively. This corresponded to a rate reduction of 58.5% based on an ARR ratio of 0.42 (95% CI, 0.31 to 0.56; P < 0.001) in favour of ofatumumab.

A sensitivity analysis on the primary outcome that included all relapses (rather than only confirmed relapses) was conducted. The rate reduction was similar in ASCLEPIOS I (ARR ratio, 0.50; 95% CI, 0.39 to 0.64; P < 0.001) and ASCLEPIOS II (ARR ratio, 0.45; 95% CI, 0.35 to 0.59; P < 0.001) at 49.7% and 54.6%, respectively, compared to the analyses with only confirmed relapses.

Relapses that occurred during the 2 studies were reported by select characteristics, which included MS relapses that required steroid treatment and hospitalization (Table 14). In the ofatumumab groups, confirmed relapses that required steroid treatment ranged from 13.5% to 15.7%, and 26.6% of confirmed relapses required steroid treatment in the teriflunomide groups in both studies. As for hospitalizations, 4.1% and 4.6% of patients in the ofatumumab groups, and 6.3% and 9.7% of patients in the teriflunomide groups, in ASCLEPIOS I and II, respectively, had relapses that required hospitalization.

Table 14: Annualized Relapse Rate (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
ARR (confirmed relapses)[a]				
Number of patients contributing to the analysis	454	452	469	469
Adjusted ARR (95% CI)	0.11 (0.09 to 0.14)	0.22 (0.18 to 0.26)	0.10 (0.08 to 0.13)	0.25 (0.21 to 0.30)
Between-treatment comparison, ofatumumab vs. teriflunomide				
Rate reduction (%)	50.5		58.5	
Treatment-group difference vs. control, ARR ratio (95% CI)	0.50 (0.37 to 0.65)		0.42 (0.31 to 0.56)	
P value	< 0.001		< 0.001	
ARR (all relapses)[a]				
Number of patients contributing to the analysis	454	452	469	469
Adjusted ARR (95% CI)	0.15 (0.12 to 0.18)	0.30 (0.25 to 0.35)	0.14 (0.12 to 0.18)	0.32 (0.27 to 0.37)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Between-treatment comparison, ofatumumab vs. teriflunomide				
Rate reduction (%)	49.7		54.6	
Treatment-group difference vs. control, ARR ratio (95% CI)	0.50 (0.39 to 0.64)		0.45 (0.35 to 0.59)	
P value[b]	< 0.001		< 0.001	
MS relapse characteristics[c]				
Confirmed relapses				
Requiring steroid treatment, n (%)	73 (15.7)	123 (26.6)	65 (13.5)	126 (26.6)
Not requiring steroid treatment, n (%)	6 (1.3)	9 (1.9)	7 (1.5)	12 (2.5)
Hospitalization – yes, n (%)	19 (4.1)	29 (6.3)	22 (4.6)	46 (9.7)
Hospitalization – no, n (%)	60 (12.9)	103 (22.3)	50 (10.4)	92 (19.4)

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; OMB = ofatumumab; SD = standard deviation; TER = teriflunomide; vs. = versus.

[a] Analyzed using a negative binomial regression model with log-link, treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of gadolinium-enhanced T1 lesions and the patient's age at baseline as covariates.

[b] The P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[c] For each MS relapse characteristic, a patient with multiple relapses was counted only once using the worst category observed. % = n/N.

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Imaging Outcomes

The ASCLEPIOS studies evaluated the number of gadolinium-enhanced T1 lesions per scan, number of new or enlarging T2 lesions per year relative to baseline, and percent brain volume loss as key secondary outcomes (Table 15).

In ASCLEPIOS I, the adjusted mean number of gadolinium-enhanced T1 lesions per scan was 0.01 (95% CI, 0.01 to 0.02) for the ofatumumab group, and 0.45 (95% CI, 0.36 to 0.58) for the teriflunomide group. The results were similar in ASCLEPIOS II, in which 0.03 lesions (95% CI, 0.02 to 0.05) were reported for ofatumumab and 0.51 lesions (95% CI, 0.40 to 0.66) for teriflunomide. The treatment-group difference corresponded to a rate reduction of 97.5% (rate ratio = 0.03; 95% CI, 0.01 to 0.05) and 93.8% (rate ratio = 0.06; 95% CI, 0.04 to 0.10) in ASCLEPIOS I and II, respectively, in favour of ofatumumab in both studies (P < 0.001).

The number of new or enlarging T2 lesions per year relative to baseline were analyzed using the last scan in the double-blind treatment epoch. The difference between ofatumumab and teriflunomide groups in terms of the mean rate of new or enlarging T2 lesions per year was 0.18 (95% CI, 0.15 to 0.22; P < 0.001) in ASCLEPIOS I and 0.15 (95% CI, 0.13 to 0.19; P < 0.001) in ASCLEPIOS II, both in favour of ofatumumab. Analyses at 12 months and 24 months into the study are presented in Appendix 3 (Table 30). Briefly, the treatment-group difference at month 12 and month 24 corresponded to a higher rate ratio (lower rate reduction), which was still in favour of ofatumumab (P < 0.05) in both studies.

Brain volume loss was measured as the annual rate of change in percent brain volume, which was estimated using all available scans up to the last MRI scan evaluated. The adjusted mean difference in percent brain volume loss between treatment with ofatumumab

and teriflunomide was 0.07% (95% CI, −0.02 to 0.15; P = 0.116) in ASCLEPIOS I and 0.07% (95% CI, −0.02 to 0.15; P = 0.129) in ASCLEPIOS II. Analogous results from baseline to month 12 and baseline to month 24 are available in Appendix 3 (Table 30).

Table 15: Magnetic Resonance Imaging Outcomes (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Number of Gd-enhanced T1 lesions per scan[a]				
Number of patients contributing to the analysis	432	422	439	434
Adjusted mean number of Gd-enhanced lesions per scan (95% CI)	0.01 (0.01 to 0.02)	0.45 (0.36 to 0.58)	0.03 (0.02 to 0.05)	0.51 (0.40 to 0.66)
Between-treatment comparison, ofatumumab vs. teriflunomide				
Rate reduction (%)	97.5		93.8	
Treatment-group difference versus control, rate ratio (95% CI)	0.03 (0.01 to 0.05)		0.06 (0.04 to 0.10)	
P value	< 0.001		< 0.001	
Number of new or enlarging T2 lesions per year relative to baseline[a]				
Number of patients contributing to the analysis	440	431	448	443
Adjusted annualized mean rate at end of study (last scan in the DBT epoch) (95% CI)	0.72 (0.61 to 0.85)	4.00 (3.47 to 4.61)	0.64 (0.55 to 0.75)	4.15 (3.64 to 4.74)
Between-treatment comparison, ofatumumab vs. teriflunomide				
Rate reduction (%)	82.0		84.5	
Treatment-group difference versus control, rate ratio (95% CI)	0.18 (0.15 to 0.22)		0.15 (0.13 to 0.19)	
P value	< 0.001		< 0.001	
Percent brain volume loss (annual rate of change from baseline)[b]				
Number of patients contributing to the analysis	418	409	437	434
Adjusted mean annual rate of change from baseline (95% CI)	−0.28 (−0.34 to 0.22)	−0.35 (−0.41 to 0.29)	−0.29 (−0.35 to −0.23)	−0.35 (−0.42 to −0.29)
Between-treatment comparison, ofatumumab vs. teriflunomide				
Adjusted mean difference (95% CI)	0.07 (−0.02 to 0.15)		0.07 (−0.02 to 0.15)	
P value[c]	0.116		0.129	

CI = confidence interval; DBT = double-blind treatment; Gd = gadolinium; OMB = ofatumumab; SD = standard deviation; TER = teriflunomide; vs. = versus.

[a] Analyzed using a negative binomial model with adjustments for treatment and region (factors), and age, and corresponding baseline values (number of Gd-enhanced lesions or volume of T2 lesions) as continuous covariates.

[b] Analyzed using a random coefficients model with treatment and region as fixed effects; and time, baseline number of Gd-enhanced lesions, baseline T2 volume, and baseline normalized brain volume as continuous covariates.

[c] Statistical testing on this key secondary outcome was conducted after the statistical testing hierarchy was violated.

Note: Baseline values were not explicitly reported for imaging outcomes corresponding to the analyses presented in this table.

Source: Clinical Study Reports for ASCLEPIOS I and II.[14,15]

Health-Related Quality of Life

In the ASCLEPIOS studies, HRQoL was measured using the MSIS-29 (Table 16) and EQ-5D (Table 17).

The MSIS-29 was measured at months 6, 12, 18, 24, and 30. In ASCLEPIOS I, the adjusted mean change in the physical impact score of the MSIS-29 [redacted] for patients in the ofatumumab treatment group and [redacted] for patients in the teriflunomide treatment group. The results [redacted] In ASCLEPIOS II [redacted], the mean change in the physical impact score was [redacted] for the ofatumumab and teriflunomide treatment groups, respectively. This between-groups difference [redacted]

The psychological impact score of the MSIS-29 was evaluated in the same way as the physical impact score. The results of the psychological impact score were [redacted] (Table 16).

Last, the EQ-5D utility score was reported [redacted] as an exploratory outcome. [redacted] the treatment-group difference of the adjusted mean change from baseline for ofatumumab compared to teriflunomide was [redacted] in ASCLEPIOS I. In ASCLEPIOS II, the treatment-group difference [redacted] The VAS of the EQ-5D was also reported at the same time points. [redacted], the between-group difference for ofatumumab compared to teriflunomide was [redacted] in ASCLEPIOS I and II, respectively.

Table 16: Health-Related Quality of Life, MSIS-29 (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
MSIS-29 physical impact score at month 6[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
MSIS-29 physical impact score at month 12[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
MSIS-29 physical impact score at month 18[a]				
Number of patients contributing to the analysis	[redacted]			
Adjusted mean change (95% CI)	[redacted]			
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]			
P value[b]	[redacted]			
MSIS-29 physical impact score at month 24[a]				
Number of patients contributing to the analysis	[redacted]			
Adjusted mean change (95% CI)	[redacted]			
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]			
P value[b]	[redacted]			
MSIS-29 physical impact score at month 30[a]				
Number of patients contributing to the analysis	[redacted]			
Adjusted mean change (95% CI)	[redacted]			
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]			
P value[b]	[redacted]			
MSIS-29 psychological impact score at month 6[a]				
Number of patients contributing to the analysis	[redacted]			
Adjusted mean change (95% CI)	[redacted]			
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]			
P value[b]	[redacted]			
MSIS-29 psychological impact score at month 12[a]				
Number of patients contributing to the analysis	[redacted]			
Adjusted mean change (95% CI)	[redacted]			
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]			
P value[b]	[redacted]			
MSIS-29 psychological impact score at month 18[a]				
Number of patients contributing to the analysis	[redacted]			
Adjusted mean change (95% CI)	[redacted]			
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]			

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
P value[b]				
MSIS-29 psychological impact score at month 24[a]				
Number of patients contributing to the analysis				
Adjusted mean change (95% CI)				
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)				
P value[b]				
MSIS-29 psychological impact score at month 30[a]				
Number of patients contributing to the analysis				
Adjusted mean change (95% CI)				
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)				
P value[b]				

CI = confidence interval; FAS = full analysis set; MSIS-29 = 29-item Multiple Sclerosis Impact Scale; OMB = ofatumumab; SD = standard deviation; TER = teriflunomide; vs. = versus.

Source: Clinical Study Reports for ASCLEPIOS I and II.[14,15]

Table 17: Health-Related Quality of Life, EQ-5D-5L (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
EQ-5D-5L utility score at month 12[a]				
Number of patients contributing to the analysis				
Adjusted mean change (95% CI)				
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)				
P value[b]				
EQ-5D-5L utility score at month 24[a]				
Number of patients contributing to the analysis				
Adjusted mean change (95% CI)				
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)				
P value[b]				
EQ-5D-5L VAS at month 12[a]				
Number of patients contributing to the analysis				

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
EQ-5D-5L VAS at month 24[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimensions 5-levels; OMB = ofatumumab; SD = standard deviation; TER = teriflunomide; VAS = Visual Analogue Scale; vs. = versus.

[redacted]

Source: Clinical Study Reports for ASCLEPIOS I and ASCLEPIOS II.[14,15]

Mobility

Mobility was assessed using the T25FW and 9-HPT in ASCLEPIOS I and II and analyzed in the pooled analysis of these 2 studies (Table 18). The results from the individual studies are presented in Table 18. Based on the pooled analysis, [redacted] of patients in the ofatumumab and teriflunomide treatment groups, respectively, experienced worsening of at least 20% in the T25FW at 6 months [redacted] of patients in the ofatumumab and teriflunomide treatment groups, respectively, experienced a 6mCDW of at least 20% in the 9-HPT [redacted]

Table 18: Mobility Outcomes, T25FW and 9-HPT (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II		ASCLEPIOS I and II (pooled)	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474	OMB 20 mg	TER 14 mg
Time to first 6-month confirmed worsening of ≥ 20% in the T25FW[a]						
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with 6-month confirmed worsening of ≥ 20% in the T25FW (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-treatment comparison, ofatumumab vs. teriflunomide						
Risk reduction (%)	[redacted]		[redacted]		[redacted]	
Hazard ratio (95% CI)	[redacted]		[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]		[redacted]	
Time to first 6-month confirmed worsening of ≥ 20% in the 9-HPT[a]						
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with 6-month confirmed worsening of ≥ 20% in the 9-HPT (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-treatment comparison, ofatumumab vs. teriflunomide						
Risk reduction (%)	[redacted]		[redacted]		[redacted]	
Hazard ratio (95% CI)	[redacted]		[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]		[redacted]	

9-HPT = 9-hole peg test; CI = confidence interval; OMB = ofatumumab; SD = standard deviation; T25FW = Timed 25-Foot Walk; TER = teriflunomide; vs. = versus.

[redacted]

Source: Clinical Study Report for ASCLEPIOS I and II meta-analysis.[16]

Cognitive Function

Cognitive function was evaluated using the SDMT and reported as the time to 6-month confirmed cognitive decline. Only results for the pooled analysis were available for this review. There was [redacted] between treatment groups for this outcome based on the pooled analysis of the pivotal trials [redacted].

Symptoms of Multiple Sclerosis

Specific outcomes related to the symptoms of MS, such as fatigue, cognition, and visual disturbance, were not evaluated in any of the included studies for this review.

Ability to Work or Attend School

The ability to work was evaluated using the WPAI:MS in ASCLEPIOS I and II and the items pertaining to percent work time missed due to health and the percent overall work impairment due to health were reported for this review (Table 19). The WPAI:MS

[redacted] of patients in both trials were included in the analyses.

The treatment-group difference in the "percent work time missed due to health" item [redacted] for ofatumumab compared to teriflunomide was [redacted] in ASCLEPIOS I and [redacted] in ASCLEPIOS II. The results for ASCLEPIOS I [redacted] the results in ASCLEPIOS II [redacted].

The treatment-group difference in the "percent overall work impairment due to health" item [redacted] for ofatumumab compared to teriflunomide was [redacted] in ASCLEPIOS I and [redacted] in ASCLEPIOS II. The results for this item at earlier time points [redacted].

Table 19: Ability to Work by the WPAI:MS (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Percent work time missed due to health (outcome 1 of WPAI:MS) – month 6[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value [b]	[redacted]		[redacted]	
Percent work time missed due to health (outcome 1 of WPAI:MS) – month 12[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
Percent work time missed due to health (outcome 1 of WPAI:MS) – month 18[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
Percent work time missed due to health (outcome 1 of WPAI:MS) – month 24[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
Percent work time missed due to health (outcome 1 of WPAI:MS) – month 30[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
Percent overall work impairment due to health (outcome 2 of WPAI:MS) – month 6[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
Percent overall work impairment due to health (outcome 2 of WPAI:MS) – month 12[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
Percent overall work impairment due to health (outcome 2 of WPAI:MS) – month 18[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
Percent overall work impairment due to health (outcome 2 of WPAI:MS) – month 24[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean change (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]		[redacted]	
P value[b]	[redacted]		[redacted]	
Percent overall work impairment due to health (outcome 2 of WPAI:MS) – month 30[a]				
Number of patients contributing to the analysis	[redacted]	[redacted]	[redacted]	[redacted]

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Adjusted mean change (95% CI)	[redacted]			
Treatment-group difference (OMB vs. TER), adjusted mean difference (95% CI)	[redacted]			
P value[b]	[redacted]			

CI = confidence interval; OMB = ofatumumab; SD = standard deviation; TER = teriflunomide; WPAI:MS = Work Productivity and Activity Impairment questionnaire for Multiple Sclerosis; vs. = versus.

[redacted]

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Use of Rescue Medication

Relapses that required steroid treatment and occurred during the 2 studies were evaluated as a supportive analysis of the primary analysis. These results were described under outcomes related to relapses. No other assessments of the use of rescue medication were reported for ASCLEPIOS I and II.

Disability Progression or Improvement

Outcomes related to disability progression or improvement were evaluated using the pooled dataset of ASCLEPIOS I and II and included as key secondary end points in the statistical testing hierarchy. The results of 3mCDW and 6CDW, as well as 6mCDI, are summarized in Table 20.

The between-treatment comparison of ofatumumab to teriflunomide (pooled analysis) in time to 3mCDW during the treatment period corresponded to a risk reduction of 34.4% based on an HR of 0.66 (95% CI, 0.50 to 0.86; P = 0.002) in favour of ofatumumab. This was consistent with the results in the individual studies. In the pooled analysis, time to 6mCDW corresponded to a risk reduction of 32.5% based on an HR of 0.68 (95% CI, 0.50 to 0.92; P = 0.012) in favour of ofatumumab; however, in ASCLEPIOS I, the HR was 0.61 (95% CI, 0.40 to 0.93; P = 0.022), indicating a treatment effect in favour of ofatumumab, but the HR in ASCLEPIOS II was 0.76 (95% CI, 0.49 to 1.17; P = 0.209). The between-groups comparison for 6mCDI in the pooled analysis resulted in an HR of 1.35 (95% CI, 0.95 to 1.92; P = 0.094), which was consistent with the results of the individual trials.

Table 20: Disability-Related Outcomes (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II		ASCLEPIOS I and II (pooled)	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474	OMB 20 mg	TER 14 mg
Time to 3-month confirmed disability worsening during the treatment epoch[a]						
Number of patients contributing to the analysis	465	459	479	472	944	931
Proportion of patients with 3-month confirmed disease worsening (%)	9.7	13.7	9.0	13.1	9.3	13.4
Between-treatment comparison, ofatumumab vs. teriflunomide						
Risk reduction (%)	34.8		34.0		34.4	
Hazard ratio (95% CI)	0.65 (0.45 to 0.96)		0.66 (0.45 to 0.97)		0.66 (0.50 to 0.86)	
P value	0.029		0.036		0.002	
Time to 6-month confirmed disability worsening during the treatment epoch[a]						
Number of patients contributing to the analysis	465	459	479	472	944	931
Proportion of patients with 6-month confirmed disease worsening (%)	7.5	11.5	7.5	9.7	7.5	10.6
Between-treatment comparison, ofatumumab vs. teriflunomide						
Risk reduction (%)	39.3		24.4		32.5	
Hazard ratio (95% CI)	0.61 (0.40 to 0.93)		0.76 (0.49 to 1.17)		0.68 (0.50 to 0.92)	
P value	0.022		0.209		0.012	
Time to 6-month confirmed disability improvement during the treatment epoch[a]						
Number of patients contributing to the analysis	375	363	374	360	749	723
Proportion of patients with 6-month confirmed disease improvement (%)	8.8	7.2	11.0	7.2	9.9	7.3
Between-treatment comparison, ofatumumab vs. teriflunomide						
Risk reduction (%)	–18.6		–51.6		–35.2	
Hazard ratio (95% CI)	1.19 (0.71, 1.98)		1.52 (0.93, 2.47)		1.35 (0.95, 1.92)	
P value	0.515		0.094		0.094	

CI = confidence interval; OMB = ofatumumab; SD = standard deviation; TER = teriflunomide; vs. = versus.

[a] Cox regression adjusted for study as stratum, treatment and region as factors, and baseline EDSS as a continuous covariate.

Note: Baseline values were not explicitly reported for the disability outcomes corresponding to the analyses presented in this table.

Source: Clinical Study Report for ASCLEPIOS I and II meta-analysis.[16]

Composite Outcomes: NEDA-4 (Relapses and Imaging)

The results of the analyses of the proportion of patients that were free of clinical and MRI disease activity, as measured by the NEDA-4 composite outcome at month 12 and month 24, are provided in Table 21. At month 12, the proportion of patients that were free of disease activity based on the NEDA-4 criteria were greater for patients in the ofatumumab treatment groups compared to teriflunomide based on an odds ratio (OR) of 1.97 (95% CI,

1.35 to 2.86; P < 0.001) in ASCLEPIOS I and 1.68 (95% CI, 1.19 to 2.39; P = 0.004) in ASCLEPIOS II. The results were consistent at month 24 in ASCLEPIOS I (OR = 6.34, 95% CI, 1.65 to 24.44; P = 0.007), but not in ASCLEPIOS II (OR = 2.57, 95% CI, 0.71 to 9.22; P = 0.149).

Table 21: Composite End Point, NEDA-4 (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
NEDA-4 – month 12[a]				
Number of patients contributing to the analysis	428	413	433	427
Proportion of patients meeting criteria for NEDA-4, % (95% CI)	23.4 (19.4 to 27.4)	14.8 (11.3 to 18.2)	23.8 (19.8 to 27.8)	17.8 (14.2 to 21.4)
Between-treatment comparison, ofatumumab vs. teriflunomide				
Odds ratio (95% CI)	1.97 (1.35 to 2.86)		1.68 (1.19 to 2.39)	
P value[b]	< 0.001		0.004	
NEDA-4 – month 24[a]				
Number of patients contributing to the analysis	104	95	92	78
Proportion of patients meeting criteria for NEDA-4, % (95% CI)	14.4 (7.7 to 21.2)	3.2 (0.0 to 6.7)	9.8 (3.7 to 15.9)	5.1 (0.2 to 10.0)
Between-treatment comparison, ofatumumab vs. teriflunomide				
Odds ratio (95% CI)	6.34 (1.65 to 24.44)		2.57 (0.71 to 9.22)	
P value[b]	0.007		0.149	

CI = confidence interval; NEDA-4 = 4-item no evidence of disease activity; OMB = ofatumumab; TER = teriflunomide; vs. = versus.

[a] Logistic regression analysis adjusted age, baseline Expanded Disability Status Scale, and number of gadolinium-enhanced lesions at baseline as covariates.

[b] The P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Subgroup Analyses

Subgroup analyses on ARR and confirmed disability worsening by age (≤ 40 versus > 40 years), MS type (RRMS versus SPMS), baseline EDSS score (≤ 3.5 or > 3.5), number of relapses in the previous 2 years (≤ 2 or > 2), gadolinium-enhanced T1 lesions at baseline (0 or > 0), and prior MS DMTs (experienced or naive) were reported for the primary and key secondary outcomes of ASCLEPIOS I and II using the pooled dataset (Appendix 3). The subgroup analyses of the primary end point, ARR, were consistent across all subgroups (Appendix 3, Figure 13). Subgroup analyses for confirmed disability worsening (3mCDW and 6mCDW) appeared to be potentially more evident in patients at least 40 years old, or without (0) gadolinium-enhanced T1 lesions at baseline (Appendix 3, Figure 14 and 15). The treatment effect on confirmed disability worsening for the other subgroups described was consistent, indicating there was no signal in treatment effect heterogeneity by disease severity (EDSS score ≥ 3.5 versus < 3.5), number of relapses in the previous 2 years, or prior treatment experience.

Harms

Only those harms identified in the review protocol are reported. See Table 22 for detailed harms data.

Adverse Events

The majority of patients reported at least 1 treatment-emergent adverse event in both the ASCLEPIOS I and II studies. Overall adverse events were similar between treatment groups in both of the studies (82.2% versus 82.3% in ASCLEPIOS I and 85.0% versus 86.1% in ASCLEPIOS II, for the ofatumumab versus teriflunomide treatment groups, respectively). The most commonly reported adverse events overall were injection-related reactions (ranging from 13.9% to 24.7% across all study groups), nasopharyngitis (ranging from 14.9% to 18.4% of patients), headache (ranging from 11.0% to 14.3%), and upper respiratory tract infections (ranging from 9.9% to 15.8%). In both studies, injection-site reactions were reported in a greater proportion of patients in the ofatumumab treatment groups (9.0% and 12.7%) compared to the teriflunomide groups (5.6% and 5.5%) in ASCLEPIOS I and II, respectively. Alopecia and diarrhea were reported in a greater proportion of patients in the teriflunomide groups (alopecia, 13.9% and 15.6%; diarrhea, 13.4% and 10.3%) than in the ofatumumab groups (alopecia, 5.8% and 5.6%; diarrhea, 4.5% and 5.8%) in ASCLEPIOS I and ASCLEPIOS II, respectively. Additionally, there was a difference in the proportion of ASCLEPIOS II patients reporting injection-related reactions, which were reported by 24.7% of patients in the ofatumumab treatment group and 13.9% of patients in the teriflunomide group, as well as upper respiratory tract infections in ASCLEPIOS I, with 10.3% of patients in the ofatumumab group and 15.8% in the teriflunomide group reporting infections.

Serious Adverse Events

In ASCLEPIOS I, serious adverse events were reported by 10.3% of patients in the ofatumumab group and 8.2% of patients in the teriflunomide group. In ASCLEPIOS II, serious adverse events were reported by 7.9% of patients in the ofatumumab group and 7.6% of patients in the teriflunomide group. The most common type of serious adverse events among both studies were infections and infestations (reported by 1.5% to 2.6% of patients), injury poisoning and procedural complications (reported by 0.2% to 1.7% of patients), and nervous system disorders (reported by 0.6% to 2.4% of patients). In ASCLEPIOS I, psychiatric disorders were more common in the ofatumumab group than in the teriflunomide group (1.9% versus 0%, respectively) and nervous system disorders were more common in the teriflunomide group than in the ofatumumab group (2.4% versus 0.6%, respectively).

Withdrawals Due to Adverse Events

The proportion of patients who stopped treatment due to adverse events ranged from 5.2% to 5.8% of patients between treatment groups and across the 2 pivotal trials. The most common adverse events leading to treatment discontinuation was a decrease in blood immunoglobulin M, which occurred in 2.2% and 1.9% of patients in the ofatumumab groups and 0.6% and 0.6% in the teriflunomide groups of ASCLEPIOS I and II, respectively. Other reasons for discontinuing treatment included immunoglobulin decrease, alanine aminotransferase increase, and more broadly, gastrointestinal disorders and skin and subcutaneous tissue disorders, all of which occurred in 1.5% or less of patients in either treatment group of either study.

Mortality

No deaths were reported during the treatment period in either of the pivotal trials. One patient in the teriflunomide group in ASCLEPIOS II died during the post-treatment follow-up period due to aortic dissection.

Notable Harms

Across the 2 studies, injection-related reactions were reported among 13.9% to 24.7% of patients and reductions in serum immunoglobulins (specifically, decreases in blood immunoglobulin M) were reported in 1.7% to 6.2% of patients, as described previously. Both of these events were more common among patients in the ofatumumab treatment groups than in the teriflunomide treatment groups. Other notable harms (as per the CADTH systematic review protocol) that were reported in the 2 studies include malignancies, neutropenia, decreased blood immunoglobulin G, and lymphopenia. Each of these events was reported in no more than 2.4% of patients in any treatment group, with no major differences between treatment groups. There were no cases of opportunistic infections such as cryptococcal meningitis and serious infections such as progressive multifocal leukoencephalopathy reported in ASCLEPIOS I or II.

Table 22: Summary of Harms

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Patients with ≥ 1 adverse event				
n (%)	382 (82.2)	380 (82.3)	409 (85.0)	408 (86.1)
Most common events,[a] n (%)				
Nasopharyngitis	82 (17.6)	69 (14.9)	88 (18.3)	87 (18.4)
Injection-related reaction	76 (16.3)	77 (16.7)	119 (24.7)	66 (13.9)
Headache	57 (12.3)	51 (11.0)	69 (14.3)	65 (13.7)
Upper respiratory tract infection	48 (10.3)	73 (15.8)	49 (10.2)	47 (9.9)
Fatigue	46 (9.9)	40 (8.7)	25 (5.2)	32 (6.8)
Injection-site reaction	42 (9.0)	26 (5.6)	61 (12.7)	26 (5.5)
Urinary-tract infection	42 (9.0)	41 (8.9)	55 (11.4)	37 (7.8)
Back pain	37 (8.0)	34 (7.4)	35 (7.3)	24 (5.1)
Influenza	32 (6.9)	29 (6.3)	30 (6.2)	30 (6.3)
Nausea	31 (6.7)	32 (6.9)	30 (6.2)	32 (6.8)
Alopecia	27 (5.8)	64 (13.9)	27 (5.6)	74 (15.6)
Blood immunoglobulin M decreased	26 (5.6)	13 (2.8)	30 (6.2)	8 (1.7)
Arthralgia	25 (5.4)	23 (5.0)	24 (5.0)	21 (4.4)
Pain in extremity	23 (4.9)	36 (7.8)	23 (4.8)	30 (6.3)
Depression	21 (4.5)	24 (5.2)	24 (5.0)	24 (5.1)
Diarrhea	21 (4.5)	62 (13.4)	28 (5.8)	49 (10.3)
Paresthesia	16 (3.4)	31 (6.7)	11 (2.3)	21 (4.4)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Hypertension	15 (3.2)	24 (5.2)	20 (4.2)	31 (6.5)
Anxiety	15 (3.2)	15 (3.2)	28 (5.8)	18 (3.8)
Insomnia	15 (3.2)	14 (3.0)	24 (5.0)	19 (4.0)
Patients with ≥ 1 serious adverse event				
n (%)	48 (10.3)	38 (8.2)	38 (7.9)	36 (7.6)
Most common events,[b] n (%)				
Infections and infestations	12 (2.6)	7 (1.5)	12 (2.5)	10 (2.1)
Appendicitis	3 (0.6)	1 (0.2)	5 (1.0)	1 (0.2)
Psychiatric disorders	9 (1.9)	0	1 (0.2)	2 (0.4)
Injury, poisoning and procedural complications	6 (1.3)	1 (0.2)	7 (1.5)	8 (1.7)
Musculoskeletal and connective tissue disorders	4 (0.9)	6 (1.3)	4 (0.8)	2 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (0.9)	2 (0.4)	5 (1.0)	2 (0.4)
Nervous system disorders	3 (0.6)	11 (2.4)	4 (0.8)	4 (0.8)
Reproductive system and breast disorders	3 (0.6)	3 (0.6)	1 (0.2)	5 (1.1)
Patients who stopped treatment due to adverse events				
n (%)	27 (5.8)	24 (5.2)	27 (5.6)	25 (5.3)
Most common events,[b] n (%)				
Investigations	18 (3.9)	6 (1.3)	18 (3.7)	13 (2.7)
Blood immunoglobulin M decreased	10 (2.2)	3 (0.6)	9 (1.9)	3 (0.6)
Immunoglobulins decreased	3 (0.6)	0	7 (1.5)	0
Alanine aminotransferase increased	1 (0.2)	0	0	5 (1.1)
Gastrointestinal disorders	1 (0.2)	6 (1.3)	1 (0.2)	2 (0.4)
Skin and subcutaneous tissue disorders	0	5 (1.1)	1 (0.2)	3 (0.6)
Deaths				
n (%)	0	0	0	0[c]
Notable harms				
Event, n (%)				
Injection-related reactions	76 (16.3)	77 (16.7)	119 (24.7)	66 (13.9)
Opportunistic infections (e.g., cryptococcal meningitis)	0	0	0	0
Serious infections (e.g., progressive multifocal leukoencephalopathy)	0	0	0	0
Lymphopenia	1 (0.2)	0	2 (0.4)	2 (0.4)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Neutropenia	1 (0.2)	8 (1.7)	1 (0.2)	3 (0.6)
Reduction in serum immunoglobulins				
Blood immunoglobin G decreased	2 (0.4)	4 (0.9)	0	0
Blood immunoglobin M decreased	26 (5.6)	13 (2.8)	30 (6.2)	8 (1.7)
Malignancies[d]	11 (2.4)	11 (2.4)	0	1 (0.2)

OMB = ofatumumab; TER = teriflunomide.

[a] Frequency 5% or more of patients. Reported for all treatment groups if the frequency of events was 5% or more in any individual treatment group.

[b] Frequency 1% or more of patients. Reported for all treatment groups if the frequency of events was 1% or more in any individual treatment group.

[c] No deaths occurred during the treatment periods in the study. However, 1 patient in the teriflunomide group died during the post-treatment follow-up period due to aortic dissection. The event was considered not related to the study treatment.

[d] Neoplasms benign, malignant, and unspecified (including cysts and polyps).

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Critical Appraisal

Internal Validity

ASCLEPIOS I and II were identically designed, double-blind, double-dummy studies that implemented adaptive design features. Randomization and allocation concealment were likely maintained; however, adverse events such as alopecia (13.9% and 15.6% versus 5.8% and 5.8%) and diarrhea (13.4% and 10.3% versus 4.5% and 5.8%) as shown in ASCLEPIOS I and II, respectively, occurred more frequently in the teriflunomide group than in the ofatumumab group. It is unknown whether these could have led to more patients withdrawing from the study in the teriflunomide group compared with the ofatumumab group as observed in ASCLEPIOS I. However, injection-site reactions occurred more frequently in the ofatumumab group versus the teriflunomide group (9.0% and 12.7% versus 5.6% and 5.5%) in ASCLEPIOS I and II, respectively. Moreover, considerable proportions of patients discontinued early from the study (approximately 17% to 18% in all treatment groups except ofatumumab in ASCLEPIOS I) due to various reasons, but discontinuations were driven by a patient or guardian decision, adverse events, and lack of efficacy. This may have led to the uncertainty and inconsistencies in some results, such as in the difference in 3mCDW or 6mCDW, which was statistically significant based on the pooled analysis and the individual trial data for ASCLEPIOS I, but inconsistent with what was observed in ASCLEPIOS II.

Some of the results from the ASCLEPIOS trials were also limited by missing data, which created uncertainty for the MSIS-29 and WPAI:MS assessments. Missing data were not imputed and at least 46% of data were missing for the MSIS-29 at month 24 and later, and the WPAI:MS was missing more than 50% of data at all time points. Outcomes that were noted as important to patients such as those related to HRQoL (MSIS-29 and EQ-5D) and the ability to attend work (WPAI:MS) were not included in the hierarchical testing procedure and not controlled for potential inflated type I error. Patients were also interested in MS relapses that lead to hospitalization, and while such data were reported, they were only available in the form of descriptive supportive analysis of the primary end point.

Treatment groups were well balanced in terms of baseline characteristics, both within each study and between the 2 studies. Prior use of DMTs for MS was reported, with slight differences in the use of glatiramer acetate (26.7% versus 22.9% in ASCLEPIOS I and

24.5% versus 31.4% in ASCLEPIOS II for ofatumumab versus teriflunomide) and fingolimod in ASCLEPIOS I (5.8% versus 9.5% for ofatumumab versus teriflunomide), although this prior treatment experience was not expected to have a differential impact on the treatment effect observed in the studies, according to the clinical expert consulted for this review.

The primary end point in the ASCLEPIOS studies was ARR and the key secondary end points included confirmed disability worsening based on the EDSS over 3 and 6 months. The selection and implementation of these outcomes in the 2 studies are aligned with industry guidance for MS trials from the EMA regarding treatments intended to modify the natural course of RMS.[64] Despite this, the duration of the 2 studies limits the ability to reliably evaluate the treatment effect of ofatumumab on outcomes such as HRQoL, mobility, cognitive function, and disability. The majority of patients (54% to 65%) were exposed to the study drug for 1 to 2 years; however, the clinical expert on this review noted that it is unlikely that a meaningful change in these outcomes could be observed within 2 years.

A statistical testing hierarchy was implemented to control for the type I error rate of the primary and key secondary outcomes in both studies, which included ARR, disability-related outcomes, and imaging outcomes. Of note, disability-related outcomes (3mCDW, 6mCDW, and 6mCDI) were analyzed in the pooled dataset of ASCLEPIOS I and II; this was pre-planned and adequately powered based on sample size calculations.

The EMA guidance also recommends that the use of corticosteroids and other concomitant treatments of acute relapses used during the trial be carefully standardized.[64] High concomitant use of systemic corticosteroids was reported in ASCLEPIOS I and II, predominantly methylprednisolone sodium succinate (40% and 44% overall, respectively), methylprednisolone (33% and 25%), and prednisone (6% and 6%). In addition, characteristics of MS relapses, such as whether steroids were required to treat a relapse, were reported; however, subgroup analyses by steroid use were not available and therefore the impact of steroid use on the efficacy and safety of treatment is unknown.

Subgroup analyses that were available included analyses by age, MS type, baseline EDSS score, number of relapses in the previous 2 years, gadolinium-enhanced T1 lesions at baseline, and prior use of DMTs for MS. However, details regarding the methodology of the subgroup analyses reported in this review were unclear, which limited the ability to adequately interpret the results.

External Validity

Patients included in the ASCLEPIOS studies were generally representative of the Canadian patient population living with MS, although this characterization is subject to certain limitations. Four Canadian study centres were included in each of the 2 multi-centre, international ASCLEPIOS trials. Included patients had a diagnosis of MS according to the 2010 Revised McDonald criteria,[18] and either RRMS or SPMS with disease activity, as defined by Lublin et al.[6] However, the proportion of patients with a confirmed diagnosis of SPMS at study entry was small, ranging from 5% to 6% across the 2 trials. While this group of patients is unlikely to affect the efficacy results for patients with RRMS, it is unclear whether there were enough data to reliably inform the treatment effect in patients with SPMS. The clinical expert consulted for this review noted that certain groups of patients who may be suitable for treatment with ofatumumab in clinical practice, patients with various comorbidities, those over 55 years of age, and those with an EDSS score greater

than 5.5, were excluded from the study. According to the clinical expert consulted by CADTH, ofatumumab would be suitable for treatment of patients older than 55 and those with an EDSS score of up to 6.5. The clinical expert also suggested that the exclusion of patients with neurologic or psychiatric disorders was a generalizability issue as rates of depression and bipolar disorder, as well as certain CNS diseases, are more prevalent among patients with MS, who would likely be candidates for treatment with ofatumumab. Patients who had lived with MS for at least 10 years with an EDSS score of 2 or less were also excluded from the pivotal trials. The reason for this is unclear but may indicate that the trial population excluded patients with well-controlled MS, thus limiting the applicability of the results to this group of patients. Further, the mean (SD) number of relapses in the 12 months prior to screening ranged from 1.2 (0.6) to 1.3 (0.7) across the treatment groups of the 2 trials, which, according to the clinical expert, is suggestive of patients with more highly active disease,[65] although 38% to 41% of patients were also naive to DMTs for MS, which may also explain the high disease activity.

The ofatumumab dosing regimen used in the ASCLEPIOS trials followed the general dosing recommendation included in the product monograph for ofatumumab and is consistent with its anticipated use in clinical practice. Concomitant medications such as dalfampridine were permitted throughout the study if used on a stable dose, and acetaminophen and/or antihistamines were recommended prior to the subcutaneous injection, both of which were consistent with clinical practice, as noted by the clinical expert. The 2 trials also allowed 3 to 5 days of use up to 1,000 mg of the corticosteroid methylprednisolone (or equivalent) per day as rescue medication for MS relapses, which was also consistent with clinical practice.

The primary end point, ARR, was relevant to clinical practice as indicated by the clinical expert, as well as the imaging outcomes regarding new or enlarging T2 lesions and number of gadolinium-enhanced T1 lesions, although the clinical expert noted that gadolinium-enhanced MRI scans are used less often due to concerns with gadolinium accumulation in the brain with frequent use.[8] The 2020 treatment optimization guidelines recommend follow-up MRIs should be obtained annually for the first few years of treatment, which is also consistent with assessments conducted in ASCLEPIOS I and II. Confirmed disability worsening sustained for 3 months and 6 months, which were included as key secondary outcomes in the trials, are also considered clinically relevant outcomes by the clinical expert, although it was noted that the latter (6mCDW) is a more clinically meaningful time period to assess disability worsening. This is also supported by the 2020 treatment optimization guidelines, which recommend the T25FW and 9-HPT as validated measures of disability that are important to patients.[8] These measures of disability are also considered useful to clinicians as they are easy to perform and are recommended as part of a routine patient assessment.[8] The T25FW and 9-HPT were included as secondary outcomes in the 2 trials, but were not included in the statistical testing hierarchy.

Last, scheduled study visits in ASCLEPIOS I and II occurred every 3 months, with monthly telephone interviews between scheduled visits. The clinical expert consulted for this review suggested that, ideally, patients with MS would be seen by a health care professional every 6 months, although an annual visit is more realistic. The frequency at which patients were assessed in the trials is therefore higher than in clinical practice and, as a result, had potential to inflate adherence and subsequently the treatment effect reported in both treatment groups.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

Currently, the only available head-to-head comparison of ofatumumab for treating patients with RMS is provided in the ASCLEPIOS I and II trials, which compared ofatumumab against teriflunomide.[5] The objective of this section is to summarize and appraise information on the relative efficacy and safety comparisons of ofatumumab against other available DMTs by using an ITC methodology, also known as analysis of multiple comparisons, mixed-treatment comparisons, or NMA.

One sponsor-submitted ITC is included in this analysis.[66] However, a supplemental literature search was conducted to identify ITCs of ofatumumab subcutaneous against other approved drugs for the treatment of adult patients with relapsing forms of multiple sclerosis. Based on a literature search conducted by CADTH, no additional ITCs were included in this review for the specific intervention and population of interest.

Description of Indirect Comparison

The included ITC is a systematic review and NMA of ofatumumab and other DMTs for the treatment of patients with RMS. The sponsor-submitted study selection criteria and methods for the ITC are provided in Table 23.

Table 23: Study Selection Criteria and Methods for Indirect Treatment Comparisons

	Indirect treatment comparison
Population	Adult patients ≥ 18 years of age with relapsing multiple sclerosis.
Intervention	Ofatumumab
Comparator	• Interferon beta-1a • Interferon beta-1b • Pegylated IFN beta-1a • Glatiramer acetate • Natalizumab • Fingolimod • Teriflunomide • Alemtuzumab • Cladribine • Dimethyl fumarate • Mitoxantrone • Ocrelizumab • Siponimod • Unlicensed therapies (ATX-MS-1467, ALKS 8700 [diroximel fumarate], ozanimod, ponesimod, ublituximab, rituximab, laquinimod) • Placebo • Best supportive care
Outcomes	Efficacy outcomes • Annualized relapse rate (all relapses) • 3-month confirmed disability progression • 6-month confirmed disability progression Safety • Adverse events

	Indirect treatment comparison
	• Serious adverse events • Withdrawals
Study design	Randomized controlled trials
Exclusion criteria	• Studies with patients with other types of MS (i.e., clinically isolated syndrome or progressive) • Studies assessing only unlicensed doses of approved DMTs • Non-comparative studies • Other designs (e.g., observational studies) • Studies published in non-English language
Databases searched	Embase, MEDLINE, CCRCT, HTA database, DARE, conferences and grey literature
Selection process	Articles were screened independently by 2 researchers using pre-specified criteria and discrepancies solved by a third reviewer
Data extraction process	Data extraction performed by 2 independent reviewers using standardized data extraction forms (by trial design, intervention details, patient eligibility, and outcomes)
Quality assessment	Risk of bias assessed by outcome using CRD guidance

ITC = indirect treatment comparison; RMS = relapsing multiple sclerosis; DMT = disease-modifying therapy; CCRCT = Cochrane Central Register of Controlled Trials; HTA = health technology assessment; DARE = Database of Abstracts of Reviews of Effects; CRD = Centre for Reviews and Dissemination.

Source: Sponsor-submitted indirect treatment comparison.[66]

Methods of Indirect Treatment Comparison

Objectives

The objectives of the submitted report addressed the following questions:

- Based on available randomized controlled trials (RCTs), is it feasible to conduct NMAs to evaluate the relative efficacy of ofatumumab compared with other DMTs for the treatment of patients with RMS?
- What are the relative efficacy and safety of ofatumumab compared with other DMTs for RMS?
- How do newer DMTs (cladribine, ocrelizumab, and ofatumumab) fit in to the efficacy classes described in the 2015 Association of British Neurologists treatment guidelines?

For the purpose of this CADTH report, we focused on the second objective — the efficacy and safety of ofatumumab as compared to other DMTs for RMS.

Study Selection Methods

The selection of studies was based on the identification of evidence gathered in a systematic literature search following NICE and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The aim of the systematic literature review was to identify all RCTs assessing the efficacy and safety of DMTs used for the treatment of patients with RMS. The search was conducted in December 2019.

Inclusion criteria included those RCTs (published in the English language) evaluating the efficacy and safety of any of the DMTs for the treatment of adult patients (≥ 18 years of age) with RMS (Table 23).

Trials were excluded if more than 25% of the included population was classified as SPMS (without relapses), PPMS, and/or progressive-relapsing MS; the only interventions and comparators were inappropriate or irrelevant (see Table 23 for a list of relevant DMTs); the

only comparator was best supportive care; the trial objectives did not include comparing the efficacy of any of the aforementioned interventions directly to any other included DMT or placebo; the trial did not report any of ARR, time to 3mCDP or time to 6mCDP; or if the trial duration was less than 48 weeks.

The literature search included Embase, MEDLINE, Cochrane Central Register of Controlled Trials, health technology assessment databases, the Database of Abstracts of Reviews of Effects, the Centre for Reviews and Dissemination (CRD), conference abstracts, and grey literature. Two reviewers independently screened the titles and abstracts of additional retrieved records against the eligibility criteria. Citations considered to describe potentially eligible articles were independently evaluated in full-text form by 2 reviewers according to the same criteria. Disagreements were resolved by a third independent reviewer.

Data extraction was performed by 2 independent reviewers using a standardized data extraction form. Trial design characteristics (e.g., author, year, and journal), intervention details (e.g., treatment, dose, route, and frequency), patient eligibility criteria, patient characteristics (e.g., age, gender, baseline EDSS score, and duration of disease), target outcomes (i.e., ARR and time to CDP) and trial-specific outcome definitions were extracted for all RCTs, where reported. Discrepancies in collected data were resolved by consensus or a third independent reviewer.

Risk of bias of the included studies was assessed with the risk of bias assessment principles recommended in the CRD guidance for undertaking reviews in health care. The risk of bias domains includes appropriate randomization processes and concealment of treatment allocation, similarity in groups of study and prognostic factors, blinding of participants, imbalances in drop-outs, selection of reported outcomes, and accounting for missing data.

Efficacy outcomes included ARR, time to 3mCDP, and time to 6mCDP.

There were differences in how studies defined ARR (Table 24). The term “confirmed disease progression” was used globally in the ITC, and it is equivalent to the 3mCDW and 6mCDW of the ASCLEPIOS trials. For the definition of time to 3mCDP (Table 25) and time to 6mCDP (Table 26) some between-trial differences were noted for the magnitude of increase in EDSS score required to qualify as progression. Apart from ocrelizumab (OPERA I and II trials), definitions for the pivotal ofatumumab trials (ASCLEPIOS I and II) were in alignment with those used for pivotal trials of the other monoclonal antibody therapies alemtuzumab (CAMMS223, CARE-MS I, and CARE-MS II) and natalizumab (AFFIRM). Lublin et al. and ASCLEPIOS recommended limiting the use of the term disability progression to the progressive phase of MS (i.e., PPMS or SPMS) and using the more general term “disability worsening” in RMS. However, most RMS trials have used the term “disability progression.” Given its ubiquity, the term “confirmed disability progression” is used throughout the ITC report.

Table 24: Definition of Annualized Relapse Rate by Study Included in the ITC

Definition	Trials using the definition
Estimated using a negative binomial model with the cumulative number of confirmed relapses by patient as the response variable and the natural log of time in study in years as an offset variable	ASCLEPIOS I and II
Total number of relapses divided by the total number of patient-years in the study	ADVANCE, AFFIRM, CombiRx, CONFIRM, DEFINE, MSCRG, and OPERA I and II
Total number of confirmed relapses divided by the total days in the study multiplied by 365.25	ASSESS, CLARITY, and FREEDOMS II
MRI-confirmed exacerbations per patient per year Note: also reported number of relapses regardless MRI confirmation, allowing ARR to be calculated without that constraint	Boikoet al. (2018)
Estimated using a negative binomial model with the total number of confirmed relapses on study	BRAVO
Estimated using a Poisson regression model with the number of relapses as the dependent variable and the log total amount of follow-up for each participant as an offset variable	CAMMS223
Estimated using a negative binomial model with the total number of relapses by patient as the dependent variable and the log total amount of follow-up for each participant as an offset variable	CARE-MS I and II
Relapses per patient per time on study	EVIDENCE
Number of confirmed relapses per year	FREEDOMS
Cumulative number of confirmed relapses divided by the number of person-years of exposure to treatment	GALA
Total number of relapses across all patients divided by the total time on study across all patients	REGARD
Total number of confirmed relapses that occurred during the treatment period divided by the sum of the treatment durations	TEMSO, TENERE, and TOWER
The number of confirmed relapses during a 12-month period	TRANSFORMS

Note: Outcome not reported in Bornstein (1987) and PRISMS. No definition reported in BEYOND, Calabrese (2012), Copolymer 1 MS trial, IFNB MS, INCOMIN, and Stepien (2013).

Source: Sponsor-submitted indirect treatment comparison.[66]

Table 25: Definition of Time to 3mCDP in the Studies Included in the ITC

Trial name	Efficacious treatment	Definition
ASCLEPIOS I and II	Ofatumumab	An increase in EDSS score of at least 1.5 points if baseline score was 0, of at least 1 point if baseline score was 1 to 5, or of at least 0.5 points if baseline score was at least 5.5, sustained for at least 3 months.
ADVANCE	—	≥ 1.0-point increase on the EDSS from a baseline EDSS score ≥ 1.0 sustained for 12 weeks or an increase of at least a 1.5 points on the EDSS from a baseline EDSS of 0 sustained for 12 weeks.
AFFIRM	Natalizumab	An increase of 1.0 or more on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 12 weeks (progression could not be confirmed during a relapse).
BEYOND	—	A 1-point change in the score that was sustained for 3 months.
Bornstein (1987)	—	An increase of at least 1 unit in a Kurtzke score that was maintained for at least 3 months.

Trial name	Efficacious treatment	Definition
BRAVO	—	A 1.0-point increase in EDSS score if the baseline score was between 0 and 5.0, or a 0.5-point increase if the baseline score was 5.5, sustained for 3 months.
CAMMS223	Alemtuzumab	An increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 for patients with a baseline score of 1.0 or more; all scores were confirmed twice during a 6-month period. The onset of a sustained level of disability was timed to the first recorded increase in the EDSS score aside from relapse.
CLARITY	—	Time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score was 0. (The definition on ClinicalTrials.gov differs from the study publication; it also specifies an increase of 0.5 required for baseline EDSS 5 or greater.)
CONFIRM	—	An increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later.
Copolymer 1 MS trial	—	An increase of at least 1 full step on the EDSS that persisted for at least 3 months.
DEFINE	—	An increase of at least 1.0 points on the EDSS in patients with a baseline score of 1.0 or higher, or an increase of at least a 1.5 points in patients with a baseline score of 0, with the increased score sustained for at least 12 weeks.
EVIDENCE	—	Progression by 1 point on the EDSS scale confirmed at a visit 3 or 6 months later without an intervening EDSS value that would not meet the criteria for progression.
FREEDOMS	—	An increase of 1 point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.
FREEDOMS II	—	A 1-point EDSS increase from baseline or 0.5-point increase if baseline EDSS is ≥ 5.5, confirmed 3 months later.
IFNB MS	—	Two consecutive EDSS scores, separated by 90 days, that were identical, with both showing a 1.0-point increase over the baseline score.
OPERA I and II	Ocrelizumab	An increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was > 5.5) that was sustained for at least 12 weeks.
PRISMS	—	An increase in EDSS of at least 1 point sustained over at least 3 months.
TEMSO	—	An increase from baseline of at least 1.0 points in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks.
TOWER	—	An increase from baseline of at least 1 EDSS point (or ≥ 0.5 points when the baseline EDSS score was > 5.5 points) that persisted for at least 12 weeks. For clarification, a score of 5.5 points or more could occur in patients whose EDSS score deteriorated between screening and baseline.
TRANSFORMS	—	A 1.0-point increase in EDSS score (0.5-point increase for baseline EDSS score ≥ 5.5), confirmed 3 months later in the absence of relapse.

EDSS = Expanded Disability Status Scale.

Source: Sponsor-submitted indirect treatment comparison.[66]

Table 26: Definition of Time to 6mCDP in the Studies Included in the ITC

Trial name	Efficacious treatment	Definition
ASCLEPIOS I and II	Ofatumumab	An increase in EDSS score of at least 1.5 points if baseline score was 0, of at least 1 point if baseline score was 1 to 5, or of at least 0.5 points if baseline score was at least 5.5 and sustained for at least 6 months.
ADVANCE	—	At least a 1-point increase from baseline EDSS ≥ 1- or 1.5-point increase for patients with baseline EDSS of 0, sustained for 24 weeks.
AFFIRM	Natalizumab	An increase of 1.0 or more on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 24 weeks (progression could not be confirmed during a relapse).
BRAVO	—	A 1.0-point increase in EDSS score if baseline score was between 0 and 5.0, or a 0.5 point increase if baseline score was 5.5, sustained for 6 months.
CAMMS223	Alemtuzumab	An increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more; all scores were confirmed twice during a 6-month period. The onset of a sustained level of disability was timed to the first recorded increase in the EDSS score aside from relapse.
CARE-MS I	Alemtuzumab	An increase from baseline of at least 1 EDSS point (or ≥ 1.5 points if baseline EDSS score was 0) confirmed over 6 months.
CARE-MS II	Alemtuzumab	An increase from baseline of at least 1 EDSS point (or ≥ 1.5 points if the baseline EDSS score was 0) confirmed over 6 months.
CLARITY	—	Definition for 6-month CDP was not reported. Definition was assumed to match that reported for time to 3mCDP with regards to required increase in EDSS: Time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score was 0 (The definition on ClinicalTrials.gov differs from publication; additionally it specifies an increase of 0.5 required for a baseline EDSS score of 5 or greater.)
CombiRx	—	A 1.0 increase in the EDSS from baseline, when baseline ≤ 5.0; or an increase of 0.5 from baseline, when baseline ≥ 5.5, sustained for 6 months (2 successive quarterly visits) as assessed by the blinded EDSS examiner and confirmed centrally.
CONFIRM[a]	—	A ≥ 1.0-point increase on the EDSS from a baseline EDSS score ≥ 1.0 that was confirmed at least 24 weeks later, or a ≥ 1.5-point increase on the EDSS from a baseline EDSS score of 0 that was confirmed at least 24 weeks later.
DEFINE[a]	—	A ≥ 1.0-point increase on the EDSS from a baseline EDSS score ≥ 1.0 that was confirmed at least 24 weeks later, or a ≥ 1.5-point increase on the EDSS from a baseline EDSS score of 0 that was confirmed at least 24 weeks later.
EVIDENCE	—	Progression by 1 point on the EDSS scale confirmed at a visit 3 or 6 months later without an intervening EDSS value that would not meet the criteria for progression.
FREEDOMS	—	An increase of 1 point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 6 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.
FREEDOMS II	—	A 1-point EDSS increase from baseline or 0.5-point increase if baseline EDSS is ≥ 5.5 and confirmed 6 months later.
INCOMIN	—	An increase in EDSS of at least 1 point sustained for at least 6 months and confirmed at the end of follow-up.
MSCRG	—	Deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months.

Trial name	Efficacious treatment	Definition
OPERA I and II	Ocrelizumab	An increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was > 5.5) that was sustained for at least 24 weeks.
REGARD	—	Disability progression at the 6-month follow-up visit was confirmed as follows: if the EDSS score at baseline was 0, then a change of 1.5 points or more was required; if the EDSS was 0.5 to 4.5 at baseline, then a change of 1.0 points or more was required; and if the EDSS at baseline was 5 points or more, then the change required was 0.5 points or more.
TEMSO[a]	—	An increase of at least 1 point on EDSS score from baseline if the baseline EDSS score was ≤ 5.5, or time to at least 0.5 increase on EDSS score from baseline if the baseline EDSS score was > 5.5; this increase in EDSS score was to be persistent for at least 24 weeks.
TOWER[a]	—	An increase of at least 1 point on EDSS score from baseline if the baseline EDSS score was ≤ 5.5, or time to at least 0.5 increase on EDSS score from baseline, if the baseline EDSS score was > 5.5; this increase in EDSS score was to be persistent for at least 24 weeks.

EDSS = Expanded Disability Status Scale.

[a] The sponsor's ITC noted that the definition of 6mCDP was not found in the primary trial publication; therefore, a Summary of Product Characteristics or European Medicines Agency assessment report associated with the trial was used as a reference.

Source: Sponsor-submitted indirect treatment comparison.[66]

The outcome of relapse was defined as "new/recurrent/worsening neurological symptoms/abnormalities that lasted for at least 24 hours" in 23 studies (including the ASCLEPIOS studies), and as "new/recurrent/worsening neurological symptoms/abnormalities that lasted for at least 48 hours" in 9 studies.

Safety (harms) outcomes were reported narratively (as a "qualitative assessment"), referring to limitations associated with quantitative results when comparing safety outcomes and the diversity of safety profiles across the various classes of DMTs used to treat RMS. Three safety outcomes groups were evaluated, including all-cause discontinuation, discontinuation due to adverse events, and serious adverse events. Within these, the main safety issues to be looked for and reported were injection or infusion reactions, and infections or infestations.

Although the outcome definitions varied across trials, they were considered by the authors of the ITC similar enough for comparison.

Indirect Treatment Comparison Analysis Methods

The NMA approach used by the authors of the ITC was based on the evidence synthesis techniques described by the NICE Decision Support Unit Technical Support Document 2. This is based on a standard Bayesian framework using the Markov Chain Monte Carlo simulation[67] with a random-effects model and vague priors of treatment effects. Network diagrams were created to visualize the evidence base for each analysis. In the network, the size of the treatment nodes reflects the proportionate numbers of patients randomized to each treatment, with larger nodes implying more patients. Lines that connect nodes signify the presence of 1 or more RCTs that directly compare treatments, with the thickness of each line reflecting the number of RCTs informing the comparison; thicker lines signify more RCTs comparing treatments. Version 3.6.1 of R software, Just Another Gibbs Sampler (JAGS) version 4.3.0, and WinBUGS version 1.4.3 were used to conduct the analyses. All analyses were based on burn-in and sampling durations of 60,000 iterations each.

For the outcome ARR, the NMA methodology used a Poisson model with a vague prior distribution (τ ~ uniform [0,5]). For the outcomes CPD-3 and CPD-6, the NMA used a continuous survival model (log hazard scale) with informative prior distribution for between-trial variances with τ^2 ~ log normal (–3.95 to 1.792). Mean HR for the time-to-event outcome and its 95% CI were preferentially extracted for CDP. Log-HR and its standard error were derived for the analysis by taking the natural log (Ln) of the mean HR and dividing the width of Ln of the CI limits by 1.96 x 2, respectively. When the time-to-event outcome was not reported, but the proportion of patients with the event was, the log-HR and its standard error were derived using a published formula. To assess whether the models had adequate fit to the data, the posterior mean of the residual deviance from each NMA was compared to the corresponding number of unconstrained data points (approximately equal if the fit is adequate), as well as the deviance information criterion. To ensure that convergence was reached, the Brooks-Gelman-Rubin statistic was used (Table 27).

Four scenario (sensitivity) analyses were conducted to evaluate the impact of excluded trials on NMA results: (1) inclusion of pegylated IFN beta-1a (i.e., the ADVANCE trial), (2) inclusion of the INCOMIN trial, (3) inclusion of abstracts and posters, and (4) inclusion of noninferiority trials comparing different formulations of the same DMT. An additional scenario analysis was conducted for each efficacy outcome to evaluate the impact of using fixed-effect models instead of random-effects models.

Two approaches were used for the NMAs of the outcomes of time to 3mCDP and time to 6mCDP due to between-trial differences in outcome definitions. The first approach was to use the predefined criteria for CDP in the ASCLEPIOS I and II trials (i.e., CDP as predefined in the trial protocol). The second approach was to use aligned criteria where ASCLEPIOS data were recalculated to align with the reported definition of CDP in the OPERA I and II trials (i.e., aligned with respect to disability progression criteria, definition of baseline EDSS score, confirmatory time window during which the initial progression had to be sustained, and confirmation of progression). Analyses for both the predefined and aligned criteria are presented for the outcomes of time to 3mCDP and time to 6mCDP as sensitivity analyses — or modifications of the NMAs.

As an exploratory analysis, authors of the ITC used a third approach for the CDP NMAs that recalculated ASCLEPIOS data based only on the EDSS score thresholds used in the OPERA trials (“EDSS-only aligned criteria”) with respect to the minimum increase in EDSS score required for progression.

The authors qualitatively assessed the heterogeneity of pairwise comparisons by evaluating the similarities of studies comparing the same treatments. This was based on an assessment of heterogeneity with respect to trial design, eligibility criteria, baseline patient characteristics, placebo response, and trial-specific outcome definitions.

A formal section of the statistical assessment of the inconsistency of the network (i.e., coherence of direct and indirect evidence where closed loops were present) was not reported. However, the authors presented an inconsistency assessment based on the comparison of the posterior mean deviance of the individual data points in the random-effects inconsistency model (i.e., unrelated mean effect model) against their posterior mean deviance in the random-effects consistency model (i.e., base-case analysis) to help identify loops where inconsistency was present.

Table 27: Indirect Treatment Comparison Analysis Methods

	ITC submitted by the sponsor
ITC methods	Standard Bayesian approach framework based on Markov Chain Monte Carlo simulation using a random-effects model
Priors	For the general NMA, vague priors for treatment effects were used. For the annualized relapse rate outcome, the NMA methodology used a Poisson model with a vague prior distribution (τ ~ uniform [0,5]); for the outcomes CPD-3 and CPD-6, the NMA used a continuous survival model (log hazard scale) with informative prior distribution for between-trial variances with τ^2 ~ log normal (–3.95 to 1.792)
Assessment of model fit	By comparing the posterior mean of the residual deviance from each NMA to the corresponding number of unconstrained data points, and using the deviance information criterion
Assessment of consistency	Based on the comparison of the random-effects inconsistency model (i.e., unrelated mean effect model) against the random-effects consistency model (i.e., base-case analysis)
Assessment of convergence	Assessed with the Brooks-Gelman-Rubin statistic
Follow-up time points	Minimum trial duration was 48 weeks and a maximum of 3 years of follow-up
Construction of nodes	(See note related to dosing; pooling by drug class)
Sensitivity analyses	Four sensitivity analyses (scenarios) were conducted to evaluate the impact of excluded trials on NMA results: (1) inclusion of pegylated IFN beta-1a (i.e., the ADVANCE trial), (2) inclusion of the INCOMIN trial, (3) inclusion of abstracts and posters, and (4) inclusion of noninferiority trials comparing different formulations of the same DMT. An additional scenario analysis was conducted for each efficacy outcome to evaluate the impact of using fixed-effect models instead of random-effects models.
Subgroup analysis	Not reported
Methods for pairwise meta-analysis	Not reported

3mCDP = 3-month confirmed disease progression; 6mCDP = 6-month confirmed disease progression; DMT = disease-modifying therapy; IFN = interferon; ITC = indirect treatment comparison; NMA = network meta-analysis.

Source: Sponsor-submitted indirect treatment comparison.[66]

Results of the Indirect Treatment Comparison

Summary of Included Studies

The systematic literature search identified 82 trials, of which 50 trials were excluded due to duration of the studies (< 48 weeks), population not in the age range of eligibility, interventions not clinically relevant, or the use of other designs and outcomes. After including both ASCLEPIOS trials, 34 studies were finally included for feasibility assessment. Trials were all multi-centric RCTs and were relatively similar in design. Most trials were phase III (25 or 34), double-blind (21 of 34), and had parallel allocation (33 of 34). Notably, all trials including alemtuzumab (CAMMS223, CARE-MS I, and CARE-MS II) were open-label. The characteristics of the 34 studies are presented in Table 28.

Table 28: Trials Included in the Indirect Treatment Comparison

Trial name	Sample size[a]	MS population	Treatments	Trial duration
ADVANCE	1,512	RRMS	Pegylated IFN beta-1a SC 125 mcg q.2.w. Placebo	2 years
AFFIRM	942	RRMS (i.e., RMS but not PPMS, SPMS, or PRMS)	Natalizumab IV 300 mg q.4.w. Placebo	2+ years
ASCLEPIOS I	927	RMS (i.e., RRMS or SPMS) (94% RRMS)	Ofatumumab SC 20 mg q.4.w. Teriflunomide PO 14 mg q.d.	30 months
ASCLEPIOS II	955	RMS (i.e., RRMS or SPMS) (94% RRMS)	Ofatumumab SC 20 mg q.4.w. Teriflunomide PO 14 mg q.d.	30 months
ASSESS	1,064	RRMS	Fingolimod PO 0.5 mg q.d. Glatiramer acetate SC 20 mg q.d.	12 months
BEYOND	2,244	RRMS	IFN beta-1b SC 250 mcg q.2.w. Glatiramer acetate SC 20 mg q.d.	2+ years
Boiko (2018a)	158	RRMS	Glatiramer acetate SC 20 mg q.d. Glatiramer acetate SC 20 mg q.d. Placebo	48 weeks
Bornstein (1987)	50	RRMS (i.e., exacerbating-remitting MS)	Glatiramer acetate SC 20 mg q.d. Placebo	2 to 3 years
BRAVO	1,331	RRMS	IFN beta-1a IM 30 mcg q.w. Placebo	2 years
Calabrese (2012)	165	RRMS	IFN beta-1a SC 44 mcg t.i.w. IFN beta-1a IM 30 mcg q.w Glatiramer acetate SC 20 mg q.d.	2 years
CAMMS223	334	RRMS	Alemtuzumab IV 12 mg, IFN beta-1a SC 44 mcg t.i.w.	3 years
CARE-MS I	581	RRMS	Alemtuzumab IV 12 mg IFN beta-1a SC 44 mcg t.i.w.	2 years
CARE-MS II	840	RRMS	Alemtuzumab IV 12 mg, IFN beta-1a SC 44 mcg t.i.w.	2 years
CLARITY	1,326	RRMS	Cladribine PO 3.5 mg/kg Cladribine PO 5.25 mg/kg Placebo	96 weeks
CombiRx	1,008	RRMS	IFN beta-1a IM 30 mcg q.w. Glatiramer acetate SC 20 mg q.d.	3+ years
CONFIRM	1,430	RRMS	Dimethyl fumarate PO 240 mg b.i.d. Glatiramer acetate SC 20 mg q.d. Placebo	2 years
Copolymer 1 MS trial	251	RRMS	Glatiramer acetate SC 20 mg q.d Placebo	2 years
DEFINE	1,237	RRMS	Dimethyl fumarate PO 240 mg b.i.d. Placebo	2 years
EVIDENCE	677	RRMS	IFN beta-1a SC 44 mcg t.i.w. IFN beta-1a IM 30 mcg q.w.	48 weeks
FREEDOMS	1,272	RRMS	Fingolimod PO 0.5 mg q.d. Placebo	24 months

Trial name	Sample size[a]	MS population	Treatments	Trial duration
FREEDOMS II	1,083	RRMS	Fingolimod PO 0.5 mg q.d. Placebo	24 months
GALA	1,404	RRMS	Glatiramer acetate SC 40 mg t.i.w. Placebo	12+ months
IFNB MS	372	RRMS	IFN beta-1b SC 250 mcg q.2.d, Placebo	2 years
INCOMIN	188	RRMS	IFN beta-1a IM 30 mcg q.w. IFN beta-1b SC 250 mcg q.2.d.	24 months
MSCRG	301	RMS (not chronic-progressive MS)	IFN beta-1a IM 30 mcg q.w. Placebo	2 years
OPERA I	821	RMS (not PPMS)	Ocrelizumab IV 600 mg q.24.w. IFN beta-1a SC 44 mcg t.i.w.	96 weeks
OPERA II	835	RMS (not PPMS)	Ocrelizumab IV 600 mg q.24.w. IFN beta-1a SC 44 mcg t.i.w.	96 weeks
PRISMS	560	RRMS	IFN beta-1a SC 22 mcg t.i.w. IFN beta-1a SC 44 mcg t.i.w. Placebo	2 years
REGARD	764	RRMS	IFN beta-1a SC 44 mcg t.i.w. Glatiramer acetate SC 20 mg q.d.	96 weeks
Stepien (2013)	68	RRMS	IFN beta-1a IM 30 mcg q.w. IFN beta-1b SC 250 mcg q.2.d.	3 years
TEMSO	1,088	RMS (i.e., RRMS, SPMS, or PRMS) (91% RRMS)	Teriflunomide PO 7 mg q.d. Teriflunomide PO 14 mg q.d. Placebo	108 weeks
TENERE	324	RMS (i.e., RRMS, SPMS, or PRMS) (99% RRMS)	Teriflunomide PO 7 mg q.d. Teriflunomide PO 14 mg q.d. IFN beta-1a SC 44 mcg t.i.w.	48 weeks
TOWER	1,169	RMS (i.e., RRMS, SPMS, or PRMS) (97% RRMS)	Teriflunomide PO 7 mg q.d. Teriflunomide PO 14 mg q.d. Placebo	48+ weeks
TRANSFORMS	1,292	RRMS	Fingolimod PO 0.5 mg q.d. IFN beta-1a IM 30 mcg q.w.	12 months

b.i.d. = twice a day; IFN = interferon; IM = intramuscular; PO = orally; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; PRMS = progressive-relapsing multiple sclerosis; q.2.d. every 2 days; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.24.w. = every 24 weeks; q.d. = every day; q.w. = every week; RMS = relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; t.i.w. = 3 times a week.

Note: For all trials, patients were randomly assigned to treatment arms and allocation was parallel (with 1 exception: CombiRx had a factorial allocation).

[a] Includes all treatment arms (i.e., may include treatment arms that do not match the eligibility criteria of the present study).

Source: Sponsor-submitted indirect treatment comparison.[66]

Overall, trial design was consistent with some differences in most categories (phase of study, blinding, allocation, specific MS definition, and duration).

Eligibility criteria were broadly similar across RCTs for the following:

- Age
  - 18 to 55 years for 19 of 34 trials
  - 18 to 50 years for 5 of 34 trials
  - Other or not reported for 10 of 34 trials

- MS type
  - RRMS for 26 of 34 trials
  - RMS for 8 of 34 trials
- Baseline EDSS score
  - 0.0 to 5.5 for 18 of 34 trials
  - 0.0 to 5.0 for 9 of 34 trials
  - Other for 7 of 34 trials
- Relapse history
  - At least 1 relapse in 1 year prior and/or at least 2 relapses in 2 years prior for 20 of 34 trials
  - Other or not reported for 14 of 34 trials
- Recent relapses
  - No relapses within 28 to 30 days (4 weeks or 1 month) prior for 19 of 34 trials
  - No relapses within 50 to 60 days (2 months) prior for 6 of 34 trials
  - Not reported for 9 of 34 trials

Some differences were noted in patient eligibility criteria for the required disease duration and previous DMT experience.

Heterogeneity in several baseline characteristics was observed across the included RCTs, such as time since first symptoms, number of gadolinium-positive lesions on the MRI, volume of T2 lesions, and proportion of patients with previous DMT experience.

Across the 34 trials, the outcome ARR was more commonly reported than time to 3mCDP and time to 6mCDP.

Placebo response (i.e., baseline risk) was compared across placebo-controlled trials (to assess as a proxy for overall heterogeneity). Of the 34 RCTs included in the analysis, 17 had a placebo arm. For ARR and the proportion of patients with 3mCDP and 6mCDP, placebo-arm outcomes were generally consistent across trials of similar duration. Numerically, placebo-arm ARRs were relatively higher in older (1987 to 2003) trials.

As mentioned in the study selection methods section (Table 24, Table 25, and Table 26), the outcome definition varied across trials, but the authors of the ITC considered that they were sufficiently similar for comparison. For the outcome of time to CDP, some between-trial differences were noted for the magnitude of increase in EDSS score required to qualify as progression. Apart from ocrelizumab (OPERA I and II trials), definitions for the pivotal ofatumumab trials (ASCLEPIOS I and II) were in alignment with those used for pivotal trials of the other monoclonal antibody therapies — alemtuzumab (CAMMS223, CARE-MS I, and CARE-MS II) and natalizumab (AFFIRM).

Some trials were excluded for the base-case NMA but were included in sensitivity analyses. These were the ADVANCE trial (pegylated IFN beta-1a), as done by a recent NICE assessment that disregarded the comparison with pegylated IFN as it appeared to be more effective than other beta interferons as well as high-efficacy treatments (i.e., monoclonal antibodies), which was contrary to clinical experience. The ASSESS trial was excluded as the data were from a poster. The INCOMIN trial was excluded because its result was

considered to be an outlier not reflective of clinical practice. The Boiko (2018) trial was excluded as it was a noninferiority trial comparing different formulations of the same drug.

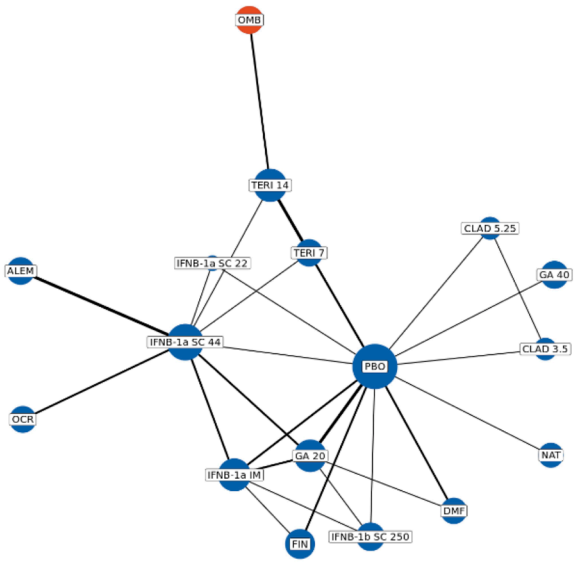
Based on the principles recommended in the CRD guidance, the risk of bias of individual studies presented across the 34 trials included in the NMAs for efficacy outcomes was generally low. There was some risk of bias related to the adequate concealment of treatment allocation and the blinding of care providers, participants, and outcome assessors. Otherwise, the risk of bias was low in terms of randomization, prognostic factors, withdrawals and discontinuations, outcomes measured, and an appropriate intention-to-treat analysis.

Results

Results of the NMA are presented based for 3 outcomes: ARR, time to 3mCDP, and time to 6mCDP. These last 2 outcomes are presented using both the predefined and aligned criteria.

For the outcome of ARR, 17 treatments, including placebo, were available and conformed with the network, with 30 trials in total. The ResDev indicated a reasonable fit for the model. Based on the ARR results of the NMA, ofatumumab was statistically superior to dimethyl fumarate, fingolimod, glatiramer acetate 20 mg, glatiramer acetate 40 mg, IFN beta-1a intramuscular, IFN beta-1a subcutaneous 22 mcg, IFN beta-1a subcutaneous 44 mcg, IFN beta-1b subcutaneous 250 mcg, placebo, teriflunomide 7 mg, and teriflunomide 14 mg. Ofatumumab was numerically but not statistically superior to cladribine 3.5 mg/kg, cladribine 5.25 mg/kg, natalizumab, and ocrelizumab. Finally, ofatumumab was numerically inferior to alemtuzumab, but this result was not statistically significant. Overall, the NMA results demonstrated that ofatumumab was similar in efficacy to the other highly efficacious monoclonal antibody DMTs (i.e., alemtuzumab, natalizumab, and ocrelizumab) and ranked among the most efficacious therapies in terms of ARR. The network diagram, the league table, and forest plot of effect estimates of ofatumumab against other DMTs are presented in Figure 4, Figure 5, and Figure 6, respectively.

Figure 4: Network of Included Comparisons and Interventions in the Indirect Treatment Comparison for Annualized Relapse Rate



Abbreviation	Name
ALEM	Alemtuzumab IV 12 mg
CLAD 3.5	Cladribine PO 3.5 mg/kg
CLAD 5.25	Cladribine PO 5.25 mg/kg
DMF	Dimethyl fumarate PO 240 mg BID
FIN	Fingolimod PO 0.5 mg
GA 20	Glatiramer acetate SC 20 mg
GA 40	Glatiramer acetate SC 40 mg
IFNB-1a IM 30	Interferon beta-1a IM 30 µg
IFNB-1a SC 22	Interferon beta-1a SC 22 µg
IFNB-1a SC 44	Interferon beta-1a SC 44 µg
IFNB-1b SC 250	Interferon beta-1b SC 250 µg
NAT	Natalizumab IV 300 mg
OCR	Ocrelizumab IV 600 mg
OMB	Ofatumumab SC 20 mg
PBO	Placebo
TERI 7	Teriflunomide PO 7 mg
TERI 14	Teriflunomide PO 14 mg

Note: The network includes 17 interventions and 30 trials.

Source: Sponsor-submitted indirect treatment comparison.[66]

Figure 5: League Table of Included Comparisons and Interventions in the Indirect Treatment Comparison for Annualized Relapse Rate

ALEM																
0.93 (0.6 to 1.32)	OMB															
0.87 (0.57 to 1.25)	0.94 (0.62 to 1.44)	NAT														
0.82 (0.59 to 1.11)	0.89 (0.61 to 1.37)	0.95 (0.64 to 1.45)	OCR													
0.65 (0.41 to 0.96)	0.7 (0.45 to 1.09)	0.74 (0.48 to 1.15)	0.79 (0.5 to 1.19)	CLAD 3.5												
0.61 (0.38 to 0.91)	0.66 (0.42 to 1.03)	0.7 (0.45 to 1.08)	0.74 (0.46 to 1.12)	0.94 (0.66 to 1.33)	CLAD 5.25											
0.6 (0.42 to 0.81)	0.65 (0.46 to 0.94)	0.69 (0.49 to 0.98)	0.73 (0.51 to 1.01)	0.92 (0.63 to 1.36)	0.99 (0.68 to 1.46)	FIN										
0.55 (0.38 to 0.74)	0.59 (0.41 to 0.86)	0.63 (0.44 to 0.91)	0.66 (0.46 to 0.94)	0.84 (0.57 to 1.25)	0.9 (0.61 to 1.33)	0.91 (0.68 to 1.22)	DMF									
0.44 (0.33 to 0.57)	0.48 (0.35 to 0.68)	0.51 (0.37 to 0.71)	0.53 (0.4 to 0.72)	0.68 (0.48 to 0.99)	0.72 (0.52 to 1.06)	0.73 (0.59 to 0.94)	0.81 (0.64 to 1.04)	GA 20								
0.44 (0.35 to 0.53)	0.48 (0.35 to 0.68)	0.5 (0.37 to 0.72)	0.53 (0.42 to 0.68)	0.68 (0.48 to 0.99)	0.72 (0.51 to 1.07)	0.73 (0.58 to 0.95)	0.81 (0.62 to 1.07)	1 (0.84 to 1.2)	IFNB-1a SC 44							
0.42 (0.27 to 0.61)	0.45 (0.3 to 0.7)	0.48 (0.32 to 0.73)	0.51 (0.33 to 0.76)	0.65 (0.41 to 1)	0.69 (0.44 to 1.08)	0.7 (0.48 to 1)	0.77 (0.53 to 1.1)	0.95 (0.66 to 1.31)	0.95 (0.66 to 1.32)	GA 40						
0.41 (0.29 to 0.54)	0.45 (0.35 to 0.56)	0.47 (0.33 to 0.67)	0.5 (0.35 to 0.68)	0.64 (0.44 to 0.92)	0.68 (0.47 to 0.98)	0.69 (0.52 to 0.88)	0.76 (0.56 to 1)	0.94 (0.72 to 1.15)	0.94 (0.73 to 1.15)	0.99 (0.68 to 1.39)	TERI 14					
0.41 (0.28 to 0.54)	0.44 (0.31 to 0.63)	0.47 (0.32 to 0.66)	0.49 (0.34 to 0.68)	0.62 (0.42 to 0.92)	0.66 (0.45 to 0.98)	0.68 (0.5 to 0.88)	0.74 (0.55 to 0.98)	0.92 (0.73 to 1.1)	0.92 (0.7 to 1.16)	0.97 (0.67 to 1.39)	0.98 (0.75 to 1.3)	IFNB-1b SC 250				
0.4 (0.28 to 0.55)	0.43 (0.3 to 0.66)	0.46 (0.31 to 0.69)	0.49 (0.34 to 0.69)	0.62 (0.41 to 0.95)	0.66 (0.44 to 1.01)	0.67 (0.48 to 0.93)	0.73 (0.52 to 1.03)	0.91 (0.68 to 1.2)	0.91 (0.69 to 1.18)	0.95 (0.65 to 1.45)	0.97 (0.72 to 1.36)	0.99 (0.73 to 1.4)	IFNB-1a SC 22			
0.35 (0.26 to 0.45)	0.38 (0.27 to 0.53)	0.4 (0.29 to 0.56)	0.42 (0.31 to 0.56)	0.54 (0.38 to 0.77)	0.57 (0.4 to 0.83)	0.58 (0.46 to 0.72)	0.64 (0.49 to 0.83)	0.79 (0.66 to 0.93)	0.79 (0.65 to 0.94)	0.83 (0.6 to 1.17)	0.84 (0.68 to 1.09)	0.86 (0.69 to 1.1)	0.87 (0.65 to 1.16)	IFNB-1a IM		
0.35 (0.24 to 0.45)	0.37 (0.28 to 0.5)	0.4 (0.28 to 0.55)	0.42 (0.29 to 0.57)	0.53 (0.36 to 0.76)	0.57 (0.39 to 0.82)	0.58 (0.43 to 0.74)	0.63 (0.47 to 0.83)	0.79 (0.6 to 0.96)	0.79 (0.6 to 0.96)	0.83 (0.57 to 1.15)	0.84 (0.69 to 1)	0.86 (0.64 to 1.11)	0.87 (0.61 to 1.15)	1 (0.77 to 1.23)	TERI 7	
0.27 (0.2 to 0.35)	0.3 (0.22 to 0.4)	0.31 (0.24 to 0.42)	0.33 (0.25 to 0.44)	0.42 (0.31 to 0.58)	0.45 (0.33 to 0.63)	0.46 (0.37 to 0.55)	0.5 (0.4 to 0.62)	0.62 (0.52 to 0.71)	0.62 (0.52 to 0.72)	0.65 (0.48 to 0.88)	0.66 (0.56 to 0.81)	0.68 (0.55 to 0.83)	0.69 (0.52 to 0.88)	0.79 (0.67 to 0.91)	0.79 (0.67 to 0.97)	PBO

Abbreviation	Name
ALEM	Alemtuzumab IV 12 mg
CLAD 3.5	Cladribine PO 3.5 mg/kg
CLAD 5.25	Cladribine PO 5.25 mg/kg
DMF	Dimethyl fumarate PO 240 mg BID
FIN	Fingolimod PO 0.5 mg
GA 20	Glatiramer acetate SC 20 mg
GA 40	Glatiramer acetate SC 40 mg
IFNB-1a IM 30	Interferon beta-1a IM 30 µg
IFNB-1a SC 22	Interferon beta-1a SC 22 µg
IFNB-1a SC 44	Interferon beta-1a SC 44 µg
IFNB-1b SC 250	Interferon beta-1b SC 250 µg
NAT	Natalizumab IV 300 mg
OCR	Ocrelizumab IV 600 mg
OMB	Ofatumumab SC 20 mg
PBO	Placebo
TERI 7	Teriflunomide PO 7 mg
TERI 14	Teriflunomide PO 14 mg

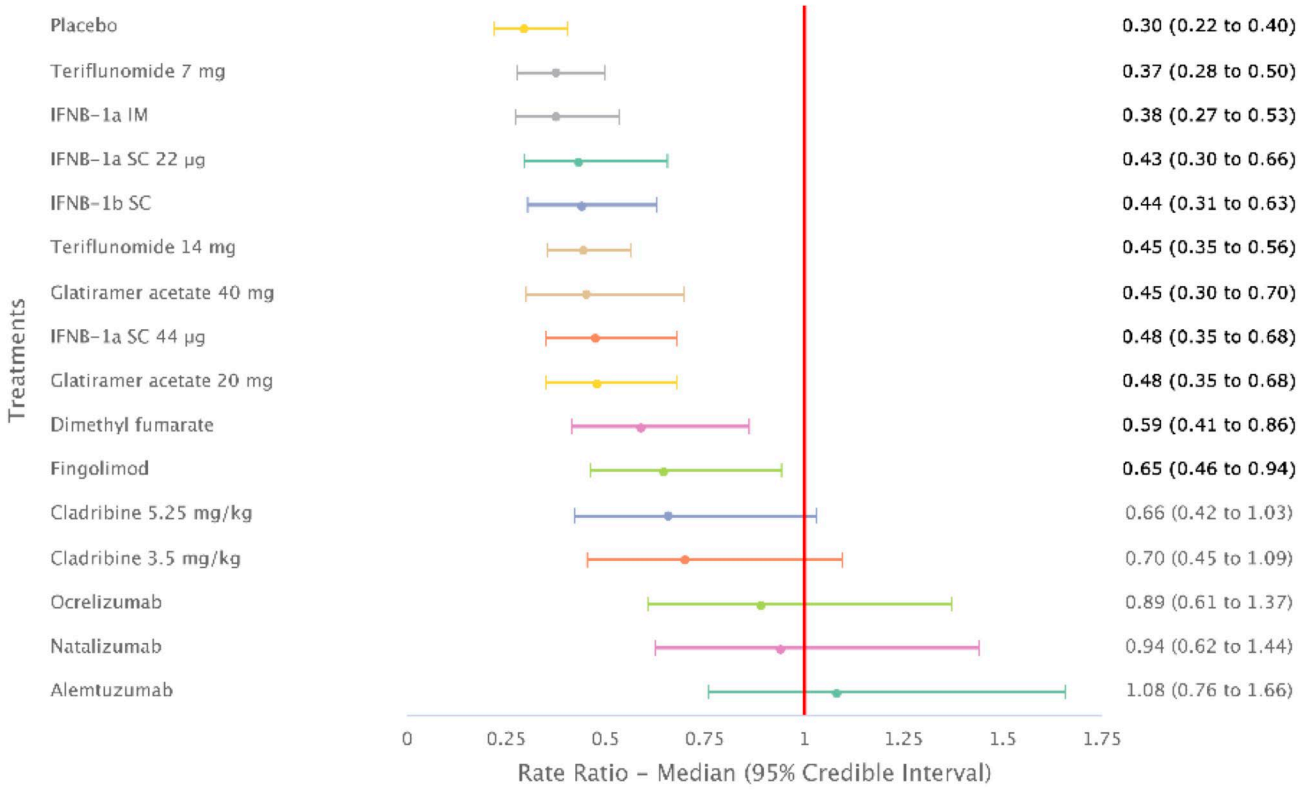
Random Effects Model
DIC: 545.03
ResDev: 78.72 (vs. 67)

Comparisons exclude unity

Note: Values are rate ratios and in parentheses the 95% credible intervals.

Source: Sponsor-submitted indirect treatment comparison.[66]

Figure 6: Forest Plot of the Indirect Treatment Comparison for Annualized Relapse Rate



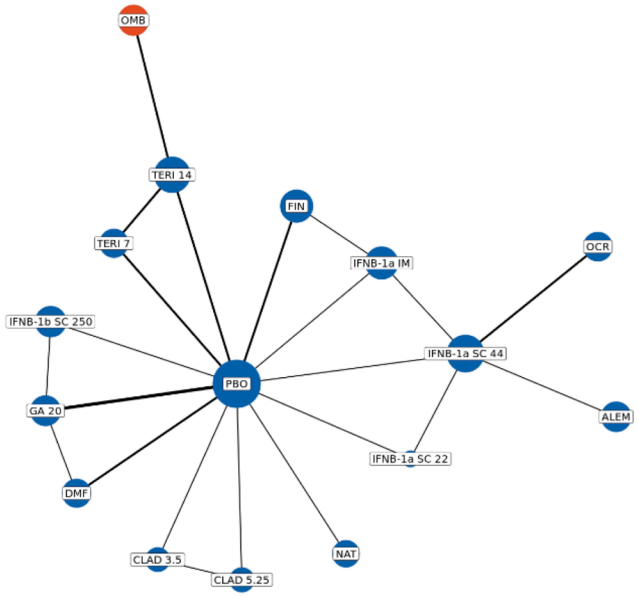
ARR = annualized relapse rate; IFNB = interferon beta; IM = intramuscular; OMB = ofatumumab; SC = subcutaneous.

Source: Sponsor-submitted indirect treatment comparison.[66]

Overall, the NMA results demonstrated that ofatumumab was similar in efficacy to the other highly efficacious monoclonal antibody DMTs (i.e., alemtuzumab, natalizumab, and ocrelizumab) for CDP outcomes. The results were similar whether the data from ASCLEPIOS used the predefined or OPERA-aligned criteria for CDP. For the outcome of time to 3mCDP, ofatumumab was statistically superior to fingolimod, glatiramer acetate 20 mg, IFN beta-1a IM, IFN beta-1b subcutaneous 250 mg, placebo, teriflunomide 7 mg, and teriflunomide 14 mg. Ofatumumab was numerically but not statistically superior to cladribine 3.5 mg/kg, cladribine 5.25 mg/kg, dimethyl fumarate, IFN beta-1a subcutaneous 22 mcg, IFN beta-1a subcutaneous 44 mcg, and natalizumab. Finally, ofatumumab was numerically inferior to alemtuzumab and ocrelizumab, but the results were not statistically significant. Residual deviance values indicated a reasonable model fit for the NMA.

The network, league table, and forest plot for time to 3mCDP are presented in Figure 7, Figure 8, and Figure 9, respectively. For this outcome, only the predesigned criteria set is presented. However, the results by using the aligned criteria were similar.

Figure 7: Network of Included Comparisons and Interventions in the Indirect Treatment Comparison for Time to 3mCDP

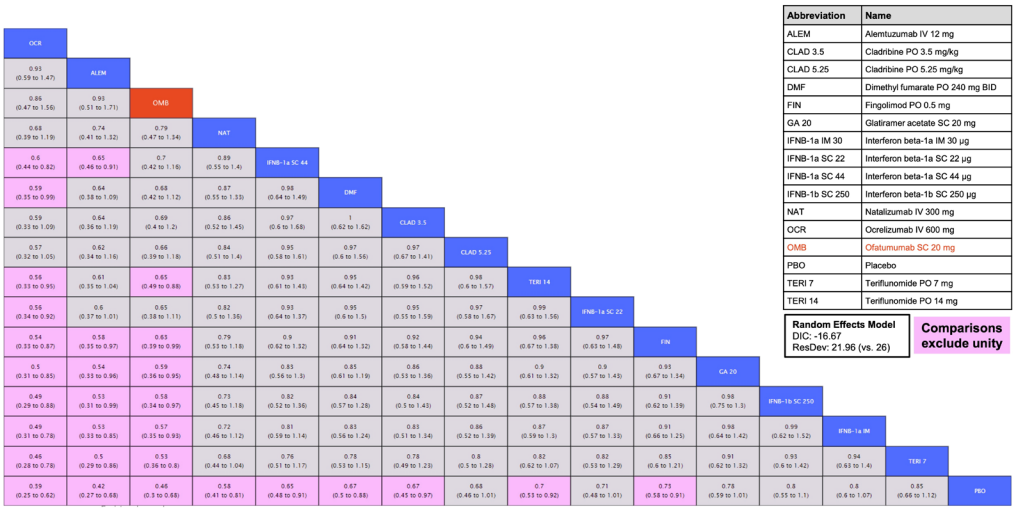


Abbreviation	Name
ALEM	Alemtuzumab IV 12 mg
CLAD 3.5	Cladribine PO 3.5 mg/kg
CLAD 5.25	Cladribine PO 5.25 mg/kg
DMF	Dimethyl fumarate PO 240 mg BID
FIN	Fingolimod PO 0.5 mg
GA 20	Glatiramer acetate SC 20 mg
IFNB-1a IM 30	Interferon beta-1a IM 30 µg
IFNB-1a SC 22	Interferon beta-1a SC 22 µg
IFNB-1a SC 44	Interferon beta-1a SC 44 µg
IFNB-1b SC 250	Interferon beta-1b SC 250 µg
NAT	Natalizumab IV 300 mg
OCR	Ocrelizumab IV 600 mg
OMB	Ofatumumab SC 20 mg
PBO	Placebo
TERI 7	Teriflunomide PO 7 mg
TERI 14	Teriflunomide PO 14 mg

The network includes 16 interventions and 21 trials.

Source: Sponsor-submitted indirect treatment comparison.[66]

Figure 8: League Table of Included Comparisons and Interventions in the Indirect Treatment Comparison for Time to 3mCDP



Abbreviation	Name
ALEM	Alemtuzumab IV 12 mg
CLAD 3.5	Cladribine PO 3.5 mg/kg
CLAD 5.25	Cladribine PO 5.25 mg/kg
DMF	Dimethyl fumarate PO 240 mg BID
FIN	Fingolimod PO 0.5 mg
GA 20	Glatiramer acetate SC 20 mg
IFNB-1a IM 30	Interferon beta-1a IM 30 µg
IFNB-1a SC 22	Interferon beta-1a SC 22 µg
IFNB-1a SC 44	Interferon beta-1a SC 44 µg
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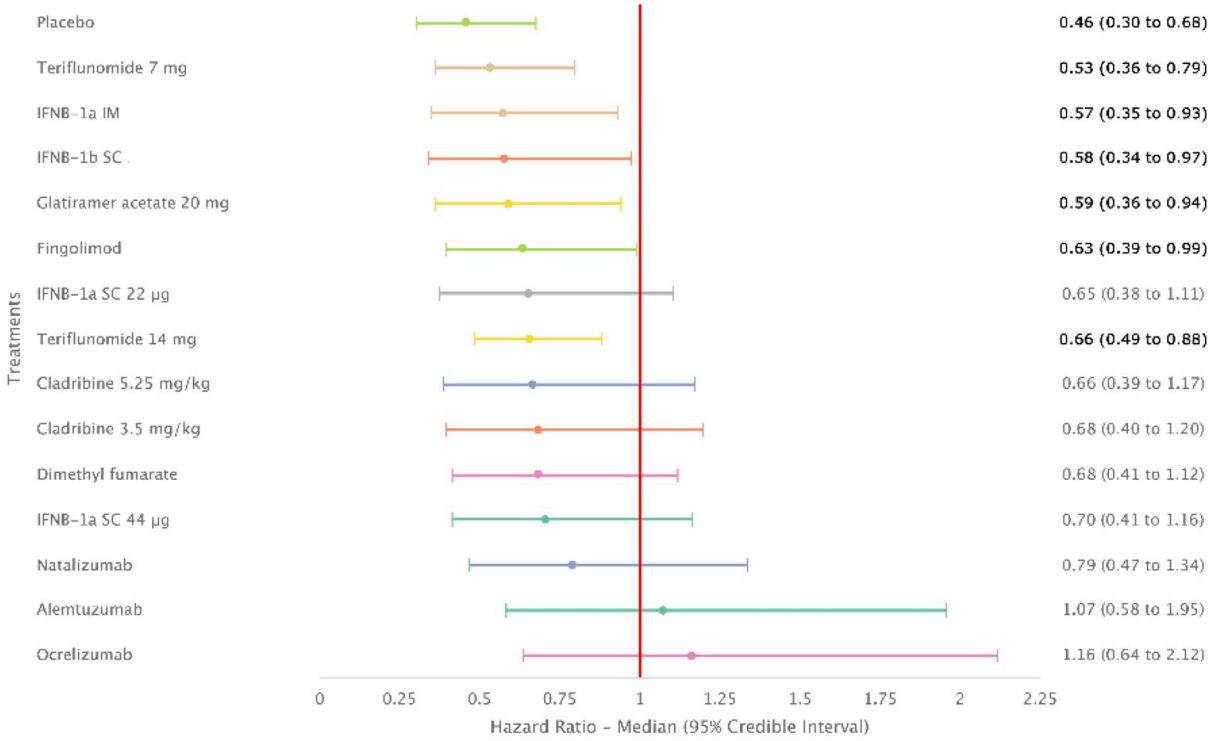
NAT	Natalizumab IV 300 mg
OCR	Ocrelizumab IV 600 mg
OMB	Ofatumumab SC 20 mg
PBO	Placebo
TERI 7	Teriflunomide PO 7 mg
TERI 14	Teriflunomide PO 14 mg

Note: Values are rate ratios and in parentheses the 95% credible intervals.

Source: Sponsor-submitted indirect treatment comparison.[66]

Figure 9: Forest Plot of the Indirect Treatment Comparison for the Outcome Time to 3mCDP

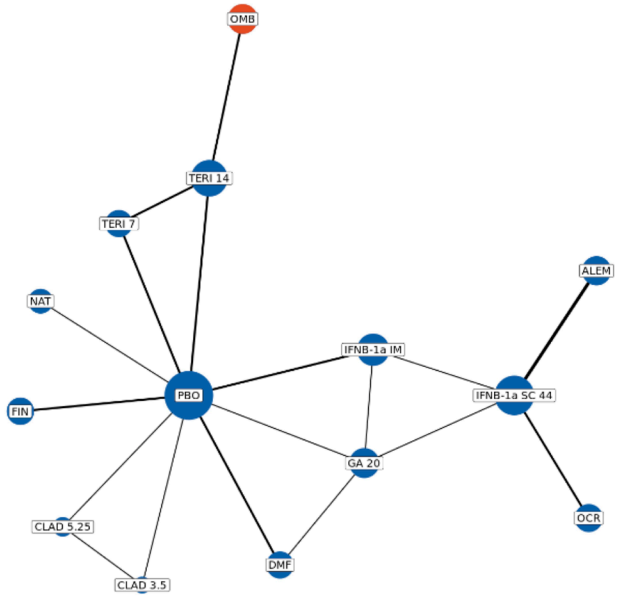


ARR = annualized relapse rate; IFNB = interferon beta; IM = intramuscular; OMB = ofatumumab; SC = subcutaneous.

Source: Sponsor-submitted indirect treatment comparison.[66]

For the outcome of time to 6mCDP, the network consisted of 14 treatments (including placebo) informed by 20 trials. Overall, ofatumumab was statistically superior to placebo, teriflunomide 7 mg, and teriflunomide 14 mg, and it was not statistically superior to cladribine 3.5 mg/kg, cladribine 5.25 mg/kg, dimethyl fumarate, fingolimod, glatiramer acetate 20 mg, IFN beta-1a intramuscular, and IFN beta-1a subcutaneous 44 mcg. Finally, ofatumumab was inferior to alemtuzumab, natalizumab, and ocrelizumab, but the results were not statistically significant. The network, league table, and forest plot are presented in Figure 10, Figure 11, and Figure 12, respectively. For this outcome, the predesigned criteria set is presented. The residual deviance values suggest a good fit for the model used.

Figure 10: Network of Included Comparisons and Interventions in the Indirect Treatment Comparison for Time to 6mCDP

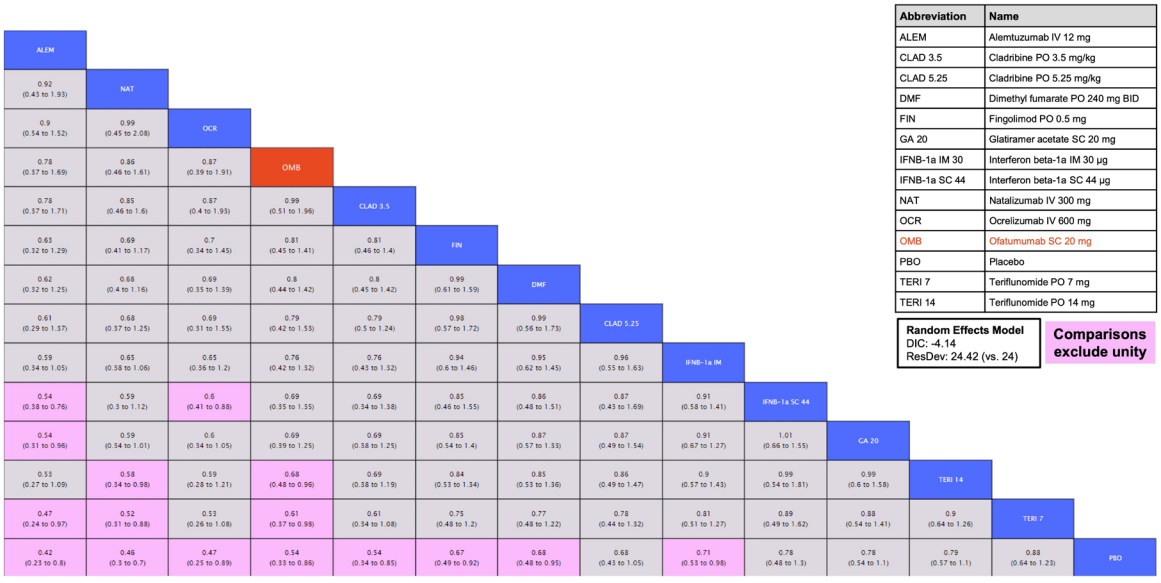


Abbreviation	Name
ALEM	Alemtuzumab IV 12 mg
CLAD 3.5	Cladribine PO 3.5 mg/kg
CLAD 5.25	Cladribine PO 5.25 mg/kg
DMF	Dimethyl fumarate PO 240 mg BID
FIN	Fingolimod PO 0.5 mg
GA 20	Glatiramer acetate SC 20 mg
IFNB-1a IM 30	Interferon beta-1a IM 30 µg
IFNB-1a SC 44	Interferon beta-1a SC 44 µg
NAT	Natalizumab IV 300 mg
OCR	Ocrelizumab IV 600 mg
OMB	Ofatumumab SC 20 mg
PBO	Placebo
TERI 7	Teriflunomide PO 7 mg
TERI 14	Teriflunomide PO 14 mg

Note: The network includes 14 interventions and 20 trials.

Source: Sponsor-submitted indirect treatment comparison.[66]

Figure 11: League Table of Included Comparisons and Interventions in the Indirect Treatment Comparison for Time to 6mCDP

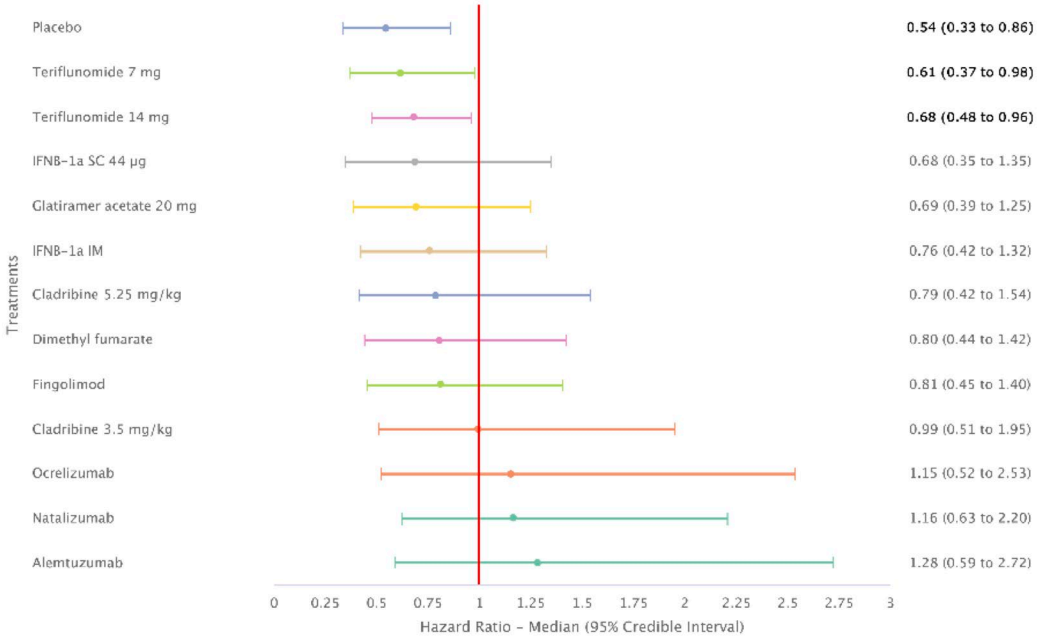


Abbreviation	Name
ALEM	Alemtuzumab IV 12 mg
CLAD 3.5	Cladribine PO 3.5 mg/kg
CLAD 5.25	Cladribine PO 5.25 mg/kg
DMF	Dimethyl fumarate PO 240 mg BID
FIN	Fingolimod PO 0.5 mg
GA 20	Glatiramer acetate SC 20 mg
IFNB-1a IM 30	Interferon beta-1a IM 30 µg
IFNB-1a SC 44	Interferon beta-1a SC 44 µg
NAT	Natalizumab IV 300 mg
OCR	Ocrelizumab IV 600 mg
OMB	Ofatumumab SC 20 mg
PBO	Placebo
TERI 7	Teriflunomide PO 7 mg
TERI 14	Teriflunomide PO 14 mg

Note: Values are rate ratios and in parentheses the 95% credible intervals.

Source: Sponsor-submitted indirect treatment comparison.[66]

Figure 12: Forest Plot of the ITC for the Outcome Time to 6mCDP



ARR = annualized relapse rate; IFNB = interferon beta; IM = intramuscular; OMB = ofatumumab; SC = subcutaneous.

Source: Sponsor-submitted indirect treatment comparison.[66]

The main sensitivity analyses were based on the definition of 3mCDP and 6mCDP as aligned versus predefined criteria and did not show significant differences in the effect estimates. The rest of the sensitivity analyses were based on the inclusion of pegylated IFN (ADVANCE trial), inclusion of the INCOMIN trial, inclusion of abstracts/posters, other formulations, and by the model utilized (fixed versus random). None of these scenarios showed important differences in the effect estimates when compared to the base-case analysis. The deviance information criterion and analysis of ResDev indicate that the random-effects model was appropriate to use.

Critical Appraisal of the Indirect Treatment Comparison

The sponsor-submitted ITC and NMA were conducted based on the NICE Decision Support Unit Technical Support Document 2 guidance. Overall, the systematic review of the literature is robust and based on a comprehensive search strategy and inclusion of an appropriate number of interventions likely to be used in clinical practice in Canada and other countries. The review provides a proper rationale of the methodology, eligibility criteria, study selection, data collection, and assessment of risk of bias of the individual studies. The use of different scenarios (sensitivity analyses) is appropriate for the sparsity of the network and the plausible heterogeneity and effect modifiers to be found among patients. The authors conducted an appropriate model-fit assessment.

Limitations of the NMA would have primarily stemmed from the heterogeneity in trial designs, including, as mentioned, the varying definitions of relapse and time to 3mCDP or 6mCDP, varying study durations, and the relatively sparse network compared to the total

number of included treatments. However, as the differences between different definitions of outcomes, for example, were likely small, the types and amount of heterogeneity may not have had a significant impact on the validity of NMA results. This was in alignment with other published NMAs.[68] As with any Bayesian NMA using non-informative priors, the effect estimates may be less precise, particularly with between-study heterogeneity in a sparse network for each of the 3 study outcomes, and when considering the node for ofatumumab, which was only compared against teriflunomide in the ASCLEPIOS trials. Nonetheless, the authors adequately present a sensitivity analysis in which no important differences were observed between random- and fixed-effects models. There is an inconsistency assessment throughout the report based on the comparison of the posterior mean deviances of the consistency and consistency models in which the posterior mean deviance contributions were similar for most studies and for both models, suggesting coherence between direct and indirect estimates.

Another limitation is the possibility of an inadequate external validity (applicability) of the effect estimates in Canadian clinical practice. Some older trials were included and they may have elevated placebo-arm relapse rates (i.e., elevated baseline risk) which also creates issues in the heterogeneity and applicability of the results. However, this concern is lessened by the sensitivity analyses based on addressing the effect of older studies.

The safety of the different interventions was assessed narratively and the rationale for this seems appropriate, although the authors present numerical data in the appendices.

Summary

The results from the indirect comparisons showed that ofatumumab was likely as effective as other monoclonal antibody DMTs (i.e., alemtuzumab, natalizumab, cladribine, and ocrelizumab) based on the assessment of ARR. For this same outcome, when compared to all conventional DMTs (IFN beta, teriflunomide, glatiramer, dimethyl fumarate, fingolimod) and placebo, ofatumumab likely showed a better improvement.

For the time to clinical disability progression as assessed by 3mCDP, ofatumumab was likely as effective as ocrelizumab, alemtuzumab, natalizumab, IFN beta, dimethyl fumarate, and cladribine, and it was also likely more effective than teriflunomide, IFN beta, glatiramer acetate, fingolimod, and placebo. Similarly, when assessed by 6mCDP, ofatumumab was likely as effective as ocrelizumab, alemtuzumab, natalizumab, IFN beta, dimethyl fumarate, cladribine, and fingolimod, and was likely more effective than teriflunomide and placebo.

However, these conclusions may suffer from a sparse network, which resulted in a wide 95% credible interval and a lack of precision in the effect estimates on ARR and CDP relative to other monoclonal antibodies (alemtuzumab, natalizumab, cladribine, and ocrelizumab).

Other Relevant Evidence

There is currently 1 ongoing single-arm, open-label, long-term safety extension study that included patients from the ASCLEPIOS trials; however, results were not available at the time of this review as the expected end date is January 2025.

Discussion

Summary of Available Evidence

Two pivotal trials for ofatumumab, ASCLEPIOS I and II, met the criteria for the CADTH systematic review. The ASCLEPIOS studies followed a randomized, double-blind, double-dummy, active comparator-controlled, parallel-group, multi-centre design, with adaptive design features (flexible duration). Patients included in the 2 studies had a diagnosis of RMS (RRMS or SPMS with disease activity as defined by Lublin et al.[6]), an EDSS score of between 0 and 5.5 (inclusive), were neurologically stable within 1 month prior to randomization, and had recent (1 to 2 years) documentation of disease activity based on relapses and/or imaging features. ASCLEPIOS I and II randomized 927 and 955 patients with RMS, respectively, at a 1:1 ratio to either of 2 treatment groups. The ofatumumab group received subcutaneous injections of ofatumumab (20 mg) administered on study days 1, 7, and 14, and month 1, then every 4 weeks until the end of study. Patients in the teriflunomide group were treated with oral teriflunomide (14 mg) once daily. The studies were designed to demonstrate superiority of ofatumumab 20 mg to teriflunomide 14 mg in terms of reducing the frequency of confirmed relapses (ARR) in patients with RMS. Key secondary objectives were to demonstrate the superiority of ofatumumab to teriflunomide in terms of disability outcomes based on the EDSS and MRI outcomes. In addition, HRQoL (MSIS-29, EQ-5D), mobility (T25FW, 9-HPT), cognitive function (SDMT), and the ability to work (WPAI:MS), as well as a composite outcome for disease activity (NEDA-4) were evaluated in the 2 trials.

Overall, the ASCLEPIOS trials were well conducted and consistent with EMA guidance on clinical trials of treatments for MS, although they were subject to certain limitations. Key limitations to the internal validity of the 2 studies include differential frequencies of adverse events and discontinuation rates, missing data for HRQoL outcomes and the WPAI:MS, and high concomitant use of systemic steroids, which may have contributed to the uncertainty and inconsistency of findings between the 2 trials. Key limitations to the generalizability include the exclusion of subsets of patients who would be suitable for treatment with ofatumumab based on expert input, and the duration of the trials, which may have been too short to obtain meaningful results in changes in mobility, cognitive function, and even disability, as well as in long-term safety as the treatment of MS is life-long.

In addition to the studies included in the systematic review, 1 sponsor-submitted ITC was 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.[8] The primary end point in the 2 pivotal trials was ARR. Treatment with ofatumumab demonstrated superiority over teriflunomide in terms of reducing the frequency of confirmed relapses based on the ARR in patients with RMS in ASCLEPIOS I and II. The use of ARR as the primary end point is aligned with guidance from the EMA,[64] and ARR is a clinically relevant outcome to clinicians, as indicated by the clinical expert consulted for this review.

Teriflunomide is a commonly used oral DMT for the treatment of RMS in Canada. Based on input from the clinical expert consulted by CADTH, it is an appropriate comparator for a treatment such as ofatumumab. However, comparative evidence of ofatumumab versus other DMTs available in Canada is lacking. The results of the ITC included in this review demonstrated that ofatumumab is likely as effective as other monoclonal antibody DMTs (i.e., alemtuzumab, natalizumab, cladribine, and ocrelizumab) for the outcome of ARR based on all relapses. Additionally, ofatumumab is likely more effective in terms of ARR when compared to all other DMTs (IFN beta, teriflunomide, glatiramer, dimethyl fumarate, fingolimod) and placebo based on the results of the sponsor-submitted ITC. It is important to note that the ITC is limited by heterogeneity in trial designs and a sparse network.

In addition to the ARR, both trials reported data about the characteristics of the MS relapses (both for confirmed only and for all relapses) experienced in the studies, such as relapses that required hospitalization and relapses that required steroid treatment. Hospitalization due to MS relapse was an outcome of importance for patients, and the use of rescue medication — or relapses that required steroid treatment — were included in the CADTH systematic review protocol and of interest to clinicians as per feedback from the clinical expert on this review. Because only descriptive results about the proportion of relapses that featured the 2 characteristics were reported and subgroup analyses by either characteristic were not available, how ofatumumab effects these outcomes compared to teriflunomide remains unknown.

Disability as confirmed disability worsening or improvement as measured by the EDSS was evaluated in ASCLEPIOS I and II as key secondary outcomes (as per the pre-specified pooled analysis). The between-treatment comparison for time to 3mCDW demonstrated the superiority of ofatumumab to teriflunomide in the pooled analysis, i.e., a reduction in the risk of time to 3mCDW for the ofatumumab group compared to the teriflunomide group. This was consistent with the results reported for the 2 trials independently. The clinical expert consulted for this review considered the between-treatment comparison for time to 6mCDW a more clinically relevant outcome than 3mCDW because a 3-month assessment window is typically not feasible in clinical practice. A 6-month assessment period would be ideal but patients in Canada are more realistically seen annually due to clinician availability. A greater risk reduction for time to 6mCDW was also demonstrated in the ofatumumab treatment group compared to the teriflunomide treatment group in the pooled analysis; however, the difference in the between-groups comparison observed in ASCLEPIOS II was not statistically significant. The clinical expert on this review did note that the 1- to 2-year duration of the ASCLEPIOS trials may not be long enough to observe an accumulation of disability in patients with RMS, and the proportion of patients with 3mCDW and 6mCDW was low in both treatment groups (between 9% to 10% and 7.5%, respectively, for ofatumumab and between 13% to 14% and 10% to 12%, respectively, for teriflunomide). Time to 6mCDI was also reported, but this outcome was not considered particularly relevant by the clinical expert, it was not included in the recommendations by the EMA, and a treatment-group difference was not observed for this outcome. A clinically meaningful change of at least 1.0 in disability progression for patients with MS has been proposed if the EDSS score at baseline was 0 to 5.5, and at least 0.5 for higher baseline EDSS scores, which is supported by the EMA.[47,64] This definition of a clinically meaningful change was used to define confirmed disability worsening in the 2 trials; the only difference was for a baseline EDSS score of 0 that only required an increase of 0.5 points for confirmed disability in the trials. Time to 3mCDP and 6mCDP were outcomes included in the sponsor-submitted ITC as well. The ITC demonstrated that ofatumumab is likely as effective as ocrelizumab, alemtuzumab, natalizumab, IFN beta (250 mcg), dimethyl fumarate, and

cladribine for 3mCDP, and superior to teriflunomide, IFN beta (22 or 44 mcg), glatiramer acetate, fingolimod, and placebo. For 6mCDP, ofatumumab is likely as effective as ocrelizumab, alemtuzumab, natalizumab, IFN beta, dimethyl fumarate, cladribine, and fingolimod, and superior only to teriflunomide and placebo.

Imaging or MRI outcomes were considered important to clinicians. The number of gadolinium-enhanced T1 lesions per scan, number of new or enlarging T2 lesions per year relative to baseline, and percent brain volume loss (as an annual rate of change from baseline) were included in the pivotal trials as key secondary outcomes, which were also included in the statistical testing hierarchy. Ofatumumab demonstrated superiority to teriflunomide in terms of reducing the number of gadolinium-enhanced T1 lesions per scan. Similarly, ofatumumab was superior to teriflunomide in terms of reducing the number of new or enlarging T2 lesions per year in ASCLEPIOS I and II. Brain volume loss did not indicate a between-treatment comparison difference in either study, but based on input from the clinical expert consulted for this review, changes in brain volume are a long-term outcome and 1 to 2 years of patient participation was not long enough to reliably assess this outcome. Gadolinium-enhanced lesions are useful for identifying active inflammation, whereas the occurrence of T2 lesions requires interpretation based on a comparison with the number of T2 lesions observed in previous scans.[41] According to the 2020 treatment optimization recommendations,[8] 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, where imaging that uses gadolinium is being used less frequently due to evidence of gadolinium accumulation in the brain with frequent use.[8]

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 ofatumumab trials, HRQoL was evaluated using the MSIS-29 as a secondary outcome not included in the statistical testing hierarchy, and EQ-5D as an exploratory outcome. The results of the MSIS-29 physical impact score [redacted] however, these data were also subject to limitations due to [redacted]

In ASCLEPIOS I and II, the results of the between-treatment comparisons for the psychological impact factor [redacted] and the statistical testing that was reported is [redacted]. Further, [redacted] and missing data were not imputed. The MSIS-29 is a well-validated HRQoL outcome for patients with MS, with an MID of 7 points when the EDSS score is between 0 and 5.0.[13] The psychological impact scale of the MSIS-29 is more relevant to the information patients are seeking (as noted in the patient input), as it addresses items such as whether patients have been bothered by limitations in their social and leisure activities at home, remaining at home more than they would like to, or difficulty doing things spontaneously (e.g., going out on the spur of the moment); however, the described limitations lead [redacted] The EQ-5D utility score and VAS were also evaluated. The [redacted] of the adjusted mean change in VAS was [redacted] for the ofatumumab treatment groups [redacted] in both trials ([redacted] ASCLEPIOS I), but the EQ-5D was an exploratory outcome limiting conclusions that can be drawn about this outcome. In summary, the limitations associated with the evidence and

[redacted] prevent the ability to conclude whether ofatumumab offers an advantage in terms of HRQoL over teriflunomide.

Decreasing work absenteeism and the ability to work are also outcomes important to patients living with MS. The WPAI:MS is a well-validated measure of work impairment, and outcomes 1 and 2 of the WPAI:MS correspond to percent work time missed due to health and percent overall work impairment due to health, respectively. The WPAI:MS was evaluated in both trials as an exploratory outcome [redacted]. Missing data [redacted] ability of patients to work as measured by the WPAI:MS.

In ASCLEPIOS I and II, mobility was measured using the T25FW and 9-HPT, which are 2 well-validated, widely used outcomes that measure mobility in patients with MS. These outcomes were included as "other secondary" outcomes in the 2 trials and analyzed using the pooled dataset. [redacted] proportion of patients with 6mCDW of at least 20% [redacted] for the T25FW or 9-HPT. Time to 6mCDW of at least 20% is considered a clinically meaningful outcome for both measures of mobility. The result of the pooled analysis was [redacted] The T25FW was assessed every [redacted] and the 9-HPT was assessed every [redacted]. The clinical expert on this review suggested that treatments such as ofatumumab 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, 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.

Subgroup analyses that were available included analyses by age, MS type, baseline EDSS score, number of relapses in the previous 2 years, gadolinium-enhanced T1 lesions at baseline, and prior use of DMTs for MS. Pre-specified subgroup analysis showed a consistent effect on the reduction of ARR by all subgroups. It also revealed that younger patients (≤ 40 years) and patients with no gadolinium-enhanced T1 lesions (0) may have been more likely to benefit from a delayed disability worsening than those patients who were older or with gadolinium-enhanced T1 lesions. However, due to various limitations, this needs to be further explored. No subgroup analysis by disease activity is available on either ARR or confirmed disability worsening, and it is unknown whether the treatment effect would be different by the level of disease activity (highly active versus not). Subgroup analyses by MS type were also limited by the small sample size for patients with SPMS, resulting in a wide CI around the results.

Harms

On average, patients were exposed to the study drug between 541.0 (SD, 181.7) days and 585.9 (SD, 180.0) days or approximately 1.5 years. No deaths were reported during the treatment period in either of the pivotal trials. The majority of patients in each study group in both trials reported at least 1 treatment-emergent adverse event. The most commonly reported adverse events overall were injection-related reactions, nasopharyngitis, headaches, and upper respiratory tract infections. Alopecia and diarrhea, both known adverse events for teriflunomide,[24] were more common in patients in the teriflunomide group compared with the ofatumumab groups. Additionally, injection-related reactions were reported by a greater proportion of patients in the ofatumumab treatment group compared

with the teriflunomide group in ASCLEPIOS II, as well as upper respiratory tract infections in ASCLEPIOS I. Serious adverse events were reported by 7.6% to 10.3% of patients in the treatment groups of both studies, but the frequency of individual serious adverse events was low. The proportion of patients who stopped treatment due to adverse events was also low, ranging from 5.2% and 5.8% of patients across the 2 pivotal trials and similar between treatment groups in each study.

Ofatumumab is a human monoclonal antibody (immunoglobulin G1). Ofatumumab works by reducing the number of immune cells, namely CD20+ B cells and T cells, through targeted cell death, which reduces inflammation mediated by the CD20+ cells of the immune system.[11] As an immunomodulator, there is a risk of adverse events related to immunosuppression, such as the development of opportunistic or serious infections. The occurrence of progressive multifocal leukoencephalopathy and cryptococcal meningitis were included as notable harms in this review because they have been reported in patients living with MS treated with other anti-CD20 therapies,[11] although no such cases were reported in either of the ASCLEPIOS studies. Other notable harms included in the CADTH systematic review protocol were injection-related reactions, lymphopenia, neutropenia, reduction in serum immunoglobulins, and malignancies. Injection-related reactions and reductions in serum immunoglobulins (specifically, decrease in blood immunoglobulin M) were more common among patients in the ofatumumab treatment groups than in the teriflunomide treatment groups, but this was expected based on the subcutaneous route of administration and mechanism of action (respectively) of ofatumumab.

Direct comparative evidence of the safety of ofatumumab is limited to the ASCLEPIOS trials, with teriflunomide as the sole comparator. The sponsor-submitted ITC provided indirect comparative evidence of the safety of ofatumumab to several DMTs for MS. The safety outcomes were evaluated qualitatively and reported narratively; however, the conclusions that can be drawn from these data are limited. While ofatumumab is unique among monoclonal antibodies for the treatment of MS due to the subcutaneous route of administration, the lack of direct comparative evidence to other monoclonal antibodies precludes drawing conclusions about the comparative safety. Other relevant evidence included an ongoing open-label safety extension study of ASCLEPIOS I and II, but the data were not available at the time of this review. Therefore, a gap remains in safety evidence regarding long-term safety and direct comparative evidence with respect to DMTs for MS other than teriflunomide.

Conclusions

ASCLEPIOS I and II demonstrated the superiority of ofatumumab to teriflunomide in adult patients with RRMS in terms of relapse, disability-related, and imaging outcomes. This includes a reduction in ARR, time to confirmed disability worsening and in the number of gadolinium-enhanced T1 lesions per MRI scan and the number of new or enlarging T2 lesions per year (relative to baseline). The patient's ability to work and HRQoL outcomes were also noted as important to patients, [redacted]

Direct comparative evidence for ofatumumab with other DMTs, including available monoclonal antibodies, is absent. One sponsor-submitted ITC comparing ofatumumab to other DMTs showed that ofatumumab is likely as effective as other monoclonal antibodies (alemtuzumab, natalizumab, cladribine, and ocrelizumab) in terms of ARR and CDP. However, these findings may suffer from a sparse network along with methodology heterogeneity, which resulted in a wide 95% credible interval and a lack of precision in the effect estimates.

Last, there was no significant signal of concerns regarding the safety of ofatumumab in the pivotal trials, other than the anticipated injection-related reactions due to the subcutaneous route of administration. Serious adverse events were reported by 7.6% to 10.3% of patients in the treatment groups of both studies, but the frequency of individual serious adverse events was low. However, considering the anticipated long-term use of ofatumumab as a chronic therapy for RRMS, evidence beyond the 1- to 2-year duration of the ASCLEPIOS trials is required to reliably assess the safety of ofatumumab.

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 21, 2020
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.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
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	ofatumumab* or Kesimpta* or arzerra* or azerra* or gsk 1841157 or gsk1841157 or HuMax CD20 or HuMaxCD20 or humac CD20 or HSDB 8170 or omb 157 or omb157 or M95KG522R0).ti,ab,kf,ot,hw,rn,nm..
2	exp Multiple sclerosis/
3	(multiple scleros* or disseminated scleros* or chariot disease* or insular scleros* or sclerosis multiplex).ti,ab,kf
4	(MS or PPMS or RRMS or SPMS).ti,ab,kf.
5	or/2-4
6	1 and 5
7	6 use medall.
8	*ofatumumab/
9	ofatumumab* or Kesimpta* or arzerra* or azerra* or gsk 1841157 or gsk1841157 or HuMax
10	8 or 9
11	exp Multiple sclerosis/
12	(multiple scleros* or disseminated scleros* or chariot disease* or insular scleros* or
13	(MS or PPMS or RRMS or SPMS).ti,ab,kw,dq.
14	or/11-13
15	10 and 14
16	15 use oemezd
17	16 not (conference review or conference abstract).pt.
18	7 or 17
19	remove duplicates from 18

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search terms: ofatumumab OR Kesimpta OR Arzerra OR GSK1841157 OR HuMax-CD20 OR HSDB 8170 OR omb 157
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search terms: ofatumumab OR Kesimpta OR Arzerra OR GSK1841157 OR HuMax-CD20 OR HSDB 8170 OR omb 157

Grey Literature

Search dates:	September 16-18, 2020
Keywords:	Ofatumumab or Kesimpta or GSK1841157 or HuMax-CD20 or HSDB 8170 or omb 157
Limits:	None
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 (https://www.cadth.ca/grey-matters) were searched:

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

Appendix 2: Excluded Studies

Table 29: Excluded Studies

Reference	Reason for exclusion
D'Souza M, Gysin S, Heikkila A, et al. Electronic Neurostatus-EDSS increases quality of expanded disability status scale (EDSS) assessments: First experience from two phase 3 clinical trials with ofatumumab in relapsing multiple sclerosis using the Web Diary. Mult Scler J. 2018;24(2 Supplement):357-358. [Abstract] Presented at: ECTRIMS 2018; 10-13 October; Berlin, Germany.	Abstract
Bar-Or A, Grove RA, Austin DJ, et al. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis: The MIRROR study. Neurology. 2018;90(20):e1805-e1814.	Phase II

Appendix 3: Detailed Outcome Data

Table 30: Additional Imaging Outcomes (Full Analysis Set)

	ASCLEPIOS I		ASCLEPIOS II	
	OMB 20 mg N = 465	TER 14 mg N = 462	OMB 20 mg N = 481	TER 14 mg N = 474
Number of new or enlarging T2 lesions per year relative to baseline[a]				
Month 12				
n	420	407	422	410
Treatment-group difference versus teriflunomide, rate ratio (95% CI)	0.26 (0.21 to 0.33)		0.21 (0.17 to 0.27)	
P value	< 0.001		< 0.001	
Month 24				
n	103	93	90	76
Treatment-group difference versus teriflunomide, rate ratio (95% CI)	0.22 (0.15 to 0.34)		0.19 (0.12 to 0.31)	
P value	< 0.001		< 0.001	
Percent brain volume loss (annual rate of change from baseline)[b]				
Month 12				
n	369	352	407	399
Adjusted mean difference (95% CI)	– 0.17 (–0.25 to –0.09)		– 0.20 (–0.27 to –0.13)	
P value	< 0.001		< 0.001	
Month 24				
n	88	78	81	74
Adjusted mean difference (95% CI)	– 0.10 (–0.20 to –0.00)		– 0.13 (–0.24 to –0.02)	
P value	0.047		0.016	

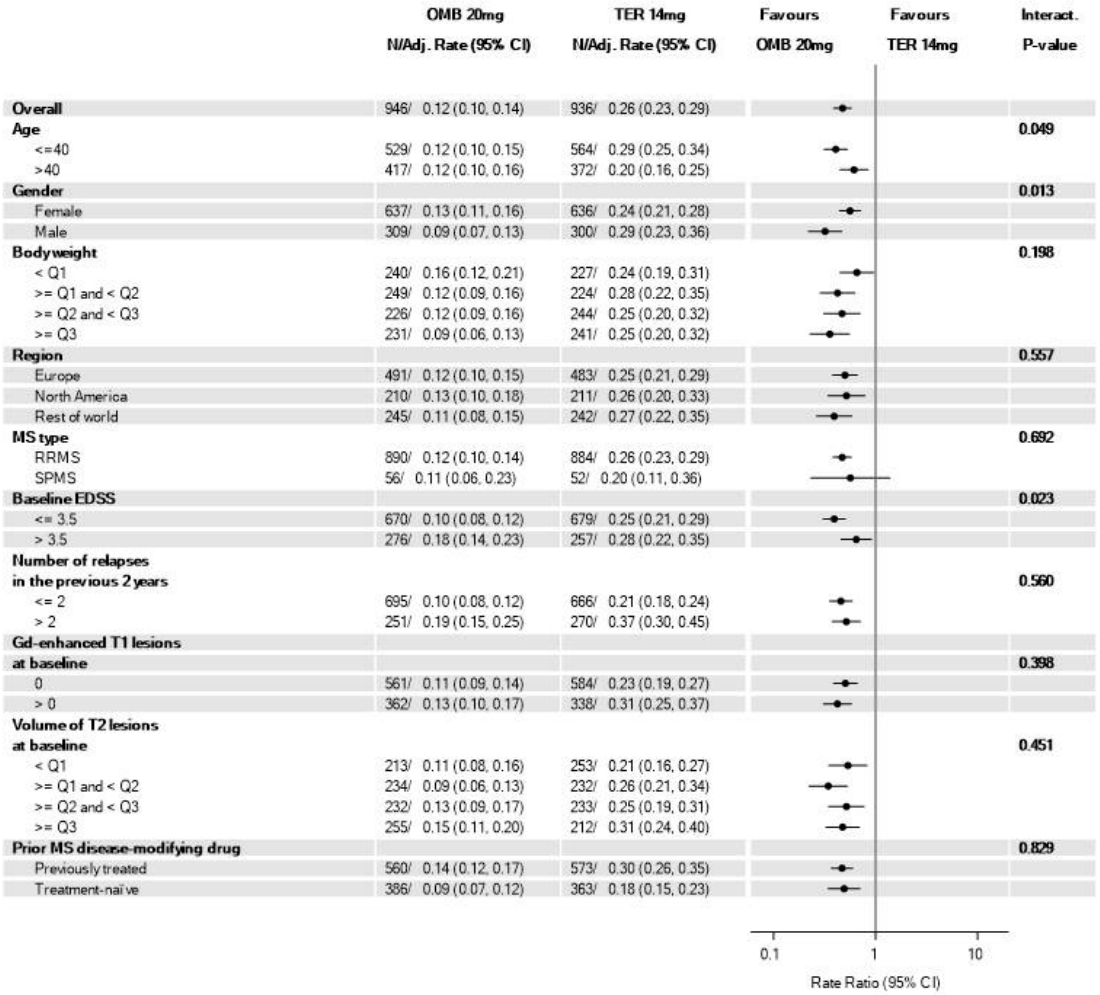
CI = confidence interval; OMB = ofatumumab; TER = teriflunomide.

[a] The number of new or enlarging T2 lesions (compared to baseline) is analyzed in a negative binomial model with adjustments for treatment and region (factors), and age, and baseline volume of T2 lesions as continuous covariates.

[b] Obtained from a random coefficients model with treatment and region as fixed effects; and time, baseline number of gadolinium-enhanced lesions, baseline T2 volume, and baseline normalized brain volume as continuous covariates.

Source: Clinical Study Reports for ASCLEPIOS I[14] and ASCLEPIOS II.[15]

Figure 13: Subgroup Analysis for ARR (Confirmed Relapses, Full Analysis Set)



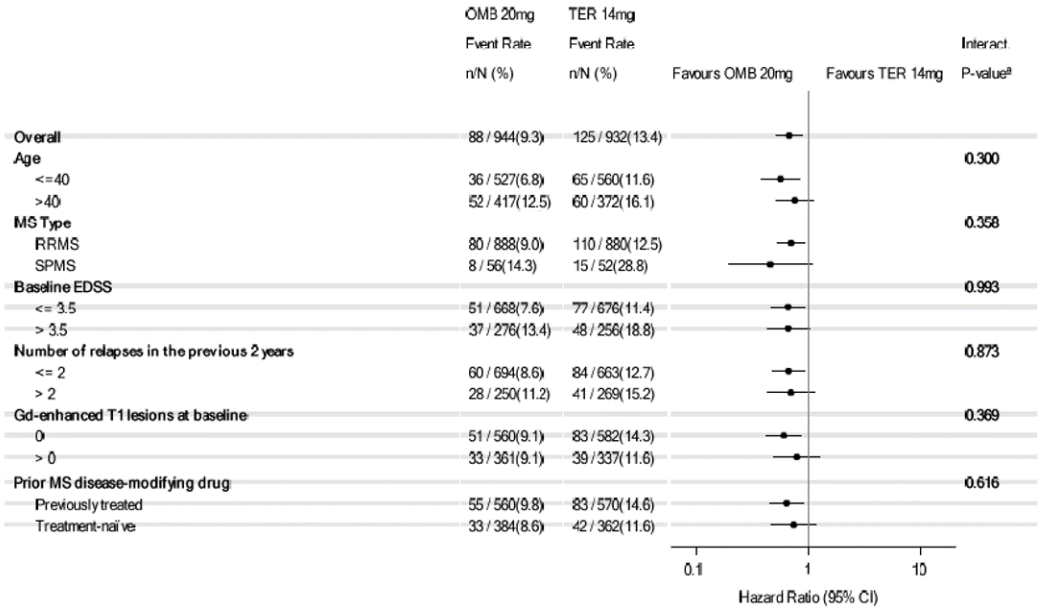
ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; Gd = gadolinium; OMB = ofatumumab; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; TER = teriflunomide.

Table 31: Subgroup Analysis for ARR (Confirmed Relapses, Full Analysis Set)

	ASCLEPIOS I and II				
ARR by subgroup	OMB 20 mg N = 946		TER 14 mg N = 936		
	N	Adjusted rate (95% CI)	N	Adjusted rate (95% CI)	Interaction P value
Age					
≤ 40	529	0.12 (0.10 to 0.15)	564	0.29 (0.25 to 0.34)	0.049
> 40	417	0.12 (0.10, 0.16)	372	0.20 (0.16 to 0.25)	
MS Type					
RRMS	890	0.12 (0.10 to 0.14)	884	0.26 (0.23 to 0.29)	0.692
SPMS	56	0.11 (0.06 to 0.23)	52	0.20 (0.11 to 0.36)	
Baseline EDSS					
≤ 3.5	670	0.10 (0.08 to 0.12)	679	0.25 (0.21 to 0.29)	0.023
> 3.5	276	0.18 (0.14 to 0.23)	259	0.28 (0.22 to 0.35)	
Number of relapses in the previous 2 years					
≤ 2	695	0.10 (0.08 to 0.12)	666	0.21 (0.18 to 0.24)	0.560
> 2	251	0.19 (0.15 to 0.25)	270	0.37 (0.30 to 0.45)	
Gd-enhanced T1 lesions at baseline					
0	561	0.11 (0.09 to 0.14)	584	0.23 (0.19 to 0.27)	0.398
> 0	362	0.13 (0.10 to 0.17)	338	0.31 (0.25 to 0.37)	
Prior MS DMTs					
Previously treated	560	0.14 (0.12 to 0.17)	573	0.30 (0.26 to 0.35)	0.829
Treatment-naive	386	0.09 (0.07 to 0.12)	363	0.18 (0.15 to 0.23)	

ARR = annualized relapse rate; CI = confidence interval; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MS = multiple sclerosis; OMB = ofatumumab; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; TER = teriflunomide.

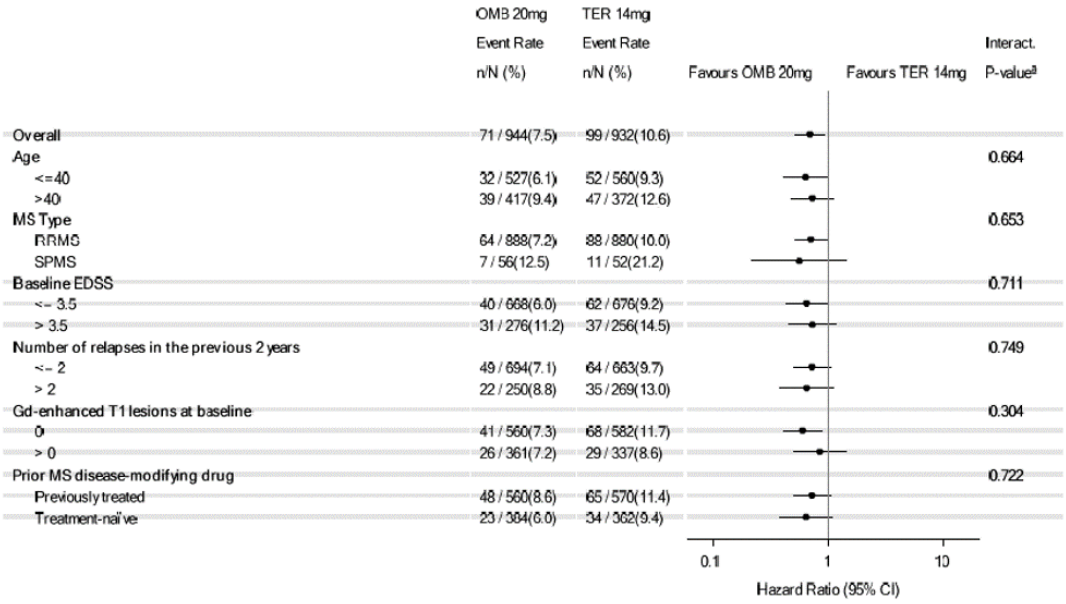
Figure 14: Subgroup Analysis for 3mCDW (Full Analysis Set)



3mCDW = 3-month confirmed disability worsening; CI = confidence interval; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MS = multiple sclerosis; OMB = ofatumumab; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; TER = teriflunomide.

Source: Ofatumumab submission.[5]

Figure 15: Subgroup Analysis for 6mCDW (Full Analysis Set)



6mCDW = 6-month confirmed disability worsening; CI = confidence interval; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MS = multiple sclerosis; OMB = ofatumumab; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; TER = teriflunomide.

Source: Ofatumumab submission.[5]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the properties of the outcome measures included in this review, including the validity, reliability, responsiveness to change, and MID of each measurement when available.

Findings

The findings about validity, reliability, responsiveness, and MID of each outcome measure are summarized in Table 32.

Interpretation of the reliability and validity metrics were based on the following criteria:

- Inter-rater reliability, kappa statistics (level of agreement):[51]
  - Less than 0 = poor agreement
  - 0.00 to 0.21 = slight agreement
  - 0.21 to 0.40 = fair agreement
  - 0.41 to 0.60 = moderate agreement
  - 0.61 to 0.8 = substantial
  - 0.81 to 1.00 = almost perfect agreement.

Internal consistency (Cronbach alpha) and test-retest reliability: ≥ 0.7 is considered acceptable.[69]

- Validity; i.e., between-scale comparison (correlation coefficient, r):[60]
  - Less than or equal to 0.3 = weak
  - 0.3 to 0.5 = moderate
  - Greater than 0.5 = strong.

Table 32: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	Minimal important difference
EDSS	Ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. The Kurtze functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, other) and ambulation are rated in the context of a standard neurological examination, and then these ratings (KFS scores) are used in conjunction with observations and information	Validity has been established. The EDSS is regarded as gold standard for evaluating new scales.[50] Reliability has low to moderate values, with inter-rater kappa values between 0.32 and 0.76 for EDSS and between 0.23 and 0.58 for the individual functional systems. For scores below 3.5, reliability is regarded as good.[50]	A clinically meaningful change for patients with MS has been proposed as a change of ≥ 1.0 if the EDSS at baseline is 0 to 5.5, and ≥ 0.5 for higher baseline EDSS scores.[47]

Outcome measure	Type	Conclusions about measurement properties	Minimal important difference
	concerning the patient's mobility, gait, and use of assistive devices to assign an EDSS score.		
Imaging findings: brain volume loss, T1, and T2 lesions per MRI	Measured in MS clinical trials with scheduled MRI scans using the number and volume of hyper-intense T2 and gadolinium-enhanced T1 lesions.	Commonly used as secondary end point measurement and as a surrogate for clinical disease activity. The effect of a treatment on relapses can be accurately predicted by the effect of that therapy on MRI lesions. MRI criteria to predict treatment response has been reported with sensitivity ranging from 24% to 71% and specificity of 71% to 97%.[42]	None identified.
EQ-5D-5L	Generic preference-based HRQoL instrument, consisting of a VAS, and a composite index score of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.	One systematic review[45] assessing the EQ-5D (9 studies) in patients with multiple sclerosis: • Content validity. The EQ-5D included certain domains such as walking (mobility) and mood (anxiety/depression) that patients considered important to their quality of life; yet, other critical domains such as fatigue and cognition are not included in EQ-5D. • Convergent validity of impairment (gait, speed, severity) was moderate (pooled correlation estimate = 0.35; 95% CI, 0.25 to 0.45). For activity limitations, the pooled correlation was 0.51 (95% CI, 0.45 to 0.57). When EQ-5D was compared against measures evaluating HRQoL the correlation value was 0.56 (95% CI, 0.54 to 0.59). • Discriminative validity was evaluated in 3 studies. The mobility item lacked discriminative ability. The EQ-5D was able to differentiate between all EDSS levels, except between EDSS levels 3 and 4. • Test-retest reliability: The intra-class correlation coefficient for test-retest reliability of the EQ-5D was 0.81 (acceptable). • One study assessed the EQ-5D as well as the validated PDDS scale and the MSWS-12 in patients with MS. Moderately strong correlations between the EQ-5D and the PDDS and MSWS-12 were observed (Spearman r = −0.56 and −0.59, respectively; P < 0.0001 for both).	For patients with MS, the MID estimates ranged from 0.050 to 0.084 when based on both the PDDS categories and MSWS-12 tertiles.

Outcome measure	Type	Conclusions about measurement properties	Minimal important difference
MSIS-29	The MSIS-29 uses a standardized psychometric approach.[43] It is a measure of the perceived physical and psychological impact of MS from the patient's perspective, structured in 2 subscales, a 20-item scale for the physical impact and a 9-item scale for the psychological impact of the disease, with the items answered in a 5-point Likert scale ranging from 1 ("not at all") to 5 ("extremely"). A final score ranging from 0 to 100 is generated by summing all the individual items, where higher scores indicate a worse outcome and disease burden.	Good to excellent internal consistency (reliability), with Cronbach alpha coefficients ranging from 0.89 to 0.97.[70,71] Reproducibility, as measured with the ICC has been also excellent in recent studies (ICC = 0.78 to 0.90).[70] Convergent validity of the tool has been demonstrated with correlations with measures of physical functioning (disability scales), physical domains of quality of life, and self-reported health status, with a strong correlation with the EDSS (r = 0.67).[70,71] The tool's construct validity (item-internal consistency) ranges from 0.59 to 0.95.[70]	A difference of 8 points is considered to be of clinical significance for EDSS in the range of 5.5 to 8.0, and 7 when the EDSS is between 0 and 5.0.[13]
T25FW	The T25FW is an objective and quantitative continuous score that assesses the leg function and ambulation of the patient (with a T25FW). It is performed by asking patients to walk to the end of a 25-foot mark and back as quickly as possible, with assistive device if needed.[47] A final score is reported in seconds with the average of 2 completed trials.[48] A higher test result represents a worse outcome for the T25FW and 9-HPT.[49]	The T25FW test has a strong correlation (convergent validity) with the EDSS (r = 0.84).[50] Test-retest reliability has been tested in small studies with values of intra-class coefficients of 0.96.[50]	A 20% change in score on T25FW trials is considered clinically meaningful.[50]
9-HPT	The 9-HPT evaluates the manual dexterity of the patient as they move 9 pegs into 9 holes on a board and back into a box; this test is done twice with each hand and the times averaged for each one separately.[52] A higher test result represents a worse outcome.	The inter-rater and test-retest reliability ranges from r = 0.86 to 0.98. Intra-class correlation coefficients are in the range of 0.69 to 0.96.[53] Validity is good but variation is wide, with correlation coefficients between 9-HPT and other outcome measures in the range of r = −0.37 to −0.79.[53]	A 20% change in score on the 9-HPT is considered clinically meaningful.[50]
SDMT	The SDMT is a neuropsychological symbol-substitution test that examines the attention and speed of processing in patients with MS. The score is the number of correct substitutions completed within the time limit with a maximum score of 110. Higher values of the score indicate better outcome. Obtaining a score under 33 is considered an indicator of a cognitive disorder.	In healthy individuals the test-retest reliability is good, with r = 0.76[72] and higher in MS patients ranging from 0.74 to 0.96. In other studies, a similar ICC is reported at 0.86 with improvements over time probably due to practice effects.[54] The SDMT has good construct validity although with modest association with other measures of physical disability (i.e., EDSS, PASAT, 9-HPT, and T25FW) with r values ranging from 0.34 to 0.47.	A raw score of 4 points has been considered a meaningful threshold for improvement for MS patients.[52,55]

Outcome measure	Type	Conclusions about measurement properties	Minimal important difference
WPAI:MS	The WPAI:MS measures impairments in both paid and unpaid work. It consists of 6 questions[56,57] that measure absenteeism and presenteeism, as well as the impairments in unpaid activity.[59] High scores indicate prolonged sick leave or impairment and decreased productivity.	It has been validated as a general instrument and within numerous clinical conditions.[57-59] Spearman correlations of the Work Productivity and Activity Impairment with other instruments for global assessment of health status measures in terms of functional disability, pain, fatigue and disease activity range from 0.34 to 0.77.[59] Good reliability and internal consistency, with an ICC ranging from 0.78 to 0.90 and Cronbach alpha from 0.80 to 0.90.[61]	No MID was identified. As a surrogate measure, changes in Work Productivity and Activity Impairment values in patients with Crohn disease of a 7% improvement have been regarded as important and sizable.[73] This number increases to 20% in patients with psoriasis and psoriatic arthritis.
NEDA	The term NEDA — previously "disease activity–free" — is a composite outcome that implies stabilization of disease as evidenced by 3 measures: lack of clinical relapses, lack of disease progression measured by EDSS, and absence of new disease activity (new T2 lesions/enhanced lesion) on MRI over a period of observation.[74,75]	In a prospective observational study of 215 patients with relapsing MS followed up for 7 years, only 7.9% maintained NEDA status after that time. NEDA at 2 years had a positive predictive value of 78.3% for no progression (EDSS ≤ 0.5) at 7 years.[76]	None identified.

9-HPT = 9-hole peg test; CI = confidence interval; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol 5-Dimensions questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HRQoL = health-related quality of Life; ICC = intra-class correlation; MID = minimal important difference; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = 29-item Multiple Sclerosis Impact Scale; MSWS-12 = 12-item Multiple Sclerosis Walking Scale; NEDA = no evidence of disease activity; PASAT = Paced Auditory Serial Addition Test; PDDS = Patient Determined Disease Steps; SF-36 = Short Form (36) Health Survey; SDMT = Symbol Digit Modalities Test; T25FW = Timed 25-Foot Walk; WPAI:MS = Work Productivity and Activity Impairment questionnaire for Multiple Sclerosis; VAS = Visual Analogue Scale.

Expanded Disability Status Scale

The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments.[47] The scale aims to capture disability in MS patients by describing symptoms or signs in 8 FSs that can be assessed in a neurological physical examination — pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral — and allows neurologists to assign an FS score in each of these. The scale also captures ambulatory function, which is rated in the context of a standard neurological examination, and then these ratings are used in conjunction with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign a final EDSS score (Table 33).

Steps 1.0 to 4.5 of the EDSS refer to people who are fully ambulatory. A patient's disability can be limited to a single FS, for example, to an EDSS score of 4.0 (e.g., bilateral vision loss, severe ataxia, paresis in at least 2 limbs, marked reduction in sensation in at least 1 limb), or involve different functional systems that may or may not be reflected in the EDSS score. Steps 5.0 to 9.5 of the EDSS are defined by impairment of ambulation and carrying out activities associated with daily living.

The EDSS is used in the ASCLEPIOS I and II studies to measure time to disability worsening as measured by 3mCDW and 6mCDW, respectively. It is also used to measure the 6mCDI.

Table 33: Expanded Disability Status Scale

0.0	Normal neurological examination
1.0	No disability, minimal signs in 1 FS
1.5	No disability, minimal signs in more than 1 FS
2.0	Minimal disability in 1 FS
2.5	Mild disability in 1 FS or minimal disability in 2 FSs
3.0	Moderate disability in 1 FS, or mild disability in 3 or 4 FSs; fully ambulatory
3.5	Fully ambulatory but with moderate disability in 1 FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 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; able to walk without aid or rest some 300 metres
5.0	Ambulatory without aid or rest for about 200 metres; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 metres with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 metres without resting
7.0	Unable to walk beyond approximately 5 metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
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
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally, has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms; retains some self-care functions
9.0	Confined to bed; can still communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

FS = functional system; MS = multiple sclerosis.

Measurement Properties

One systematic review with 54 studies addresses the validity and reliability of the EDSS.[50] Validity has been established and it is usually used as gold standard for evaluating new scales.

Reliability has been assessed as being low to moderate, with inter-rater kappa values between 0.32 and 0.76 for EDSS and between 0.23 and 0.58 for the individual functional systems. For scores below 3.5, reliability is regarded as good.

The review found that EDSS is sensitive to change in disease progression.

Minimally Important Difference

A clinically meaningful change for patients with MS has been proposed as a change of at least 1.0 if the EDSS at baseline was 0 to 5.5, and at least 0.5 for higher baseline EDSS scores.[47] This was similar to the clinically meaningful level used in 2 other studies, an increase of at least 1.5 points when the baseline was 0; an increase of at least 1 point from a baseline of 1 to 5.5; and an increase of at least 0.5 points from a baseline score 6 or greater.[62,63]

Limitations

Some limitations exist related to low reliability values and flaws that limit its usefulness, particularly the non-linearity and limited responsiveness that should be considered when interpreting changes over time.[47] Furthermore, a lack of precision has been described regarding the definition of the degree of the deficit in some functional categories of the scale and the subjective examination in the overall definition of the scale.[77]

Imaging Studies

Magnetic resonance imaging has value as a diagnostic tool due to its high sensitivity and ability to detect past disease.[47,78] It can also predict the effect of a treatment on relapses by the effect of that therapy on lesions, although these correlations vary between studies.[79,80] In the same venue, brain volume loss has been correlated with disability progression and cognitive impairment in MS, with the loss of grey matter volume more closely correlated with clinical measures than loss of white matter volume. The annual rate of brain volume loss is thought to be accelerated in patients with MS, ranging from 0.5% to 1.35% per year in patients with relapsing MS, compared with the normal age-related deterioration in healthy individuals of 0.1% to 0.3% per year.[81]

Measurement Properties

Measurement properties are not applicable in the context of measurement scales, although internal validity is reinforced by the concept of blinding of the outcome assessors in both trials. However, MRI lesions are commonly used as secondary end-point measurements and as surrogates for clinical disease activity. Based on a systematic review of 31 randomized trials of DMTs in patients with MS, the effects of medications on lesions revealed by MRI over short follow-up periods (6 to 9 months) can predict the effects on relapses over longer follow-up periods (12 to 24 months) with a derived regression equation (R^2) of 0.71, suggesting a good degree of prediction of relapse using the MRI effect.[79]

According to another review, MRI criteria to predict treatment response have been reported with sensitivities ranging from 24% to 71% and specificities from 71% to 97%.[42]

Minimally Important Difference

No MIDs were detected.

Limitations

More information is needed to increase confidence in the sensitivity and specificity values as well as the prognostic values reported in current systematic reviews.

EuroQol 5-Dimensions Questionnaire

The EQ-5D is a generic, standardized, self-administered instrument that provides a simple, descriptive profile and a single index value for health status. The EQ-5D comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of 5 levels. The response period is the day of assessment only. Assessments are also made using the VAS, which captures the self-rating of current health status using a visual "thermometer" with the end points of 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom. The EQ-5D therefore produces 3 types of data for each respondent:

- A profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor, such as 11121 or 33211
- A population preference–weighted health-index score based on the descriptive system
- A self-reported assessment of health status based on the EQ-5D VAS.

Measurement Properties

One systematic review[45] assessing the EQ-5D (9 studies) in patients with MS was available. In terms of the content validity of the EQ-5D, the instrument included domains such as walking (mobility) and mood (anxiety/depression) that patients considered important to their quality of life; yet, other critical domains such as fatigue and cognition are not included in the EQ-5D.

Convergent validity of impairment (gait, speed, severity) was moderate (pooled correlation estimate = 0.35; 95% CI, 0.25 to 0.45). For activity limitations, the pooled correlation was 0.51 (95% CI, 0.45 to 0.57). When the EQ-5D was compared against measures evaluating HRQoL, the correlation value was 0.56 (95% CI, 0.54 to 0.59). Discriminative validity was evaluated in 3 studies. The mobility item lacked discriminative ability. The EQ-5D was able to differentiate between all EDSS levels, except between levels 3 and 4.

In terms of reliability, the test-retest intra-class correlation coefficient of the EQ-5D was found to be acceptable, with a value of 0.81.

One study assessed the EQ-5D correlation by using the validated Patient Determined Disease Steps (PDDS) scale and the 12-Item Multiple Sclerosis Walking Scale (MSWS-12) in patients with MS. Moderately strong correlations between the EQ-5D and the PDDS and MSWS-12 were observed (Spearman r = −0.56 and −0.59, respectively; P < 0.0001 for both). In addition, a review determined a lack of content validity for patients with MS for the EQ-5D as it was found to be missing certain domains (i.e., mobility, mood) that were important to the disease and showed difficulty in differentiating between levels of disability.[45] Test-retest reliability in the MS population was determined to be good (intra-class correlation coefficient = 0.81).[45]

Minimally Important Difference

For patients with MS, the MID estimates ranged from 0.050 to 0.084 when based on both the PDDS categories and MSWS-12 tertiles.[46] In the general population, scores of less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MIDs for this scale in the general population ranged from 0.033 to 0.074,[82] and this has been confirmed by simulation studies for the general population.[83]

Limitations

There are still issues with content validity for patients with MS as described.

Multiple Sclerosis Impact Scale

The MSIS-29 was initially developed in 2001 as an MS-specific scale using a standardized psychometric approach,[43] and has been increasingly used by researchers and clinicians assessing patients with MS. This scale is a measure of the perceived physical and psychological impact of MS from the patient's perspective. It is structured in 2 subscales, a 20-item scale for the physical impact and a 9-item scale for the psychological impact of the disease, with the items answered on a 5-point Likert scale ranging from 1 ("not at all") to 5 ("extremely"). A final score ranging from 0 to 100 is generated by summing all the individual items, where higher scores indicate a worse outcome and disease burden.

Measurement Properties

The tool has been internally and externally validated in English and other languages with good stability.[71]

The MSIS-29 has a good to excellent internal consistency (reliability), with Cronbach alpha coefficients ranging from 0.89 to 0.97.[70,71] Reproducibility as measured with the intra-class correlation has been also excellent in recent studies, at 0.78 to 0.90.[70]

Convergent validity of the tool has been demonstrated with correlations with measures of physical functioning (disability scales), physical domains of quality of life, and self-reported health status, with a strong correlation with the EDSS (r = 0.67).[70,71] The tool's construct validity (item-internal consistency) ranges from 0.59 to 0.95.[70]

Minimally Important Difference

One study identified a difference of 8 points to be of clinical significance for an EDSS in a range of 5.5 to 8.0, and 7 when the EDSS ranged between 0 and 5.0.[13]

Limitations

Studies conducted to assess the validity and reliability still had some imprecision and risk of selection bias.[13,70,71]

Timed 25-Foot Walk Test

The T25FW test was evaluated individually as a secondary end point in the ASCLEPIOS I and II studies. It is an objective and quantitative continuous score that assesses the leg function and ambulation of the patient, making it an essential outcome measure in research and clinical practice. It is performed by asking patients to walk to the end of a 25-foot mark as quickly as possible and back, with assistive device if needed.[47] A final score is reported in seconds with the average of 2 completed trials.[48]

Measurement Properties

The T25FW test has a strong correlation (convergent validity) with the EDSS (r = 0.84).[50] Test-retest reliability has been tested in small studies with values of intra-class coefficients of 0.96.[50]

Minimally Important Difference

A 20% change in score on T25FW trials is considered clinically meaningful.[50] The change of at least 20% in the T25FW test has been corroborated by other studies using a variety of approaches, including clinical anchors, patient-reported anchors, real-life anchors, and distribution-based methods.

Limitations

More evidence is needed due to the small sample sizes in most studies, and further investigation based on thresholds associated with real-world changes in patient employment status is required.

9-Hole Peg Test

The 9-HPT was evaluated individually as a secondary end point in the ASCLEPIOS I and II studies. It is performed by evaluating the manual dexterity of patients as they move 9 pegs into 9 holes on a board and then back into a box.

A higher test result represents a worse outcome for 9-HPT.

Measurement Properties

The inter-rater and test-retest reliability of the 9-HPT are consistently high (with ranges of r = 0.86 to 0.98), independent of whether repeated testing was performed within 1 session or on different days. Intra-class correlation coefficients are in the range of 0.69 to 0.96.[53]

Validity is good but variation is wide, with correlation coefficients between 9-HPT and other outcome measures in the range of r = −0.37 to −0.79.[53]

Minimally Important Difference

A 20% change in scores on the 9-HPT is considered clinically meaningful.[50] A change of at least 20% together with the T25FW test has been corroborated by other studies using a variety of approaches, including clinical anchors, patient-reported anchors, real-life anchors, and distribution-based methods.

Limitations

More evidence is needed due to the small sample sizes in most studies, and further investigation based on thresholds associated with real-world changes in patient employment status is required.

Symbol Digit Modalities Test

The SDMT is a neuropsychological symbol-substitution test that examines the attention and speed of processing in patients with MS and other neurological conditions such as Parkinson and Alzheimer diseases, among others. It is considered a measure of information processing speed and a cognitive performance outcome measure.

It consists of a key with 2 rows, with 9 stimulus symbols in the upper row and matched numbers (1 to 9) in the lower row. The respondent is asked to fill in the corresponding numbers based on a series of symbols as fast as possible in 90 seconds. The score is the number of correct substitutions completed within the time limit, with a maximum score of 110. Higher values of the score indicate better outcome. A score of less than 33 is considered an indicator of a cognitive disorder.

Measurement Properties

In healthy individuals the test-retest reliability is good, with r = 0.76[72] and higher in MS patients ranging from 0.74 to 0.96. In other studies, a similar intra-class correlation coefficient is reported at 0.86, with improvements over time likely due to practice effects.[54]

The SDMT has good construct validity, although with modest association with other measures of physical disability (i.e., EDSS, 9-HPT, and T25FW) with r values ranging from 0.34 to 0.47. Other validity research demonstrates that the SMDT is a good measure of processing speed of efficiency and also correlates well with MRI measures of atrophy, lesion burden, and microstructural pathology.[72]

Minimally Important Difference

A raw score of 4 points has been considered a meaningful threshold for improvement for MS patients,[52,55] a threshold commonly utilized in clinical trials.

Limitations

There is still some uncertainty in the correlation between the SDMT and self-reported cognitive difficulty,[72] as well as uncertainty in the acquisition of an MID that needs further assessment with appropriate anchor-based studies.

Work Productivity and Activity Impairment Questionnaire for Multiple Sclerosis

The WPAI:MS measures impairments in both paid and unpaid work. It consists of 6 questions (1 = currently employed; 2 = hours missed due to health problems; 3 = hours missed for other reasons; 4 = hours actually worked; 5 = degree of health-affected productivity while working [using a 0-to-10 VAS]; 6 = degree of health-affected productivity in regular unpaid activities).[56,57] The tool measures absenteeism and presenteeism, as well as the impairments in unpaid activity because of health problems during the past 7 days — due to a recall period of 7 days for questions 2 to 6. Four main WPAI:MS items are generated from a version of the questionnaire for general health and expressed in percentages by multiplying the following scores by 100: 1) percent of work time missed due to health = Q2/(Q2 + Q4) for those who were currently employed; 2) percent impairment while working due to health = Q5/10 for those who were currently employed and actually worked in the past 7 days; 3) percent of overall work impairment due to health = Q2/(Q2 + Q4) + (1 − Q2/[Q2 + Q4]) × Q5/10 for those who were currently employed; 4) percent activity impairment due to health = Q6/10 for all respondents.[59] High scores indicate prolonged sick leave or impairment and decreased productivity. An advantage of this questionnaire is that it is possible to be transformed into monetary value.

Measurement Properties

No specific numbers of reliability and validity are provided for WPAI:MS, however, the instrument has been validated as a general instrument and within numerous clinical conditions.[57-59] Spearman correlations of the general-health version with other instruments for global assessment of health status measures in terms of functional disability, pain, fatigue and disease activity are in the range of 0.34 to 0.77.[59] Although these correlations are low to moderate, the general-health version has been correlated with other productivity outcomes such as hours lost due to presenteeism and hours of getting help on unpaid work activities measured using the questions adapted from the Health and Labour Questionnaire. There have been also significant positive relationships between the general-health version of the tool and the Short Form (36) Health Survey.[61]

The instrument possesses good reliability and internal consistency, with an intra-class correlation coefficient ranging from 0.78 to 0.90 and Cronbach alpha from 0.80 to 0.90.[61]

Minimally Important Difference

No MID for this outcome specific for patients with MS was identified. The only information available is in relation to changes revealed by the Work Productivity and Activity Impairment questionnaire for patients with Crohn disease, for whom a 7% improvement in work productivity loss or activity impairment has been regarded as important and sizable,[73] and this could be used as a surrogate for MS outcomes (albeit indirectly).

Similarly, based on distribution- and anchor-based methods in patients with psoriasis and arthritis, a 15% to 20% improvement in the work productivity loss or activity impairment components best represented the benefit of meeting a clinical meaningful improvement.[84,85]

No Evidence of Disease Activity

In relapsing MS, the concept of "no evidence of disease activity" — previously termed "disease activity–free" — has been recently proposed. It is a composite outcome that implies stabilization of disease as evidenced by 3 measures: lack of clinical relapses, lack of disease progression measured by EDSS, and absence of new disease activity (new T2 lesions or enhanced lesions) as revealed by MRI over a period of observation.[74,75] Some authors modify this definition by adding other outcomes such as new MRI lesions, brain volume loss, or a combination of categories to rule that there is no evidence of clinical disease activity. The interval for analyzing no evidence of disease activity has varied from 24 weeks to 3 years depending on the duration and time points of the clinical trial using this composite outcome.[76]

In the ASCLEPIOS I and II trials a NEDA-4 variation was used, and it was defined as no 3mCDW, no confirmed MS relapse, no new or enlarging T2 lesions on any MRI scan compared to baseline, and brain volume change greater than −0.4% per year on all MRI scans (brain volume as measured by the annualized rate of brain atrophy).

Measurement Properties

In a prospective observational study of 215 patients with relapsing MS followed up for 7 years, only 7.9% maintained NEDA-4 status after that time. A NEDA-4 status at 2 years had a positive predictive value of 78.3% for no progression (EDSS score ≤ 0.5) at 7 years.[76]

Minimally Important Difference

No MID was identified. Each component must be assessed individually for a MID.

Limitations

Using only 3 parameters of the composite outcome could miss other important assessments such as cognitive impairment and HRQoL. It is not yet clear which (functional) domains are important to include the NEDA-4 evaluation and when or how frequently these should be assessed.[47] The prognostic value of NEDA-4 observations at two years for predicting NEDA-4 at 7 years still requires validation.

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