CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

OCRELIZUMAB (OCREVUS)

(Hoffmann-La Roche Limited)

Indication: Treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features.

Service Line:	CADTH Common Drug Review
Version:	Version 1.0
Publication Date:	December 2017
Report Length:	118 Pages

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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Abbreviations

ARR	annualized relapse rate
CDEC	Canadian Drug Expert Committee
CDP	confirmed disability progression
CDI	confirmed disability improvement
CI	confidence interval
CNS	central nervous system
DMT	disease-modifying therapy
EMA	European Medicines Agency
EDSS	Kurtzke Expanded Disability Status Scale
FS	functional system
GdE	gadolinium-enhancing
HR	hazard ratio
IM	intramuscular
ITT	intention-to-treat
IV	intravenous
MCID	minimal clinically important difference
MCS	mental component summary
MD	mean difference
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
N/A	not applicable
NEDA	no evidence of disease activity
PASAT	Paced Auditory Serial Addition Test
PCS	physical component summary
PML	progressive multifocal leukoencephalopathy
PPMS	primary-progressive multiple sclerosis
PY	patient-year
RCT	randomized controlled trial
RR	relative risk
RRMS	relapsing-remitting multiple sclerosis
SC	subcutaneous
SD	standard deviation
SF-36	Short Form (36) Health Survey
SPMS	secondary-progressive multiple sclerosis

Drug	Ocrelizumab (Ocrevus)
Indication	Treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features
Reimbursement request	Monotherapy for the treatment of adult patients with relapsing-remitting multiple sclerosis
Dosage form(s)	300 mg vial
NOC date	August 14, 2017
Manufacturer	Hoffman-La Roche Limited

Executive Summary

Introduction

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

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets B cells that express CD20. It is indicated for the treatment of adult patients with RRMS with active disease defined by clinical and imaging features. The recommended dose of ocrelizumab is 600 mg administered intravenously (IV) once every six months. The product monograph recommends that the initial 600 mg dose be administered as two separate IV infusions: 300 mg for the first infusion, followed by a second 300 mg infusion two weeks later.

The objective of this systematic review is to examine the beneficial and harmful effects of ocrelizumab treatment for the suppression of relapses and disease progression in adult patients with relapsing forms of MS.

Results and Interpretation

Included Studies

The CADTH Common Drug Review (CDR) systematic review included two identically designed, multi-centre, parallel-group, double-blind, double-dummy, active-comparator, phase III randomized controlled trials (RCTs). Patients enrolled in the OPERA-I (N = 821) and OPERA-II (N = 835) studies were randomized (1:1) to receive ocrelizumab 600 mg IV once every six months or interferon beta-1a 44 mcg administered subcutaneously (SC) three times per week. The studies evaluated clinical end points (e.g., relapse), magnetic resonance imaging (MRI) end points (e.g., changes in lesions on T1- and T2-weighted scans), and patient-reported end points (e.g., Short Form [36] Health Survey [SF-36]). During the 96-week treatment period, patients were required to attend 10 scheduled assessment visits. Additionally, structured telephone interviews were conducted every four weeks starting at week 8 to identify any new or worsening neurological symptoms that would require an unscheduled clinic visit and to collect data on possible infections.

Patients aged 18 to 55 years with a relapsing form of MS were eligible for the OPERA-I and OPERA-II studies if they had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5.5 at the time of screening, at least two documented clinical relapses within two years of screening or one relapse within one year of screening, an MRI scan showing brain abnormalities consistent with MS, and no worsening of neurological symptoms within 30 days of screening and baseline. The MS diagnosis was made using the 2010 revised McDonald criteria. Key exclusion criteria included any previous treatment with a B cell–targeted therapy or other immunosuppressive medication, and a disease duration of more than 10 years in combination with an EDSS score of 2.0 or lower at screening.

Key limitations of the OPERA-I and OPERA-II trials include the differential rates of withdrawal between the interferon beta-1a groups (17.3% and 23.4%) and the ocrelizumab groups (10.7% and 13.7%), the potential for unblinding due to the adverse event profiles for the two treatments (particularly those related to the administration of the study drugs), prior exposure to interferon products for a minority of participants, and the need to impute a large amount of the data for some of the secondary end points (e.g., Multiple Sclerosis Functional Composite [MSFC] score, SF-36, and changes in lesions). Although the patient populations reflected the majority of MS patients in Canada, enrolment was limited to patients with an EDSS score of 0 to 5.5. This is consistent with other clinical trials conducted for MS treatments; however, it excludes a number of patients with more severe disability who could be eligible to receive ocrelizumab in clinical practice.

Efficacy

In both studies, treatment with ocrelizumab was associated with a statistically significant reduction in annualized relapse rate (ARR) compared with interferon beta-1a at 96 weeks ($P < 0.001$ for both). The rate ratios for ARR were 0.536 (95% confidence interval [CI], 0.400 to 0.719), 0.532 (95% CI, 0.397 to 0.714), and 0.535 (95% CI, 0.435 to 0.659) in OPERA-I, OPERA-II, and the pooled analysis, respectively. The rate of relapse with ocrelizumab was 46% lower than with interferon beta 1-a in OPERA-I and 47% lower in both OPERA-II and the pooled analysis. A greater proportion of ocrelizumab-treated patients remained free of relapses at 96 weeks compared with those in the interferon beta-1a group in both OPERA-I (80.4% versus 66.7%; relative risk [RR] 1.20 [95% CI, 1.10

to 1.31], *P* < 0.0001) and OPERA-II (78.9% versus 64.3%; RR 1.23 [95% CI, 1.12 to 1.35], *P* < 0.0001).

In accordance with the pre-specified statistical testing hierarchy, the following end points were tested using a pooled analysis of the results from OPERA-I and OPERA-II: confirmed disability progression (CDP) for at least 12 weeks, CDP for at least 24 weeks, and confirmed disability improvement (CDI) for at least 12 weeks. The pooled analysis demonstrated that ocrelizumab was associated with a statistically significant reduction in the hazard ratio (HR) for CDP for both 12 weeks and 24 weeks (HR 0.60 [95% CI, 0.45 to 0.81] and HR 0.60 [95% CI, 0.43 to 0.84], respectively). The pooled analysis demonstrated that ocrelizumab was associated with a statistically significant increase in the proportion of patients with CDI (RR 1.33 [95% CI, 1.05 to 1.68], *P* = 0.0194).

Ocrelizumab was associated with a statistically significant reduction in the rate of new or newly enlarged hyperintense lesions on T2-weighted scans by week 96, new hypointense lesions on T1-weighted scans by week 96, and new gadolinium-enhancing (GdE) lesions on T1-weighted scans in both the individual trials and the pooled analysis. There was no statistically significant difference between ocrelizumab and interferon beta-1a for change in brain volume from week 24 to week 96 in the OPERA-II trial (mean difference [MD] 0.112 [95%CI, −0.018 to 0.241], *P* = 0.09). Failure to demonstrate a statistically significant difference for change in brain volume stopped the statistical testing hierarchy at this end point in OPERA-II. The statistical testing hierarchy in OPERA-I had stopped at a higher-order end point; therefore, the difference between ocrelizumab and interferon beta-1a that was reported by the manufacturer for change in brain volume is not considered statistically significant (MD 0.168 [95% CI, 0.053 to 0.283], *P* = 0.0042).

In both OPERA-I and OPERA-II, the statistical testing hierarchy had been stopped prior to the evaluation of change from baseline in the SF-36 physical component summary (PCS). In both studies, the mean score for patients in the interferon beta-1a group showed a decrease from baseline (−0.833 to −0.657), whereas the mean scores in ocrelizumab groups showed a slight increase from baseline (0.036 to 0.326). While the pooled analysis of the two studies suggested a statistically significant difference between ocrelizumab-treated patients and those treated with interferon beta-1a (MD 0.918 [95% CI, 0.135 to 1.702], *P* = 0.02), the difference would not be considered clinically meaningful.

There was no statistically significant difference between ocrelizumab and interferon beta-1a for change from baseline in the MSFC score in OPERA-I (MD 0.039 [95% CI, –0.039 to 0.116], *P* = 0.3261). Failure to demonstrate a statistically significant difference for this end point stopped the statistical testing hierarchy at this end point in OPERA-I. In contrast, statistically significant differences favouring ocrelizumab over interferon beta-1a were observed in the OPERA-II trial (MD 0.107 [95% CI, 0.034 to 0.180], *P* = 0.0040) and in the pooled analysis (MD 0.077 [95% CI, 0.025 to 0.129], *P* = 0.004). The clinical significance of this difference in the MSFC score is uncertain due the absence of a validated minimal clinically important difference for this end point.

The statistical testing hierarchy had been stopped prior to the evaluation of no evidence of disease activity (NEDA) in both OPERA-I and OPERA-II. In both studies, a greater proportion of ocrelizumab-treated patients achieved NEDA at week 96 (43.9% to 47.4%) compared with those who received interferon beta-1a (24.1% to 27.1%). The RRs for NEDA were 1.74 (95% CI, 1.39 to 2.17) in OPERA-I and 1.81 (95% CI, 1.41 to 2.32) in OPERA-II.

Harms

The proportion of ocrelizumab-treated patients who experienced at least one serious adverse event was similar in the OPERA-I and OPERA-II trials (6.9% [39 events] and 7.0% [39 events], respectively). The proportion of patients treated with interferon beta-1a with at least one serious adverse event was 7.8% (38 events) in OPERA-I and 9.6% (50 events) in OPERA-II. The most commonly reported classes of serious adverse events across both studies were: infections and infestations (1.3% with ocrelizumab and 2.9% with interferon beta-1a); nervous system disorders (1.0% with ocrelizumab and 1.3% with interferon beta-1a); and injury, poisoning, and procedural complications (0.7% with ocrelizumab and 1.2% with interferon beta-1a). In both studies, withdrawals as a result of adverse events were more frequently reported in the interferon beta-1a groups (6.0% to 6.4%) compared with the ocrelizumab groups (3.2% to 3.8%). Infusion-related reactions led to the withdrawal of 11 ocrelizumab-treated patients (1.2% to 1.5%) compared with no patients for those who received the placebo infusion. There were no events of anaphylaxis reported in the studies.

Serious infections were more commonly reported for patients who received treatment with interferon beta-1a (3.8% [34 events]) compared with the ocrelizumab group (1.8% [18 events]). When adjusted for exposure, the event rate for serious infections in the ocrelizumab group was 0.83 per 100 patient-years (PYs) (95% CI, 0.43 to 1.45) compared with 1.79 per 100 PYs (95% CI, 1.16 to 2.64). The proportion of patients who experienced at least one adverse event that was classified as an opportunistic infection was greater in the ocrelizumab group (7.0%) compared with the interferon beta-1a group (4.1%). The manufacturer reported that this imbalance was due primarily to an increase in herpes infections in the ocrelizumab groups compared with the interferon groups. These included oral herpes (2.9% versus 2.1%), herpes zoster (2.1% versus 1.0%), and herpes simplex (0.8% versus 0.2%). No cases of progressive multifocal leukoencephalopathy were reported in patients who had been treated with ocrelizumab. The overall event rate for opportunistic infections was 5.25 per 100 PYs (95% CI, 4.14 to 6.57) in the ocrelizumab group and 2.79 (95% CI, 1.98 to 3.81) in the interferon beta-1a group.

Infusion-related reactions were the most commonly reported adverse event in both of the pivotal trials and occurred at a greater frequency in the ocrelizumab groups than in the interferon beta-1a groups (34.3% versus 9.7% in the pooled analysis). The most commonly reported symptoms associated with infusion-related adverse events in the ocrelizumab groups were pruritus, rash, throat irritation, and flushing. The first 300 mg dose of ocrelizumab was associated with the highest proportions of patients with an infusion-related event (27.5%), which decreased to 4.7% following the second 300 mg infusion (i.e., day 15). For the first infusion of the full 600 mg ocrelizumab dose, 13.7% of patients reported at least one infusion-related event. This proportion subsequently decreased for the third and fourth doses (9.6% and 7.8%, respectively).

Nearly all of the infusion-related adverse events were mild or moderate in severity (93% in the ocrelizumab group and 99% in the interferon beta-1a group were grade 1 or 2 events). Grade 3 infusion-related adverse events were reported in 20 ocrelizumab-treated patients (2.4%) compared with one (0.1%) patient in the interferon beta-1a group. There was one grade 4 event (bronchospasm) reported for an ocrelizumab-treated patient at the time of first 300 mg infusion. Eleven ocrelizumab-treated patients were withdrawn from the study as a result of infusion-related adverse events (1.3%) after receiving one infusion of ocrelizumab (i.e., 300 mg).

Across OPERA-I and OPERA-II, malignancy was reported for four patients treated with ocrelizumab and two patients treated with interferon beta-1a. The malignancy events in the ocrelizumab group included two invasive ductal breast carcinomas, one renal cancer, and one malignant melanoma.

Indirect Treatment Comparisons

Two network meta-analyses (NMAs) were reviewed and critically appraised by CADTH (one unpublished NMA submitted by the manufacturer and one published NMA conducted by the Institute for Clinical and Economic Review). [redacted]

Other Considerations

In their submission to CADTH, patients indicated they would prefer the dosage schedule of ocrelizumab (i.e., once every six months) compared with treatment regimens that require more frequent administration.

Conclusions

Two double-blind phase III RCTs (OPERA-I and OPERA-II) demonstrated that ocrelizumab was superior to interferon beta-1a for reducing the ARR and the HR for disability progression for three and six months. This was considered clinically relevant by regulatory authorities and the clinical expert consulted by CADTH. Treatment with ocrelizumab was also associated with an increase in the proportion of patients with disability improvement and in the proportion of patients with NEDA at 96 weeks. Evaluations using MRI suggest that lower proportions of ocrelizumab-treated patients developed new or newly enlarging hyperintense lesions on T2-weighted scans, new hypointense lesions on T1-weighted scans, and new GdE lesions on T1-weighted scans. Two NMAs suggested that [redacted]

The clinical expert consulted by CADTH indicated that the adverse event profile for ocrelizumab is consistent with other available MS treatments. The proportion of patients with at least one serious adverse event ranged from 6.9% to 7.0% with ocrelizumab and 7.8% to 9.6% with interferon beta-1a. Serious infections were more commonly reported for patients who received treatment with interferon beta-1a compared with the ocrelizumab group; however, opportunistic infections were more commonly reported in the ocrelizumab group. Withdrawals due to adverse events were more frequently reported in the interferon beta-1a groups than in the ocrelizumab groups. Infusion-related reactions were the most commonly reported adverse event in both of the pivotal trials and occurred at a greater

frequency in the ocrelizumab groups. Nearly all of the infusion-related adverse events were mild or moderate in severity and the proportion of ocrelizumab-treated patients who experienced infusion-related reactions tended to decrease over the course of the trial. Indirect treatment comparisons of safety end points were restricted to aggregate end points that cannot be used to evaluate the unique adverse event profiles of the different drugs.

Table 1: Summary of Efficacy Results

End Point (Time Point)	Scale	OPERA-1		OPERA-II		Pooled	
		IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)	IFN (N = 829)	OCR (N = 827)
ARR (96 weeks)	ARR (95% CI)	0.292 (0.235 to 0.361)	0.156 (0.122 to 0.200)	0.290 (0.234 to 0.361)	0.155 (0.121 to 0.198)	0.291 (0.250 to 0.339)	0.156 (0.131 to 0.186)
	Rate ratio (95% CI)[a]	0.536 (0.400 to 0.719)		0.532 (0.397 to 0.714)		0.535 (0.435 to 0.659)	
	P value	< 0.0001		< 0.0001		< 0.0001	
12-week CDP (96 weeks)	n	411	410	418	417	829	827
	12 week CDP, n (%)	50 (12.2)	31 (7.6)	63 (15.1)	44 (10.6)	113 (13.6)	75 (9.1)
	HR (95% CI)[b]	0.57 (0.37 to 0.90)		0.63 (0.42 to 0.92)		0.60 (0.45 to 0.81)	
	P value	0.0139		0.0169		0.0006	
24-week CDP (96 weeks)	n	411	410	418	417	829	827
	24 week CDP, n (%)	39 (9.5)	24 (5.9)	48 (11.5)	33 (7.9)	87 (10.5)	57 (6.9)
	HR (95% CI)[b]	0.57 (0.34 to 0.95)		0.63 (0.40 to 0.98)		0.60 (0.43 to 0.84)	
	P value	0.0278		0.0370		0.0025	
12-week CDI (96 weeks)	n	306	310	308	318	614	628
	CDI, n (%)	38 (12.42)	62 (20.00)	58 (18.83)	68 (21.38)	96 (15.64)	130 (20.70)
	RR (95% CI)[c]	1.61 (1.11 to 2.33)		1.14 (0.84 to 1.56)		1.33 (1.05 to 1.68)	
	P value	0.0106		0.4019		0.0194	
MSFC score (96 weeks)	n	359	360	342	358	577	630
	Mean change (SE)	0.174 (0.031)	0.213 (0.031)	0.169 (0.029)	0.276 (0.028)	0.171 (0.021)	0.248 (0.020)
	MD (95% CI)[d]	0.039 (–0.039 to 0.116)		0.107 (0.034 to 0.180)		0.077 (0.025 to 0.129)	
	P value	0.3261		0.0040		0.004	
T1 GdE lesions (96 weeks)	n	377	388	375	389	752	777
	Rate (95% CI)	0.286 (0.200 to 0.409)	0.016 (0.009 to 0.030)	0.416 (0.309 to 0.561)	0.021 (0.012 to 0.036)	0.356 (0.283 to 0.447)	0.020 (0.013 to 0.029)
	Rate ratio (95% CI)[e]	0.058 (0.032 to 0.104)		0.051 (0.029 to 0.089)		0.055 (0.037 to 0.082)	
	P value	< 0.0001		< 0.0001		< 0.001	
New/enlarging T2 hyperintense lesions (96 weeks)	n	378	390	376	390		
	Rate (95% CI)	1.413 (1.123 to 1.777)	0.323 (0.256 to 0.407)	1.904 (1.536 to 2.359)	0.325 (0.259 to 0.409)	1.684 (1.439 to 1.971)	0.331 (0.281 to 0.389)
	Rate ratio (95% CI)[e]	0.229 (0.174 to 0.300)		0.171 (0.130 to 0.225)		0.196 (0.162 to 0.238)	
	P value	< 0.0001		< 0.0001		< 0.001	
New T1 hypointense lesions (96 weeks)	n	377	388	375	389		
	Rate (95% CI)	0.982 (0.780 to 1.237)	0.420 (0.337 to 0.524)	1.255 (1.003 to 1.571)	0.449 (0.359 to 0.560)	1.140 (0.971 to 1.339)	0.437 (0.374 to 0.512)

End Point (Time Point)	Scale	OPERA-1		OPERA-II		Pooled	
		IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)	IFN (N = 829)	OCR (N = 827)
	Rate ratio (95% CI)[e]	0.428 (0.328 to 0.557)		0.357 (0.272 to 0.470)		0.384 (0.317 to 0.464)	
	P value	< 0.0001		< 0.0001		< 0.001	
Brain volume (24 to 96 weeks)	N	267	281	259	287	526	568
	Mean change (%; SE)	–0.741 (0.046)	–0.572 (0.044)	–0.750 (0.051)	–0.638 (0.049)	–0.744 (0.034)	–0.604 (0.033)
	MD (95% CI)[f]	0.168 (0.053 to 0.283)		0.112 (–0.018 to 0.241)		NR	
	P value	0.0042[g]		0.0900		0.002	
NEDA (96 weeks)	N	291	281	270	289	561	578
	n (%)	79 (27.1)	137 (47.4)	65 (24.1)	127 (43.9)	144 (25.7)	264 (45.7)
	RR (95% CI)[c]	1.74 (1.39 to 2.17)		1.81 (1.41 to 2.32)		NR	
	P value	< 0.0001[g]		< 0.0001[g]		< 0.001	
SF-36 PCS (96 weeks)	n	309	331	276	315	585	646
	Mean change (SE)	–0.657 (0.475)	0.036 (0.456)	–0.833 (0.472)	0.326 (0.444)	–0.767 (0.335)	0.152 (0.319)
	MD (95% CI)[d]	0.693 (–0.414 to 1.800)		1.159 (0.051 to 2.268)		0.918 (0.135 to 1.702)	
	P value	0.2193[g]		0.0404[g]		0.02	
SF-36 MCS (96 weeks)	Mean change (SE)	1.424 (0.565)	1.592 (0.540)	0.851	1.678	NR	
	MD (95% CI)[d]	0.168 (–1.199 to 1.534)		0.827 (–0.558 to 2.212)			
	P value	0.8095[g]		0.2413[g]			

ARR = annualized relapse rate; CDI = confirmed disability improvement; CDP = confirmed disability progression; CI = confidence interval; GdE = gadolinium-enhancing; HR = hazard ratio; IFN = interferon beta-1a; MD = mean difference; MCS = mental component summary; MSFC = Multiple Sclerosis Functional Composite; NEDA = no evidence of disease activity; NR = not reported; OCR = ocrelizumab; PCS = physical component summary; RR = relative risk; SE = standard error; SF-36 = Short Form (36) Health Survey.

[a] Negative binomial model adjusted for region (US versus non-US), baseline EDSS score (< 4.0 versus ≥ 4.0), and patient exposure (offset variable).

[b] Cox regression adjusted for region (US versus non-US) and baseline EDSS score (< 4.0 versus ≥ 4.0).

[c] Cochran–Mantel–Haenszel chi-square test adjusted for region (US versus non-US), and baseline EDSS score (< 4.0 versus ≥ 4.0).

[d] Mixed-effects model repeat measurement adjusted for baseline value, region (US versus non-US), and baseline EDSS score (< 4.0 versus ≥ 4.0).

[e] Negative binomial model adjusted for region (US versus non-US), baseline EDSS score (< 4.0 versus ≥ 4.0), baseline lesions, and number of MRIs (offset variable).

[f] Mixed-effects model repeat measurement adjusted for brain volume at week 24, baseline T1 GdE lesion (present or not), region (US versus non-US), and baseline EDSS score (< 4.0 versus ≥ 4.0).

[g] These *P* values are non-confirmatory due to the failure of the statistical testing hierarchy at a higher-order outcome.

Table 2: Summary of Adverse Events

Events, n (%)	OPERA-I		OPERA-II		Pooled RMS	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)	IFN (N = 826)	OCR (N = 825)
At least one AE	331 (80.9)	327 (80.1)	357 (85.6)	360 (86.3)	688 (83.3)	687 (83.3)
Serious AE	32 (7.8)	28 (6.9)	40 (9.6)	29 (7.0)	72 (8.7)	57 (6.9)
WDAE	26 (6.4)	13 (3.2)	25 (6.0)	16 (3.8)	51 (6.2)	29 (3.5)
WDSAE	4 (1.0)	3 (0.7)	5 (1.2)	3 (0.7)	9 (1.1)	6 (0.7)
Serious infections	12 (2.9)	5 (1.2)	12 (2.9)	6 (1.4)	24 (2.9)	11 (1.3)
Infections	222 (54.3)	232 (56.9)	219 (52.5)	251 (60.2)	441 (53.4)	483 (58.5)
AE leading to dose modification/interruption	31 (7.6)	20 (4.9)	54 (12.9)	18 (4.3)	85 (10.3)	38 (4.6)

AE = adverse event; IFN = interferon; OCR = ocrelizumab; RMS = relapsing multiple sclerosis; WDAE = withdrawal due to adverse event; WDSAE = withdrawal due to serious adverse event.

Source: Common Technical Documents 2.7.3[1] and 2.7.4.[2]

Introduction

Disease Prevalence and Incidence

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory disease of the central nervous system (CNS).[3,4] While the etiology of MS is unknown, it is believed that an abnormal immune response to environmental triggers in people who are genetically predisposed results in immune-mediated acute, and then chronic, inflammation.[3] Previous research has suggested that autoreactive T cells cross the blood–brain barrier and attack the myelin sheath and axons, causing demyelination, leading to a cascade of inflammation, and subsequently affecting the brain or spinal cord.[3,5] In the majority of patients (85%), the first presentation of MS is often a clinically isolated syndrome which is the first attack of a disease compatible with a diagnosis of MS (i.e., causing various motor or sensory deficits).[4,6] After the initial phase, a patient may experience a series of relapses and remissions. MS causes mild to disabling physical symptoms involving mobility problems, vision problems, problems with coordination, cognitive dysfunction, fatigue, and pain. Patients' quality of life is significantly impaired by mood disorders and limitations in employment and social functioning. MS is one of the major causes of disability in young adults.[7] MS affects up to three times as many women as men and typically has an age of onset of between 20 to 50 years.[8]

According to the revised McDonald criteria (2010), MS is diagnosed on the basis of evidence of at least two relapses (demonstrated clinically and/or by magnetic resonance imaging [MRI]), determined through a detailed medical history and neurological examination. Diagnosis is confirmed by objective clinical evidence of at least two lesions that are disseminated in space and time, as demonstrated clinically or by MRI.[4,9] MS is classified into four clinical subtypes: relapsing-remitting MS (RRMS); primary-progressive MS (PPMS), secondary-progressive MS (SPMS), and progressive-relapsing MS. The RRMS subtype comprises 85% to 90% of MS diagnoses at first presentation and is characterized by clearly defined relapses with full recovery or with sequelae and residual deficit upon recovery, with lack of progression of disability during the periods between relapses.[8] The relapsing forms of MS are associated with better prognoses than progressive forms of the disease.

MS places a major financial burden on the patients, their families, and the health care system.[8] The Multiple Sclerosis Society of Canada estimates there are currently 100,000 patients with MS in Canada, which is one of the highest prevalence estimates in the world.[10]

Standards of Therapy

As there is currently no cure for MS, the goal of therapy is to decrease the number and severity of relapses, reduce the burden of disease as measured by MRI, limit disability progression, and maintain patients' quality of life through the use of disease-modifying therapies (DMTs).[11] According to the Canadian Multiple Sclerosis Working Group (2013), the currently recommended first-line drugs for RRMS are interferon beta, glatiramer acetate, teriflunomide, and dimethyl fumarate, with the choice of drug being guided by the adverse effect profile, dosage schedule, reimbursement, and patient preference.[11-14] In 2013, CADTH published a Therapeutic Review of drug therapies for RRMS.[15] The report

concluded that all active treatments with DMTs produce statistically significant reductions in the annualized relapse rate (ARR) compared with no treatment, and that there are differences in ARR between various DMTs. Adverse events of note were treatment-specific and included influenza-like symptoms for interferons, injection-site reactions and hypersensitivity for glatiramer acetate, cardiovascular disorders for fingolimod, infusion reactions and progressive multifocal leukoencephalopathy (PML) for natalizumab, flushing for dimethyl fumarate, thyroid disorders for alemtuzumab, and alopecia for teriflunomide. Based on this review and accompanying pharmacoeconomic analysis, the Canadian Drug Expert Committee (CDEC) recommended glatiramer and interferon beta-1b as the initial therapies of choice for RRMS.[15]

Treatment selection or a change in therapy should be guided by the level of disease activity, disability progression, and MRI findings, and is highly individualized.[11] A lateral switch between first-line drugs may be indicated for patients who have had an adequate treatment response to but poor tolerance of a medication. Second-line therapies, including alemtuzumab, fingolimod, and natalizumab, may be indicated for patients with a suboptimal response to a first-line drug.[11] A recently published study also indicated that newer treatments (i.e., fingolimod, natalizumab, and alemtuzumab) may be more effective but may have a less favourable safety record than older treatments (i.e., interferons and glatiramer acetate) that are moderately effective but rarely have life-threatening adverse effects.[16]

Although no clinical criteria have been established to identify patients who should discontinue treatment, the Canadian Multiple Sclerosis Working Group suggests it may be necessary to consider stopping treatment in patients with significant disease progression (Kurtzke Expanded Disability Status Scale [EDSS] > 6) who have not experienced a relapse in the preceding two years.[11]

Drug

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets B cells that express CD20.[17] It is indicated for the treatment of adult patients with RRMS with active disease defined by clinical and imaging features. The recommended dose of ocrelizumab is 600 mg administered intravenously (IV) once every six months. The product monograph recommends that the initial 600 mg dose be administered as two separate IV infusions: 300 mg for the first infusion, followed by a second 300 mg infusion two weeks later.[17] To reduce the frequency and severity of infusion-related reactions, the product monograph recommends that patients be treated with the following:[17]

- 100 mg IV methylprednisolone (or an equivalent) approximately 30 minutes before each infusion
- an antihistaminic drug (e.g., diphenhydramine) approximately 30 to 60 minutes before each infusion
- an antipyretic drug (e.g., acetaminophen) may also be considered.

Table 3: Key Characteristics of Drugs Used in the Management of Relapsing-Remitting Multiple Sclerosis

INN (Brand)	Approved Indications[a]	ROA	Strength	Dosage Form(s)	Recommended Dose
Ocrelizumab (Ocrevus)	• RRMS	IV	30 mg/mL	Vial	600 mg q.6.m.
Daclizumab beta (Zinbryta)[18]	• RRMS (inadequate response to ≥ 1 DMT)	SC	150 mg/mL	PFS Pen	150 mg q.m.
Peg-IFN beta-1a (Plegridy)[19]	• RRMS	SC	125 mcg/0.5 mL	PFS Pen	125 mcg q.2.w.
Alemtuzumab (Lemtrada)[20]	• RRMS (inadequate response to IFN beta or other DMT)	IV	12 mg/1.2 mL	Vial	12 mg/day IV for 5 days then 12 mg/day IV for 3 days after 12 months
Dimethyl fumarate (Tecfidera)[14]	• RRMS	Oral	120 mg 240 mg	Capsule	240 mg b.i.d.
Fingolimod (Gilenya)[21]	• RRMS (inadequate response or intolerance to ≥ 1 DMT)	Oral	0.5 mg	Capsule	0.5 mg q.d.
Glatiramer acetate (Copaxone)[22]	• RRMS • CIS	SC	20 mg/mL	PFS	20 mg q.d.
	• RRMS	SC	40 mg/mL	PFS	40 mg t.i.w.
Glatiramer acetate (Glatect)[22]	• RRMS • CIS	SC	20 mg/mL	PFS	20 mg q.d.
Interferon beta-1a (Avonex)[23]	• RRMS • SPMS with relapses • CIS	IM	30 mcg/0.5 mL	PFS Pen	30 or 60 mcg q.w.
Interferon beta-1a (Rebif)[24]	• Relapsing forms of MS • CIS	SC	8.8 mcg/0.2 mL 22 mcg/0.5 mL 44 mcg/0.5 mL	PFS Pen	22 or 44 mcg t.i.w.
	• RRMS	SC	66 mcg/1.5 mL 132 mcg/1.5 mL	PFS PFC	
Interferon beta-1b (Extavia)[25]	• RRMS • SPMS • CIS	SC	0.3 mg	Vial	0.25 mg q.o.d.
Interferon beta-1b (Betaseron)[26]	• RRMS	SC	0.3 mg	Vial	0.25 mg q.o.d.

INN (Brand)	Approved Indications[a]	ROA	Strength	Dosage Form(s)	Recommended Dose
	• SPMS • CIS				
Natalizumab (Tysabri)[27]	• RRMS (inadequate response or intolerance to ≥ 1 DMT)	IV	300 mg/15 mL	Vial	300 mg q.4.w.
Teriflunomide (Aubagio)[21]	• RRMS	Oral	14 mg	Tablet	14 mg q.d.

b.i.d. = twice daily; CIS = clinically isolated syndrome; DMT = disease-modifying therapy; IFN = interferon; IM = intramuscular; INN = international non-proprietary name; IV = intravenous; Peg = pegylated; PF = pre-filled cartridge; PFS = pre-filled syringe; q.d. = once daily; q.o.d. = once every other day; q.w. = once weekly; q.2.w. = once every two weeks; q.4.w. = once every four weeks; q.m. = once every month; q.6.m. = once every six months; ROA = route of administration; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis; t.i.w. = three times per week.

[a] Abbreviated from Health Canada–approved product monographs.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of ocrelizumab for the treatment of adult patients with relapsing-remitting MS.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients with relapsing-remitting multiple sclerosis
Intervention	Ocrelizumab monotherapy (600 mg IV once every 6 months)
Comparators	Disease-modifying therapy: • daclizumab beta SC • dimethyl fumarate p.o. • teriflunomide p.o. • interferon beta-1a IM, SC • interferon beta-1b SC • pegylated interferon beta-1a SC • glatiramer acetate SC • natalizumab IV • fingolimod p.o. • alemtuzumab IV.
Outcomes	**Key efficacy outcomes:** • relapse (e.g., relapse rate and relapse-free rate)[a] • disability progression or improvement using a validated scale[a] • health-related quality of life using a validated scale[a] • symptoms (e.g., fatigue).[a] **Other efficacy outcomes:** • brain lesions (e.g., GdE lesions, new or enlarging T2 lesions) • brain atrophy or brain volume • productivity (ability to attend work or school)[a] • medication acceptance • relapse requiring corticosteroids. **Harms outcomes:** • adverse events, serious adverse events, withdrawals due to adverse events, mortality • adverse events of special interest: infusion-related adverse events, depression including suicidal ideation, serious infections, opportunistic infections.
Study Design	Published and unpublished phase III randomized controlled trials

GdE = gadolinium-enhancing; IM = intramuscular; IV = intravenous; p.o. = oral; SC = subcutaneous.

[a] These outcomes were identified as particularly important to patients in the input received by CADTH from patient groups.

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

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

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

The initial search was completed on June 13, 2017. Regular alerts were established to update the search until the meeting of CDEC on October 18, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (www.cadth.ca/grey-matters):

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- databases (free)
- Internet search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; there were no excluded studies.

Results

Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5: Details of Included Studies and described in Included Studies. There were no excluded studies.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

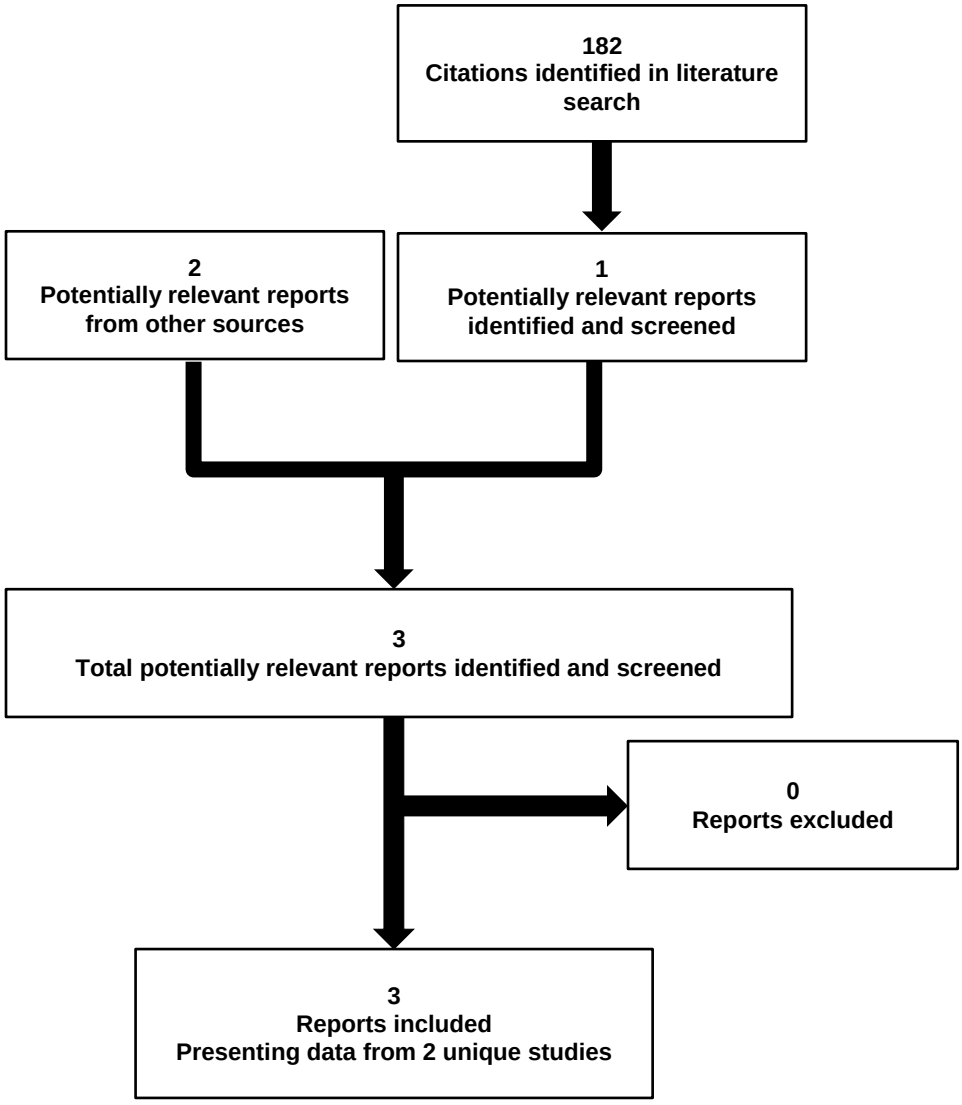


Table 5: Details of Included Studies

		OPERA-I (WA21092)	OPERA-II (WA21093)
Designs & Populations	**Study Design**	Multi-centre, parallel-group, double-blind, double-dummy, active-comparator RCT	
	Locations	141 sites across 32 countries (US, Europe, Central and South America, Africa, and Australia)	166 sites across 24 countries (US, Canada, Europe, and Central and South America)
	Randomized (N)	821 patients • Ocrelizumab (n = 410) • Interferon beta-1a (n = 411)	835 patients • Ocrelizumab (n = 418) • Interferon beta-1a (n = 417)
	Inclusion Criteria	• Relapsing forms of multiple sclerosis (based on 2010 revised McDonald criteria) • Aged 18 to 55 years • EDSS score of 0 to 5.5 at screening • ≥ 2 documented clinical relapses within previous 2 years or 1 clinical relapse within the year before screening • MRI scan of the brain showing abnormalities consistent with MS • No worsening of neurological symptoms for at least 30 days before both screening and baseline (day 1 trial visit)	
	Exclusion Criteria	• Diagnosis of PPMS • Previous treatment with any B cell–targeted therapy or other immunosuppressive medication • Disease duration > 10 years in combination with an EDSS score of 2.0 or less at screening	
Drugs	**Intervention**	Ocrelizumab 600 mg IV once every 24 weeks	
	Comparator(s)	Interferon beta-1a 44 mcg SC three times per week	
Duration	**Phase**		
	Run-in	2 to 8 weeks	
	Double-blind	96 weeks	
	Follow-up	48 weeks	
	Extension	Up to 4 years	
Outcomes	**Primary End Point**	Annualized protocol-defined relapse rate by 96 weeks	
	Other End Points	• 12- and 24-week confirmed disability progression • 12-week confirmed disability improvement • Change in MSFC score from baseline to week 96 • Cumulative number of GdE lesions by week 96 • Total number of new or newly enlarged hyperintense lesions by week 96 • Total number of new hypointense lesions by week 96 • Brain volume change from week 24 to week 96 • Change in SF-36 PCS from baseline to week 96 • NEDA by week 96	
Notes	**Publications**	• Hauser et al., 2016[28] • FDA reviewer reports[29,30] • Clinical Study Reports[31,32] • Common Technical Document[1,2] • clinicaltrials.gov[33,34]	

EDSS = Kurtzke Expanded Disability Status Scale; GdE = gadolinium-enhancing; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; NEDA = no evidence of disease activity; PPMS = primary-progressive multiple sclerosis; RCT = randomized controlled trial; SC = subcutaneous; SF-36 PCS = Short Form (36) Health Survey physical component summary.

Sources: Common Technical Document 2.7.3[1] and Clinical Study Reports for OPERA-I and OPERA-II.[31,32]

Included Studies

Description of Studies

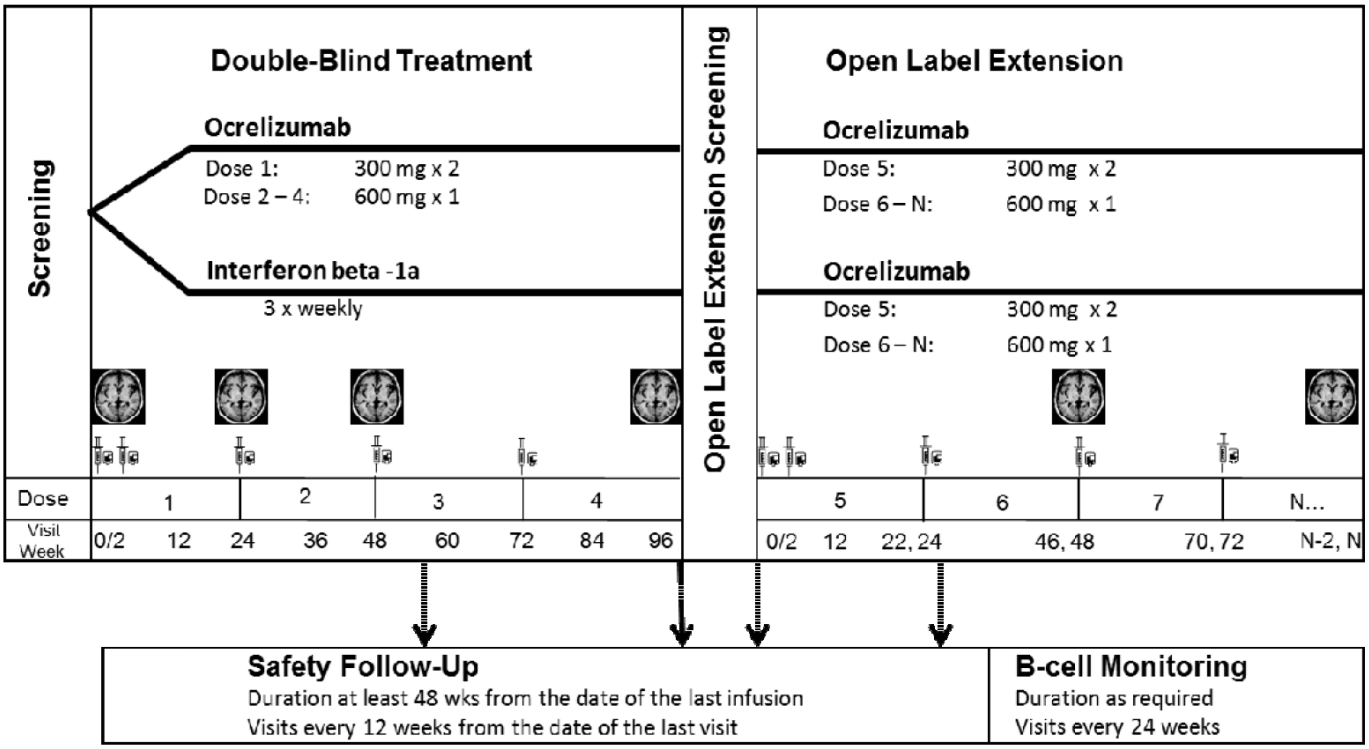
The OPERA-I and OPERA-II studies were identically designed, multi-centre, parallel-group, double-blind, double-dummy, active-comparator, phase III randomized controlled trials (RCTs). Enrolled patients were randomized (1:1) to receive ocrelizumab 600 mg IV once every six months or interferon beta-1a 44 mcg subcutaneously (SC) three times per week. Randomization was performed using an interactive voice/web response system with stratification by region (US or non-US) and baseline EDSS score (< 4.0 or ≥ 4.0). OPERA-I was conducted at 141 sites in 32 countries, and OPERA-II was conducted at 166 sites in 24 countries. The OPERA-II trial included eight Canadian sites (number of patients was not reported).[32] Figure 2 provides a schematic showing the design of the OPERA-I and OPERA-II trials as well as the open-label extension study. During the 96-week treatment period, study participants were required to attend 10 scheduled assessment visits. Additionally, structured telephone interviews were conducted every four weeks starting at week 8 to identify any new or worsening neurological symptoms that would require an unscheduled clinic visit and to collect data on possible infections.[31,32]

Each study site had the following two blinded investigators:

- Treating investigator – was responsible for patient care and had access to the patient's safety data and blinded efficacy data.
- Examining investigator – performed the neurological examination and assessed the EDSS, the Karnofsky Performance Status Scale, and the Multiple Sclerosis Functional Composite (MSFC) score.

Patients were instructed not to discuss any symptoms related to the study treatment with the examining investigator.

Figure 2: Flow Diagram for Inclusion and Exclusion of Studies



Source: Common Technical Document 2.7.3.[1]

Populations

Inclusion and Exclusion Criteria

Patients aged 18 to 55 years with a relapsing form of MS were eligible for the OPERA-I and OPERA-II studies if they had an EDSS score between 0 and 5.5 at the time of screening, at least two documented clinical relapses within two years of screening or one relapse within one year of screening, an MRI scan showing brain abnormalities consistent with MS, and no worsening of neurological symptoms within 30 days of screening and baseline. The MS diagnosis was to be made using the 2010 revised McDonald criteria. Key exclusion criteria included any previous treatment with a B cell–targeted therapy (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab) or other immunosuppressive medication (e.g., cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, or natalizumab), and a disease duration of more than 10 years in combination with an EDSS score of 2.0 or lower at screening.

Baseline Characteristics

Key baseline and demographic characteristics are summarized in Table 6. These characteristics were similar in the OPERA-I and OPERA-II trials. In both studies, the characteristics were well balanced across the ocrelizumab and interferon treatment groups. The majority of participants in both studies were white (approximately 90%) and female (approximately 65%). Participants had a mean age of 37 years and a mean body weight of approximately 75 kg. Nearly half of all patients were enrolled at sites within the European Union, Switzerland, or Norway (47% across both studies). Patients from the US, Canada, and Australia constituted 26% of the study population in OPERA-I and 37% in OPERA-II.

The median EDSS score at baseline was 2.5 across all study groups (mean ranged from 2.71 to 2.82). Nearly all randomized patients in both studies had experienced at least one relapse within one year of randomization (96% and 98% in OPERA-I and OPERA-II, respectively). In both studies, approximately half of the study participants had been diagnosed within two years of randomization. The mean duration since diagnosis was slightly lower in the OPERA-I trial (3.71 years and 3.82 years with interferon beta-1a and ocrelizumab, respectively) compared with the OPERA-II trial (4.13 and 4.15 years with interferon beta-1a and ocrelizumab, respectively). The proportion of patients who had at least one gadolinium-enhancing (GdE) lesion on T1-weighted images at baseline was similar in the ocrelizumab and interferon beta-1a groups within and across studies (approximately 40%). The number and volume of hyperintense lesions on T2-weighted images were also similar across studies and treatment groups.

Table 6: Summary of Baseline Characteristics

Characteristics		OPERA-I		OPERA-II		Pooled	
		IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)	IFN (N = 829)	OCR (N = 827)
Age, years	Mean (SD)	36.9 (9.3)	37.1 (9.3)	37.4 (9.0)	37.2 (9.1)	37.2 (9.2)	37.1 (9.2)
Sex, N (%)	Male	139 (33.8)	140 (34.1)	138 (33.0)	146 (35.0)	277 (33.4)	286 (34.6)
	Female	272 (66.2)	270 (65.9)	280 (67.0)	271 (65.0)	552 (66.6)	541 (65.4)
Weight (kg)	Mean (SD)	75.86 (17.52)	74.60 (18.35)	74.98 (18.98)	75.85 (17.14)	75.42 (18.26)	75.22 (17.75)
BMI (kg/m^2)	Mean (SD)	26.37 (6.03)	25.88 (5.93)	26.34 (6.33)	26.42 (5.69)	26.35 (6.18)	26.15 (5.82)
Race, N (%)	American Indian/Alaska Native	0	1 (0.2)	4 (1.0)	2 (0.5)	4 (0.5)	3 (0.4)
	Asian	1 (0.2)	0	2 (0.5)	2 (0.5)	3 (0.4)	2 (0.2)
	African American	12 (2.9)	19 (4.6)	20 (4.8)	21 (5.0)	32 (3.9)	40 (4.8)
	Pacific Islander	0	0	0	1 (0.2)	0	1 (0.1)
	White	375 (91.2)	375 (91.5)	382 (91.4)	368 (88.2)	757 (91.3)	743 (89.8)
	Other	14 (3.4)	10 (2.4)	9 (2.2)	19 (4.6)	23 (2.8)	29 (3.5)
	Multiple	9 (2.2)	5 (1.2)	1 (0.2)	4 (1.0)	10 (1.2)	9 (1.1)
Region	EU/Switzerland/Norway	204 (49.6)	211 (51.5)	182 (43.5)	187 (44.8)	386 (46.6)	398 (48.1)
	Latin America	35 (8.5)	26 (6.3)	26 (6.2)	19 (4.6)	61 (7.4)	45 (5.4)
	Non-EU/Israel/Africa	64 (15.6)	68 (16.6)	53 (12.7)	58 (13.9)	117 (14.1)	126 (15.2)
	US/Canada/Australia	108 (26.3)	105 (25.6)	157 (37.6)	153 (36.7)	265 (32.0)	258 (31.2)
Duration since diagnosis	Mean (SD) (years)	3.71 (4.63)	3.82 (4.80)	4.13 (5.07)	4.15 (4.95)	3.99 (4.88)	3.92 (4.86)
	≤ 2 years, n (%)	219 (53.3)	219 (53.4)	220 (52.6)	206 (49.4)	439 (53.0)	425 (51.4)
	< 2 years, n (%)	192 (46.7)	191 (46.6)	198 (47.4)	211 (50.6)	390 (47.0)	402 (48.6)
Relapses	Events in past year	1.33 (0.64)	1.31 (0.65)	1.34 (0.73)	1.32 (0.69)	1.33 (0.69)	1.32 (0.67)
	0, n (%)	10 (2.4)	17 (4.1)	16 (3.8)	15 (3.6)	26 (3.1)	32 (3.9)
	≥ 1, n (%)	400 (97.6)	393 (95.9)	401 (96.2)	401 (96.4)	801 (96.9)	794 (96.1)
Relapses in the past 2 years	Mean (SD)	1.74 (0.91)	1.79 (0.87)	1.78 (0.92)	1.78 (0.95)	1.76 (0.92)	1.79 (0.91)
	≤ 2, n (%)	352 (85.9)	350 (85.4)	354 (84.9)	341 (82.0)	706 (85.4)	691 (83.7)
	> 2, n (%)	58 (14.1)	60 (14.6)	63 (15.1)	75 (18.0)	121 (14.6)	135 (16.3)

Characteristics		OPERA-I		OPERA-II		Pooled	
		IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)	IFN (N = 829)	OCR (N = 827)
T1 lesions	Mean (SD)	1.87 (5.17)	1.69 (4.16)	1.95 (4.86)	1.82 (4.96)	1.91 (5.01)	1.76 (4.58)
	0, n (%)	252 (61.9)	233 (57.5)	243 (58.6)	252 (61.0)	495 (60.2)	485 (59.3)
	1, n (%)	52 (12.8)	64 (15.8)	62 (14.9)	58 (14.0)	114 (13.9)	122 (14.9)
	> 1, n (%)	103 (25.3)	108 (26.7)	110 (26.5)	103 (25.0)	213 (25.9)	211 (25.8)
T2 lesions	Mean volume (cm^3) (SD)	9.74 (11.28)	10.84 (13.90)	10.61 (12.30)	10.73 (14.28)	10.18 (11.81)	10.79 (14.09)
	Mean number (SD)	51.06 (39.90)	51.04 (39.00)	51.01 (35.69)	49.26 (38.59)	51.04 (37.81)	50.14 (38.78)
	0 to 9, n (%)	29 (7.1)	28 (6.9)	35 (8.4)	35 (8.5)	64 (7.8)	63 (7.7)
	> 9, n (%)	379 (92.9)	380 (93.1)	381 (91.6)	379 (91.5)	760 (92.2)	759 (92.3)
EDSS score	Mean (SD)	2.71 (1.29)	2.82 (1.24)	2.79 (1.38)	2.73 (1.29)	2.75 (1.33)	2.77 (1.27)
	< 4.0, n (%)	318 (77.6)	314 (76.6)	309 (73.9)	315 (75.5)	627 (75.7)	629 (76.1)
	≥ 4.0, n (%)	92 (22.4)	96 (23.4)	109 (26.1)	102 (24.5)	201 (24.3)	198 (23.9)
MSFC z score	Mean (SD)	0.03 (0.64)	−0.01 (0.76)	−0.02 (0.67)	0.01 (0.64)	0.01 (0.65)	0.00 (0.70)

EDSS = Kurtzke Expanded Disability Status Scale; EU = European Union; IFN = interferon; MSFC = Multiple Sclerosis Functional Composite; OCR = ocrelizumab; SD = standard deviation.

Source: Common Technical Document 2.7.3.[1]

Prior Exposure to Multiple Sclerosis Treatments

Table 7 provides a summary of prior exposure to MS treatments. The majority of patients in both trials had no exposure to any MS treatments within two years of screening (73.3% and 73.4% in the pooled ocrelizumab and interferon beta-1a groups, respectively). Of those with prior exposure, the most commonly used medications were (ocrelizumab and interferon beta-1a groups, respectively): glatiramer acetate (9.3% and 9.8%), interferon beta-1a SC (7.6% and 8.4%), interferon beta-1a administered intramuscularly (IM) (5.2% and 6.1%), and interferon beta-1b SC (6.5% and 5.0%).[1]

Table 7: Summary of Prior Exposure to Multiple Sclerosis Treatments

Prior MS Treatment n (%)	OPERA-I		OPERA-II		Pooled RMS Population	
	IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)	IFN (N = 829)	OCR (N = 827)
No prior MS treatment within 2 years	292 (71.4)	301 (73.8)	314 (75.3)	304 (72.9)	606 (73.4)	605 (73.3)
Any MS treatment within 2 years	117 (28.6)	107 (26.2)	103 (24.7)	113 (27.1)	220 (26.6)	220 (26.7)
IFN beta-1a IM	22 (5.4)	23 (5.6)	28 (6.7)	20 (4.8)	50 (6.1)	43 (5.2)
IFN beta-1a SC	38 (9.3)	31 (7.6)	31 (7.4)	32 (7.7)	69 (8.4)	63 (7.6)
IFN beta-1b SC	25 (6.1)	27 (6.6)	16 (3.8)	27 (6.5)	41 (5.0)	54 (6.5)
IFN beta NOS or IFN NOS or IFN blinded	1 (0.2)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Glatiramer acetate	37 (9.0)	38 (9.3)	44 (10.6)	39 (9.4)	81 (9.8)	77 (9.3)
Natalizumab	1 (0.2)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Fingolimod	0	1 (0.2)	0	4 (1.0)	0	5 (0.6)
Dimethyl fumarate	0	1 (0.2)	0	0	0	1 (0.1)
Teriflunomide	0	0	0	0	0	0
Alemtuzumab	0	0	0	0	0	0
Any of the above	114 (27.9)	106 (26.0)	102 (24.5)	113 (27.1)	216 (26.2)	219 (26.5)
Unapproved treatments	3 (0.7)	2 (0.5)	1 (0.2)	1 (0.2)	4 (0.5)	3 (0.4)

IFN = interferon; IM = intramuscular; MS = multiple sclerosis; NOS = not otherwise specified; OCR = ocrelizumab; RMS = relapsing multiple sclerosis; SC = subcutaneous.

Source: Common Technical Document 2.7.3.[1]

Interventions

Study Treatments

Ocrelizumab (and matching placebo) was supplied in vials, and interferon beta-1a (and matching placebo) was supplied as pre-filled syringes. In the double-dummy design, patients received an active medication and a dummy placebo for the comparator during the same period. Thus, patients who were randomized to the ocrelizumab group received infusions of 300 mg ocrelizumab on day 1 and day 15, then a 600 mg infusion once every 24 weeks as well as SC injections of the interferon placebo three times per week. Patients randomized to the interferon beta-1a (Rebif) group received the following dosage regimen: 8.8 mcg SC injections three times weekly for weeks 1 and 2; 22 mcg SC injections three times weekly for weeks 3 and 4; and 44 mcg SC injections three times weekly for weeks 5 to 96. These patients also received infusions of the ocrelizumab placebo on days 1 and 15, then once every 24 weeks (Table 8).

The first injection of interferon beta-1a (or matching placebo) was administered by the patient under the supervision of a nurse or a physician on day 1 of the trial. Patients subsequently self-administered the treatment (or placebo) three times weekly. Patients were

instructed to administer the treatment at the same time in the late afternoon or evening on the same three weekdays at least 48 hours apart. No dose modifications were permitted with ocrelizumab; the dosage of interferon beta-1a could be modified after day 29 (down to 22 mcg three times per week) for safety reasons at the discretion of the investigator.

Table 8: Dose Titration Algorithm in OPERA-I and OPERA-II

Ocrelizumab	Interferon beta-1a
• 300 mg IV on day 1 • 300 mg IV on day 15 • 600 mg IV once every 24 weeks	• 8 mcg SC t.i.w. for weeks 1 and 2 • 22 mcg SC t.i.w. for weeks 3 and 4 • 44 mcg SC t.i.w. for weeks 5 to 96

IV = intravenous; SC = subcutaneous; t.i.w. = three times per week.

Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

In the event of an infusion-related reaction, the infusion rate could be reduced or interrupted according to the following pre-specified protocols:[31,32]

- Grade 1 or 2 reaction: The infusion rate was reduced to half the rate that was being given at the time of onset of the event, and, if tolerated, increased again 30 minutes after the event had resolved.
- Grade 3 reaction, or flushing, fever, and throat pain cluster: The infusion was interrupted immediately and the patient received aggressive symptomatic treatment. The infusion was restarted only after all of the symptoms had disappeared, with a rate at restart of half of the rate being given at the time of onset of the event.
- Grade 4 reaction: The infusion was stopped immediately and the patient received appropriate treatment; these patients were withdrawn from study treatment and a safety follow-up period was initiated.

Pre-Medication for Infusion-Related Reactions

All patients received prophylactic treatment with 100 mg of methylprednisolone IV approximately 30 minutes before the start of each ocrelizumab/placebo infusion. If methylprednisolone was contraindicated, the patient received an equivalent dose of an alternative steroid.[31,32] The trial protocols also recommended that the infusions be accompanied by prophylactic treatment with an analgesic/antipyretic (e.g., acetaminophen 1,000 mg) and an IV or oral antihistamine (e.g., diphenhydramine 50 mg) 30 to 60 minutes before the start of the infusion.[31,32]

Outcomes

The complete list of primary, secondary, and exploratory efficacy end points that were evaluated in OPERA-I and OPERA-II are provided in Table 9.

Table 9: Efficacy End Points in OPERA-I and OPERA-II

Category	End Point
Primary end point	ARR by 96 weeks
Secondary end points	Time to onset of CDP for at least 12 weeks
	T1 GdE lesions at weeks 24, 48, and 96
	New and/or enlarging T2 hyperintense lesions at weeks 24, 48, and 96
	Proportion with CDI for at least 12 weeks
	Time to onset of CDP for at least 24 weeks
	New T1 hypointense lesions at weeks 24, 48, and 96
	Change from baseline in MSFC to week 96
	Percentage change in brain volume from week 24 to week 96
	Change from baseline in SF-36 PCS to week 96
	NEDA by week 96
Exploratory end points	Proportion of relapse-free patients by week 96
	Percentage change in total T2 hyperintense lesion volume
	ARR based on all clinical relapses
	ARR of relapses requiring IV steroids therapy
	ARR of severe relapses
	Percentage change in brain volume
	Change in MSFC score from baseline to week 48
	Change in EDSS from baseline to week 96
	Change in T25FW from baseline to week 96
	Change in 9-HPT from baseline to week 96
	Change in PASAT from baseline to weeks 48 and 96
	Change in MFIS from baseline to week 96
	Change in CES-D from baseline to week 96
	Change in Karnofsky Performance Status Scale from baseline to week 96
	Change in cortical grey matter volume from baseline to week 96
	Change in white matter volume from baseline to week 96
	Proportion with CDI for at least 24 weeks
	Disability improvement for at least 12 weeks and until the end of 96 weeks
	Duration of CDI
	Proportion with improved, stable, or worsened disability at week 96
	Change from baseline SF-36 MCS to week 96

9-HPT = 9-Hole Peg Test; ARR = annualized relapse rate; CDI = confirmed disability improvement; CDP = confirmed disability progression; CES-D = Center for Epidemiologic Studies Depression Scale; EDSS = Kurtzke Expanded Disability Status Scale; GdE = gadolinium-enhancing; MFIS = Modified Fatigue Impact Scale; MSFC = Multiple Sclerosis Functional Composite; NEDA = no evidence of disease activity; PASAT = Paced Auditory Serial Addition Test; SF-36 MCS = Short Form (36) Health Survey mental component summary; SF-36 PCS = Short Form (36) Health Survey physical component summary; T25FW = Timed 25-Foot Walk.

Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Relapse

The ARR at 96 weeks was the primary end point of the OPERA-I and OPERA-II trials. It was calculated as the total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment. Relapses were defined in the OPERA-I and OPERA-II trials as new or worsening neurological symptoms with the following criteria:

- attributable to MS only in the absence of fever or infection
- persistent for more than 24 hours

- immediately preceded by a stable or improving neurological state for at least 30 days
- accompanied by objective worsening of neurological symptoms consistent with an increase of at least half a step on the EDSS, two points in one EDSS functional system score, or one point in each of two or more EDSS functional system scores.

All new or worsening neurological events consistent with a clinical relapse were documented on a dedicated page of the electronic case report form. Patients with clinical relapses were subsequently referred to the blinded examining investigator, who conducted an independent assessment of the EDSS to confirm whether the event met the criteria for a relapse.[31,32] Adjudication of protocol-defined relapses was performed by the manufacturer based on the pre-specified relapse criteria using the data collected by the site investigators. A description of the EDSS is provided in Appendix 5.

Confirmed Disability Progression

Confirmed disability progression (CDP) was a secondary end point of OPERA-I and OPERA-II. CDP was defined as an increase in patient's EDSS score of at least 1.0 from baseline when the baseline score was 5.5 or less; or an increase of 0.5 from baseline when the baseline score was greater than 5.5. Disability progression was considered confirmed when the increase from baseline in EDSS was documented at a regularly scheduled clinic visit 12 or 24 weeks after the worsening of the patient's neurological symptoms was initially documented. The EDSS evaluation was conducted by the blinded examining investigator.

Confirmed Disability Improvement

Confirmed disability improvement (CDI) was assessed in the subgroup of patients who had a baseline EDSS score of at least 2.0. CDI was defined as a reduction in EDSS score from baseline of at least 1.0 for those with a baseline score between 2 and 5.5, or a reduction of at least 0.5 when the baseline EDSS score was greater than 5.5. All patients without confirmed CDI were counted as "not improved" in the analysis. The EDSS evaluation was conducted by the blinded examining investigator.

MRI End Points

Efficacy end points in OPERA-I and OPERA-II that were evaluated using MRI included the following:

- change in brain volume from week 24 to week 96
- total number of new or newly enlarged hyperintense lesions on T2-weighted scans from baseline to week 96
- total number of new hypointense lesions from baseline to week 96
- total number of new GdE lesions on T1-weighted scans from baseline to week 96.

MRI scans were scheduled for day 1, week 24, week 48, and week 96. For those who withdrew early, an MRI scan was also performed at the visit when the patient withdrew.[31,32] Change in brain volume was assessed after 24 weeks of treatment because of the potential for reduced inflammation following the initiation of treatment. That is, a reduced volume immediately after beginning treatment could result from a reduction in inflammation rather than brain atrophy.[29] MRI scans for efficacy end points were evaluated by a centralized reading centre that was blinded to allocated treatment and conducted in the absence of clinical information regarding the patient.

Multiple Sclerosis Functional Composite

Change from baseline in MSFC score to 96 weeks was a secondary end point of the OPERA-I and OPERA-II trials. The MSFC includes three objective and quantitative continuous scales that assess leg function/ambulation (with a timed 25-foot walk), arm/hand function (with the 9-Hole Peg Test), and cognitive function (with the Paced Auditory Serial Addition Test [PASAT] 3). Scores on component measures are converted to standard scores (z scores), which are averaged to form a single MSFC score. A positive change in the composite z score indicates improvement, and a negative change indicates worsening. A 20% change in scores on timed 25-foot walk trials and the 9-Hole Peg Test, and a 0.5 standard deviation (SD) change on PASAT3 are considered clinically meaningful.[35,36] A minimal clinically important difference (MCID) for the overall MSFC score has not been reported. The MSFC evaluation was conducted by the blinded examining investigator.

Short Form (36) Health Survey Physical Component Score

The Short Form (36) Health Survey (SF-36) is a 36-item generic health status measure. It measures eight general health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Higher scores indicate better health-related quality of life. SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS), which are created by aggregating the eight domains according to a scoring algorithm. The PCS and MCS and eight dimensions are each measured on a scale of 0 to 100, which are T scores (mean of 50 and SD of 10) that have been standardized to the US general population. Thus, a score of 50 on any scale would be at the average or norm of the general US population and a score 10 points lower (i.e., 40) would be one SD below the norm. An increase in score indicates improvement in health status on any scale. In the general use of SF-36, a change of two points in the SF-36 PCS and three points in the SF-36 MCS indicates a clinically meaningful improvement, as determined by the patient.[37] Change from baseline in the SF-36 PCS and SF-36 MCS were secondary and exploratory end points in the OPERA-I and OPERA-II trials, respectively.[38,39]

No Evidence of Disease Activity

No evidence of disease activity (NEDA) by 96 weeks was an exploratory end point of both OPERA-I and OPERA-II. Patients who completed the 96-week treatment period were considered as having evidence of MS disease activity if they had any of the following clinical or imaging indicators reported during the double-blind study period: at least one protocol-defined relapse, a CDP event, or at least one MRI scan demonstrating GdE lesions or new or enlarging lesions on T2-weighted scans. If none of these indicators were reported, the patient was considered to have NEDA. Patients who discontinued treatment early and had at least one clinical or imaging indicator before early discontinuation were considered as having evidence of disease activity. NEDA was defined only for patients with a baseline EDSS score of 2.0 or higher.

Statistical Analysis

All statistical hypotheses for the primary and secondary end points and treatment comparisons were tested at a 5% significance level using a two-sided test. The primary end point (i.e., ARR) was analyzed using a negative binomial model that adjusted for region (US versus non-US), baseline EDSS score (< 4.0 versus ≥ 4.0), and the duration of patient exposure. To adjust for difference in exposure to the study treatments, the duration of

exposure was included in the model as an offset variable. The methods used for statistical analysis of the efficacy end points in OPERA-I and OPERA-II are summarized in Table 10.

Table 10: Statistical Analysis of Efficacy End Points in OPERA-I and OPERA-II

End Point	Model	Adjustment Factors	Sensitivity Analyses
Primary			
Annualized relapse rate	NBR	• Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0) • Patient exposure (offset variable)	• Per-protocol • Safety population • Additional covariates[a] • Poisson model • Multiple imputation (50% relapse) • Imputation (100% relapse)
Secondary			
Time to onset of CDP	Cox regression	• Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0)	• Per-protocol • Additional covariates[a] • Multiple imputation (50% CDP) • Imputation (100% CDP)
CDI for at least 12 weeks	CMH chi-square test	• Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0)	No sensitivity analyses
MSFC	MMRM	• Baseline MSFC • Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0)	
Change in brain volume	MMRM	• Brain volume at week 24 • BL T1 GdE lesion (present or not) • Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0)	
T1 GdE lesions	NBR	• Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0) • BL T1 GdE (present or not) • Number of MRIs (offset variable)	
T2 hyperintense lesions	NBR	• Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0) • BL T2 hyperintense lesion count • Number of MRIs (offset variable)	
T1 hypointense lesions	NBR	• Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0) • BL T1 hypointense lesion count • Number of MRIs (offset variable)	
SF-36 PCS	MMRM	• Baseline SF-36 PCS • Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0)	
Exploratory			
NEDA	CMH chi-square	• Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0)	
SF-36 MCS	MMRM	• Baseline SF-36 MCS • Region (US versus non-US) • BL EDSS score (< 4.0 versus ≥ 4.0)	

BL = baseline; CDI = confirmed disease improvement; CDP = confirmed disability progression; CMH = Cochran–Mantel–Haenszel; EDSS = Kurtzke Expanded Disability Status Scale; GdE = gadolinium-enhancing; MMRM = mixed-effects model repeated measures; MRI = magnetic resonance imaging; MSFC = Multiple Sclerosis Functional Composite; NBR = negative binomial regression; NEDA = no evidence of disease activity; SF-36 MCS = Short Form (36) Health Survey mental component summary; SF-36 PCS = Short Form (36) Health Survey physical component summary.

[a] The additional covariates included: number of relapses within two years prior to screening; baseline GdE lesions (presence or absence); prior MS treatment; and age (< 40 or ≥ 40 years).

Sample Size

The sample sizes for OPERA-I and OPERA-II were based on predicted ARRs of 0.165 (SD 0.60) and 0.33 (SD 0.80) in the ocrelizumab and interferon beta-1a groups, respectively (i.e., 50% relative reduction in ARR).[31,32] A sample size of 400 patients per treatment group was predicted to provide 84% power, assuming a 20% withdrawal rate, and a type I error rate of 0.05. For CDP, the sample size of 400 patients in each treatment group was predicted to provide 80% power to detect a relative reduction of 30% in CDP between ocrelizumab and interferon beta-1a.[31,32]

Analysis Populations

Three analysis populations were used in the evaluation of efficacy and safety end points in the OPERA-I and OPERA-II studies: intention-to-treat (ITT), per-protocol, and safety populations. Details of each analysis population are provided in Table 11.

Table 11: Efficacy and Safety Analysis Populations in OPERA-I and OPERA-II

Population	Description
Intention-to-treat	All randomized patients were included in the ITT population. All efficacy analyses wereperformed using the ITT population.
Per-protocol	The PP population included all patients in the ITT population provided they did not have any major protocol violations that had been deemed to have the potential to affect the efficacy of the study treatment. The PP population was used in sensitivity analyses for ARR and CDP.
Safety	The safety population included all patients who received any study drug. This population was used for all summaries of safety data.

ARR = annualized relapse rate; CDP = confirmed disability progression; ITT = intention-to-treat; PP = per-protocol.

Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Multiple Comparisons

A summary of the statistical testing hierarchy using the OPERA-I and OPERA-II trials is provided in Table 12. The manufacturer reported that the hierarchical order of the secondary end points was based primarily on the clinical importance of the end points. Any end points with similar clinical importance were ordered based on the perceived chance of achieving a statistically significant difference between the treatments.[31,32] The following secondary end points were pre-specified to be analyzed using pooled data from both OPERA-I and OPERA-II: 12-week CDP, 24-week CDP, and 12-week CDI.[31,32] All secondary efficacy end points were tested only in a confirmatory manner, if and only if the secondary end point located immediately above it in the hierarchy was statistically significant at $P < 0.05$.[31,32] However, the manufacturer reported non-confirmatory *P* values for end points analyzed after the statistical testing hierarchy had failed (i.e., changes in brain volume in OPERA-I, and changes in SF-36 PCS and NEDA in both OPERA-I and OPERA-II).[1]

Table 12: Statistical Testing Hierarchy in OPERA-I and OPERA-II

End Point	OPERA-I	OPERA-II	Pooled
Annualized relapse rate	< 0.0001	< 0.0001	NA
Clinical disease progression for 12 weeks (pooled)	N/A	N/A	0.0006
T1 GdE lesions	< 0.0001	< 0.0001	NA
New and/or enlarging T2 hyperintense lesions	< 0.0001	< 0.0001	NA
Clinical disease improvement for 12 weeks (pooled)	NA	NA	0.0194
Clinical disease progression for 24 weeks (pooled)	NA	NA	0.0025
New T1 hypointense lesions	< 0.0001	< 0.0001	NA
Multiple Sclerosis Functional Composite	0.3261	0.0040	NA
Brain volume	0.0042[a]	0.0900	NA
SF-36 PCS	0.2193[a]	0.0404[a]	NA
No evidence of disease activity	< 0.0001[a]	< 0.0001[a]	NA

GdE = gadolinium-enhancing; NA = not applicable; SF-36 PCS = Short Form (36) Health Survey physical component summary.
[a] The *P* values reported in the shaded cells are not statistically significant due to the failure of the statistical testing hierarchy at a higher-order outcome.
Source: Common Technical Document 2.7.3.[1]

Handling of Missing Data

Sensitivity analyses were performed for ARR using two different approaches for handling missing data. A multiple imputation approach was used for patients who discontinued early without a protocol-defined relapse in the 30 days prior to discontinuation. In this analysis, 50% of patients were randomly assigned a relapse event on day of discontinuation, and the other 50% were censored on day of discontinuation. The imputation approach counted all patients who discontinued early without a protocol-defined relapse in the 30 days prior to discontinuation as having had a relapse event on day of discontinuation. Similar sensitivity analyses were conducted for CDP (i.e., modelling early discontinuations as 50% or 100% CDP events on the day of discontinuation).

Patient Disposition

Table 13 provides a summary of patient disposition from the OPERA-I and OPERA-II trials. A total of 1,051 patients were screened for inclusion in OPERA-I, and 821 were randomized.[31] In OPERA-II, a total of 1,045 patients were screened, and 835 patients were randomized.[32] For both studies, the manufacturer cited the failure to meet the inclusion/exclusion criteria or unacceptable laboratory values as the primary reasons for screening failures. In both trials, a greater proportion of IFN-treated patients discontinued treatment prior to completion of the study (17.3% and 23.4% in OPERA-I and OPERA-II, respectively) compared with the ocrelizumab groups (10.7% and 13.7% in OPERA-I and OPERA-II, respectively). Adverse events were the most commonly cited reason for early discontinuation in both treatment groups and were more common with patients treated with interferon beta-1a (6.0% to 6.1%) than with ocrelizumab-treated patients (3.2% to 3.8%). A greater proportion patients treated with interferon beta-1a (2.9% to 3.6%) cited lack of efficacy as the reason for discontinuation compared with those treated with ocrelizumab (1.4% to 2.0%). Deaths were reported for one patient treated with interferon beta-1a in OPERA-I and OPERA-II and one ocrelizumab-treated patient in OPERA-II.[1] The overall proportion of early discontinuations was greater in the OPERA-II trial than in the OPERA-I study (19% versus 14%), primarily as a result of an increase in patients who were lost to follow-up in OPERA-II (i.e., two patients in OPERA-I compared with 16 patients in OPERA-II) and because of patient self-withdrawal (21 patients in OPERA-I and 37 patients in OPERA-II).[1]

Table 13: Patient Disposition

Disposition, n (%)	OPERA-I		OPERA-II	
	IFN	OCR	IFN	OCR
Screened	1,051		1,045	
Randomized	411	410	418	417
Discontinued treatment	71 (17.3)	44 (10.7)	98 (23.4)	57 (13.7)
Adverse event	25 (6.1)	13 (3.2)	25 (6.0)	16 (3.8)
Death	1 (0.2)	0	1 (0.2)	1 (0.2)
Lack of efficacy	12 (2.9)	8 (2.0)	15 (3.6)	6 (1.4)
Lost to follow-up	1 (0.2)	1 (0.2)	10 (2.4)	6 (1.4)
Non-compliance	2 (0.5)	0	1 (0.2)	3 (0.7)
Non-compliance with study drug	3 (0.7)	0	1 (0.2)	1 (0.2)
Other	11 (2.7)	8 (2.0)	16 (3.8)	10 (2.4)
Physician decision	0	1 (0.2)	0	1 (0.2)
Pregnancy	2 (0.5)	3 (0.7)	3 (0.7)	0
Protocol violation	1 (0.2)	2 (0.5)	1 (0.2)	1 (0.2)
Self-withdrawal by patient	13 (3.2)	8 (2.0)	25 (6.0)	12 (2.9)
ITT population	411 (100.0)	410 (100.0)	418 (100.0)	417 (100.0)
Per-protocol population	386 (93.9)	394 (96.1)	396 (94.7)	402 (96.4)
Safety population	409 (99.5)	408 (99.5)	417 (99.8)	417 (100.0)

IFN = interferon; ITT = intention-to-treat; OCR = ocrelizumab.

Source: Common Technical Document 2.7.3[1] and Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Exposure to Study Treatments

Study Treatments

Exposure to the study treatments is summarized in Table 14. In both studies, the mean number of doses was slightly greater in the ocrelizumab treatment groups (3.7 to 3.8 doses) compared with the IFN beta-1a (placebo) treatment group (3.5 to 3.6 doses). A larger proportion of ocrelizumab-treated patients received all four scheduled doses (87.5% to 90.0%) compared with patients treated with interferon beta-1a (76.2% to 84.6%). Similarly, the proportion of patients with at least 96 weeks of exposure was greater in the ocrelizumab groups (84.9% to 88.7%) than with the interferon beta-1a groups (76.2% to 81.4%). Adherence to interferon beta-1a (and matching placebo) was assessed by counting the number of syringes returned. In both studies, the rate of adherence was high, exceeding 90% in all treatment groups.[29]

Table 14: Exposure to Study Treatments

Exposure, n (%) Unless Otherwise Specified		OPERA-I		OPERA-II		Pooled RMS Population	
		IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)	IFN (N = 826)	OCR (N = 825)
Ocrelizumab							
Duration (weeks)	0 to 23	24 (5.9)	16 (3.9)	26 (6.3)	21 (5.0)	Not reported	
	24 to 47	18 (4.4)	7 (1.7)	37 (8.9)	11 (2.6)		
	48 to 71	15 (3.7)	12 (2.9)	22 (5.3)	10 (2.4)		
	72 to 95	19 (4.6)	11 (2.7)	14 (3.4)	21 (5.0)		
	96 to 110	333 (81.4)	362 (88.7)	317 (76.2)	354 (84.9)		
Number of IV doses	1	34 (8.3)	20 (4.9)	40 (9.6)	26 (6.2)	74 (9.0)	46 (5.6)
	2	15 (3.7)	8 (2.0)	34 (8.2)	12 (2.9)	49 (5.9)	20 (2.4)
	3	14 (3.4)	13 (3.2)	25 (6.0)	14 (3.4)	39 (4.7)	27 (3.3)
	4	346 (84.6)	367 (90.0)	317 (76.2)	365 (87.5)	663 (80.4)	732 (88.7)
	Mean (SD)	3.6 (0.9)	3.8 (0.7)	3.5 (1.0)	3.7 (0.8)	3.6 (1.0)	3.8 (0.8)
	Median	4.0	4.0	4.0	4.0	4.0	4.0
Interferon beta-1a							
Dose intensity (%)	Mean (SD)	92.5 (15.2)	94.9 (9.9)	92.3 (38.3)	94.2 (11.6)	Not reported	
	< 80%	50 (12.3)	27 (6.7)	70 (17.1)	37 (9.0)		
	≥ 80%	357 (87.7)	376 (93.3)	340 (82.9)	373 (91.0)		

IFN = interferon; IV = intravenous; OCR = ocrelizumab; SD = standard deviation.

Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Concomitant Medications

Table 15 provides a summary of the concomitant medications used in the OPERA-I and OPERA-II trials by at least 2% of patients in at least one of the treatment groups. The proportion of patients who used at least one concomitant medication was similar in the ocrelizumab (71.6% and 73.6%) and interferon beta-1a groups (70.9% and 72.2%). The concomitant medications were generally balanced across the groups in the individual studies, with the following exceptions in the OPERA-I trial: nonsteroidal anti-inflammatory drug use was greater in the interferon group (17.1% versus 10.5%), and anticonvulsant use was greater in the ocrelizumab group (12.7% versus 6.6%).

The protocols for the OPERA-I and OPERA-II trials specified a standardized treatment regimen for the treatment of a relapse that included IV infusion of 1,000 mg of methylprednisolone per day for up to five consecutive days. At the discretion of the investigator, corticosteroids could be either stopped abruptly or tapered over a maximum of 10 days (tapering regimens were not specified). Concomitant use of corticosteroids was reported more frequently in the interferon beta-1a groups (40.3% to 40.8%) compared with the ocrelizumab groups (34.1% to 34.3%). Methylprednisolone was the most commonly used corticosteroid (29.5% to 30.6% in the interferon beta-1a groups and 21.6% to 22.8% in the ocrelizumab groups), followed by prednisone (5.6% to 5.8% in the interferon beta-1a groups and 4.3% to 6.1% in the ocrelizumab groups).[31,32] This use of concomitant medications did not include the protocol-mandated pre-treatment with corticosteroids to manage infusion-related reactions. Details regarding concomitant use of corticosteroids are provided in Table 25.

Table 15: Concomitant Medications Used by 2% or More in at Least One Treatment Group

Class of Medication, n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
At least one concomitant medication	290 (70.9)	292 (71.6)	301 (72.2)	307 (73.6)
Vitamins and minerals	123 (30.1)	112 (27.5)	101 (24.2)	118 (28.3)
Contraceptives	72 (17.6)	74 (18.1)	65 (15.6)	65 (15.6)
NSAIDs	70 (17.1)	43 (10.5)	63 (15.1)	73 (17.5)
SSRIs	50 (12.2)	49 (12.0)	53 (12.7)	58 (13.9)
Anticonvulsants	27 (6.6)	52 (12.7)	49 (11.8)	44 (10.6)
Supplements	40 (9.8)	25 (6.1)	41 (9.8)	47 (11.3)
Analgesics	34 (8.3)	28 (6.9)	45 (10.8)	43 (10.3)
Antihistamines	29 (7.1)	33 (8.1)	28 (6.7)	28 (6.7)
Benzodiazepines	26 (6.4)	32 (7.8)	38 (9.1)	45 (10.8)
Muscle relaxants	25 (6.1)	29 (7.1)	42 (10.1)	34 (8.2)
Sex hormones	24 (5.9)	24 (5.9)	27 (6.5)	20 (4.8)
Proton pump inhibitors	26 (6.4)	20 (4.9)	13 (3.1)	26 (6.2)
Thyroid hormones	19 (4.6)	21 (5.1)	15 (3.6)	21 (5.0)
Antidepressants	16 (3.9)	13 (3.2)	22 (5.3)	16 (3.8)
Beta-adrenoceptor blocking drugs	9 (2.2)	18 (4.4)	13 (3.1)	16 (3.8)
Dopaminergic drugs	13 (3.2)	14 (3.4)	14 (3.4)	10 (2.4)
Anorexiants and CNS stimulants	16 (3.9)	10 (2.5)	20 (4.8)	14 (3.4)
Antispasmodics and anticholinergics	18 (4.4)	8 (2.0)	11 (2.6)	15 (3.6)
Sedatives and hypnotics	14 (3.4)	12 (2.9)	21 (5.0)	13 (3.1)
ACE inhibitors	10 (2.4)	11 (2.7)	7 (1.7)	18 (4.3)
Calcium compounds and regulators	9 (2.2)	12 (2.9)	2 (0.5)	11 (2.6)
Salicylates	12 (2.9)	7 (1.7)	10 (2.4)	18 (4.3)
Statins	9 (2.2)	9 (2.2)	13 (3.1)	12 (2.9)
Botanicals	8 (2.0)	9 (2.2)	21 (5.0)	16 (3.8)
Peripheral/cerebral vascular drugs	6 (1.5)	11 (2.7)	10 (2.4)	13 (3.1)
5-HT1-receptor agonists	9 (2.2)	7 (1.7)	6 (1.4)	12 (2.9)
Tricyclic antidepressants	8 (2.0)	7 (1.7)	11 (2.6)	17 (4.1)
Analgesic/other drug combinations	5 (1.2)	9 (2.2)	8 (1.9)	3 (0.7)
Opioid analgesics	9 (2.2)	5 (1.2)	15 (3.6)	18 (4.3)
Anti-anemic drugs	5 (1.2)	8 (2.0)	8 (1.9)	9 (2.2)
Calcium channel blocking drugs	8 (2.0)	4 (1.0)	8 (1.9)	11 (2.6)
Bronchodilators and anti-asthmatics	6 (1.5)	7 (1.7)	19 (4.6)	15 (3.6)
Corticosteroids	7 (1.7)	5 (1.2)	17 (4.1)	14 (3.4)
Thiazide and related diuretics	6 (1.5)	4 (1.0)	7 (1.7)	9 (2.2)
Angiotensin-II receptor antagonists	4 (1.0)	3 (0.7)	9 (2.2)	4 (1.0)

5-HT1 = serotonin; ACE = angiotensin-converting enzyme; CNS = central nervous system; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin re-uptake inhibitor.

Critical Appraisal

Internal Validity

Randomization in the OPERA-I and OPERA-II trials was conducted using appropriate methods with adequate measures to conceal treatment allocation (i.e., independent interactive voice/web response system). The randomization list was not available to the study personnel. Randomization was stratified by region (US or non-US) and baseline EDSS score (< 4.0 or ≥ 4.0). Key baseline and demographic characteristics were generally balanced between the ocrelizumab and interferon groups in both studies.[29] The eligibility criteria for OPERA-I and OPERA-II are generally similar to those used in the clinical studies for the other drugs approved for the treatment of relapsing MS, based on EDSS scores, age range, and diagnostic criteria. FDA reviewers also noted that the criteria used in the ocrelizumab trials were similar to those used in previous pivotal studies.[29]

The study treatments in both OPERA-I and OPERA-II were administered in a double-blind manner. Since ocrelizumab and interferon beta-1a require a different route of administration (i.e., IV and SC, respectively) a double-dummy design was used to preserve blinding. The matching placebo injections were identical to the active treatments. Differences in the adverse event profiles related to the administration of the study drugs could have allowed some patients and investigators to infer which active treatment had been administered. For example, injection-site erythema was more commonly reported in the interferon beta-1a groups (12.7% and 18.1%) compared with the ocrelizumab groups (0% to 0.2%), and infusion-related reactions were more commonly reported in the ocrelizumab groups (30.9% and 37.6%) compared with the interferon beta-1a groups (7.3% and 12.0%). Although EDSS was evaluated by a blinded examining investigator who was not involved in the medical management of patients and who did not have access to the patients' data, reviewers for the FDA noted that the most important decisions made to determine whether a relapse had occurred involved the patient and treating physician.[29] It is unclear whether this may have influenced the results of the study or whether any such bias would be in favour or against ocrelizumab. MRI scans for efficacy end points were evaluated by a centralized reading centre that was blinded to allocated treatment.

The number of enrolled patients who completed the studies was consistent with the sample-size calculations reported by the manufacturer. The disposition of patients who were screened and enrolled in OPERA-I and OPERA-II was appropriately reported in the clinical study reports.[31,32] In both trials, the rate of withdrawal was disproportionate, with more patients discontinuing in the interferon beta-1a groups (17.3% and 23.4%) compared with the ocrelizumab groups (10.7% and 13.7%). The FDA noted that this difference between the treatment groups may indicate that the rate of withdrawal was influenced by unblinding or post-randomization events.[29]

It was reported that all efficacy end points were analyzed using the ITT population, which consisted of all randomized patients (Table 13).[29,31,32] However, as shown in Table 23, the evaluation of the MRI end points, MSFC score, and the SF-36 were conducted with a subset of randomized patients. The rationale for reporting that these analyses were conducted in the ITT population is unclear, and the impact of excluding certain patients was not investigated in the study. Numerous pre-specified sensitivity analyses were conducted to examine the robustness of the primary end point evaluation (Table 26). Adherence with the study treatments was greater than 90% in both studies.[29] A hierarchical testing procedure was used to control the overall type I error rate at 0.05 for the primary and

secondary end points in OPERA-I and OPERA-II. However, the manufacturer reported non-confirmatory *P* values for end points analyzed after the statistical testing hierarchy had failed (i.e., changes in brain volume in OPERA-I, and changes in SF-36 PCS and NEDA in both OPERA-I and OPERA-II).[1] No formal statistical conclusions can be made for these outcomes.[40] Statistical tests for the pooled analyses were conducted without adjustment for multiple comparisons, with the exception of CDP for 12 weeks, CDP for 24 weeks, and CDI for 12 weeks.

Using the data collected by the site investigators, the adjudication of protocol-defined relapses was performed by the manufacturer based on the pre-specified relapse criteria. An independent evaluation committee was not used to confirm relapse events, as the adjudication was performed using a computer algorithm that evaluated the data provided in the electronic case report form. Reviewers for the FDA raised no objections to this approach and noted that this methodology relied less on clinical judgment than the methods used in previous trials of drugs to treat relapsing MS.[29]

Any patients with previous treatment with a B cell–targeted therapy (e.g., rituximab or ocrelizumab) were excluded from the study; however, patients could have been previously treated with an interferon product, with prior use reported for interferon beta-1a SC (7.6% and 8.4%), interferon beta-1a IM (5.2% and 6.1%), and interferon beta-1b SC (6.5% and 5.0%).[1] Patients with prior exposure to interferon beta-1a may have been less likely to demonstrate a response to interferon beta-1a. With respect to adverse events, any patients who had demonstrated a previous suboptimal response to interferon beta-1a or ceased treatment with interferon beta-1a were excluded from the study. This may have resulted in a larger population of patients who are likely to tolerate interferon beta-1a; however, this level of detail was not reported for the reasons for screening failure. It is also possible that patients previously treated with an interferon product could have inferred their allocated study treatment based on the presence or absence of familiar adverse events.

External Validity

The majority of study participants were female, which is consistent with the population of patients with relapsing MS. Diagnosis of MS was based on the 2010 revised McDonald criteria, which is consistent with Canadian clinical practice and guidance from regulatory authorities.[41] The clinical expert consulted by CADTH suggested the patients enrolled in the pivotal trials were reasonably reflective of patients encountered in routine Canadian practice. Patients were required to have an EDSS score of 0 to 5.5 to be eligible for the OPERA-I or OPERA-II trials. This is consistent with other clinical trials conducted for MS treatments; however, it excludes patients with more severe disability, who could be eligible to receive ocrelizumab in clinical practice. The efficacy and safety of ocrelizumab in such patients is uncertain. The majority of patients in both trials (73%) had had no exposure to any disease-modifying MS treatments within at least two years of their screening visit. The clinical expert consulted by CADTH suggested that the place in therapy for ocrelizumab is likely as a second-line treatment after the first drug fails to adequately control the MS. Patients who had experienced a failure of initial therapy represented a minority of participants in the OPERA-I and OPERA-II trials, which is similar to the majority of clinical trials conducted in MS patients (Table 35).

The outcomes in the OPERA-I and OPERA-II trials included clinical end points (e.g., relapse), MRI end points (e.g., changes in lesions on T1- and T2-weighted MRI scans), and patient-reported end points (e.g., SF-36 PCS and SF-36 MCS). The primary and secondary end points are in accordance with guidance from the European Medicines

Agency (EMA) on the design of trials for relapsing MS treatments.[41] The clinical expert indicated that the definition for relapse was appropriate and reflective of clinical practice. The clinical expert also noted that the CDP end points studied in the pivotal trials are typically used only in clinical trials, as disability progression is evaluated over a much longer period in Canadian clinical practice.

Interferon beta-1a is considered an appropriate comparator and is aligned with guidance from the EMA, which states that a superiority trial versus a first-line DMT, such as an interferon beta, is an appropriate trial design.[41] The dosage of interferon beta-1a used in the OPERA-I and OPERA-II is consistent with recommendations in the Canadian product monograph (i.e., 44 mcg three times per week or 22 mcg three times per week if a dose reduction is required because of intolerance).[24] Similarly, ocrelizumab was administered in accordance with recommendations in the product monograph (i.e., 300 mg on day 1, 300 mg on day 15, and 600 mg once every six months).[42] The clinical expert consulted by CADTH indicated that the dosage of interferon beta-1a was consistent with Canadian practice and the dosage of ocrelizumab is likely reflective of how this drug will be used in Canada. The recommendations in the product monograph for pre-medication and dosage adjustment (i.e., slowing, interrupting, or stopping the infusion) for the management of infusion-related reactions are also consistent with the protocols used in the OPERA-I and OPERA-II studies.[17,31,32]

Patients enrolled in the OPERA-I and OPERA-II trials were required to receive both IV infusions and SC injections with the study drugs or matching placebos.[31,32] This double-dummy design is required to preserve blinding; however, the increased treatment burden for patients is not reflective of routine clinical practice, in which patients would receive either the SC injection or the IV infusion, not both. The need for both SC and IV administration could lead to an overestimation of harms related to the administration of both treatments and an increase in exposure to concomitant therapies. For example, patients in both groups received IV corticosteroid pre-medication before each ocrelizumab/placebo infusion. Furthermore, the need to administer both treatments does not reflect the relatively infrequent dosage regimen for ocrelizumab (i.e., once every six months).

In accordance with guidance from the EMA,[41] the OPERA-I and OPERA-II trials used standardized protocols for the use of corticosteroids in the management of relapse.[31,32] The clinical expert consulted by CADTH indicated that these protocols were similar to those used in Canadian clinical practice; however, not every relapse is treated in Canada. Relapses are typically treated only if they cause functional impairment, and most Canadian MS treatment centres use oral prednisone (1,250 mg) and not the IV methylprednisolone (1,000 mg) that was used in the clinical trials.

As is common in clinical trials, the study participants had extensive contact with health professionals, including 10 scheduled assessment visits and telephone interviews every four weeks.[31,32] This is not reflective of routine clinical practice in Canada, where patient follow-up is less frequent. The clinical expert consulted by CADTH indicated that patients with relapsing MS are typically seen once every six to 12 months.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported subsequently (Section 2.2, Table 4).

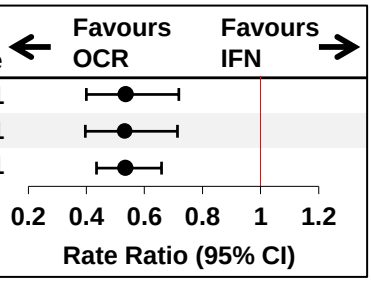
Relapse

Annualized Relapse Rate

In both studies, treatment with ocrelizumab was associated with a statistically significant reduction in ARR compared with interferon beta-1a at 96 weeks ($P < 0.001$ for both). As shown in Figure 3, the rate ratios for ARR were 0.536 (95% confidence interval [CI], 0.400 to 0.719), 0.532 (95% CI, 0.397 to 0.714), and 0.535 (95% CI, 0.435 to 0.659) in OPERA-I, OPERA-II, and the pooled analysis, respectively.[1] The risk reduction with ocrelizumab was 46% in OPERA-I and 47% in OPERA-II and the pooled analysis.[1] The ARRs for the ocrelizumab groups were 0.156 (95% CI, 0.122 to 0.200) in OPERA-I, 0.155 (95% CI, 0.121 to 0.198) in OPERA-II, and 0.156 (95% CI, 0.131 to 0.186) in the pooled analysis. The adjusted ARRs for the interferon beta-1a groups were 0.292 (95% CI, 0.235 to 0.361) in OPERA-I, 0.290 (95% CI, 0.234 to 0.361) in OPERA-II, and 0.291 (95% CI, 0.250 to 0.339) in the pooled analysis. Results for the sensitivity analyses for the primary end point were consistent with the primary analyses of OPERA-I and OPERA-II (Table 26).

Figure 3: Summary of Results for Annualized Relapse Rate

Study	ARR (95% CI) IFN	ARR (95% CI) OCR	OCR vs. IFN Rate Ratio (95% CI)	P value
OPERA-I	0.292 (0.235, 0.361)	0.156 (0.122, 0.200)	0.536 (0.400, 0.719)	<0.0001
OPERA-II	0.290 (0.234, 0.361)	0.155 (0.121, 0.198)	0.532 (0.397, 0.714)	<0.0001
Pooled	0.291 (0.250, 0.339)	0.156 (0.131, 0.186)	0.535 (0.435, 0.659)	<0.0001

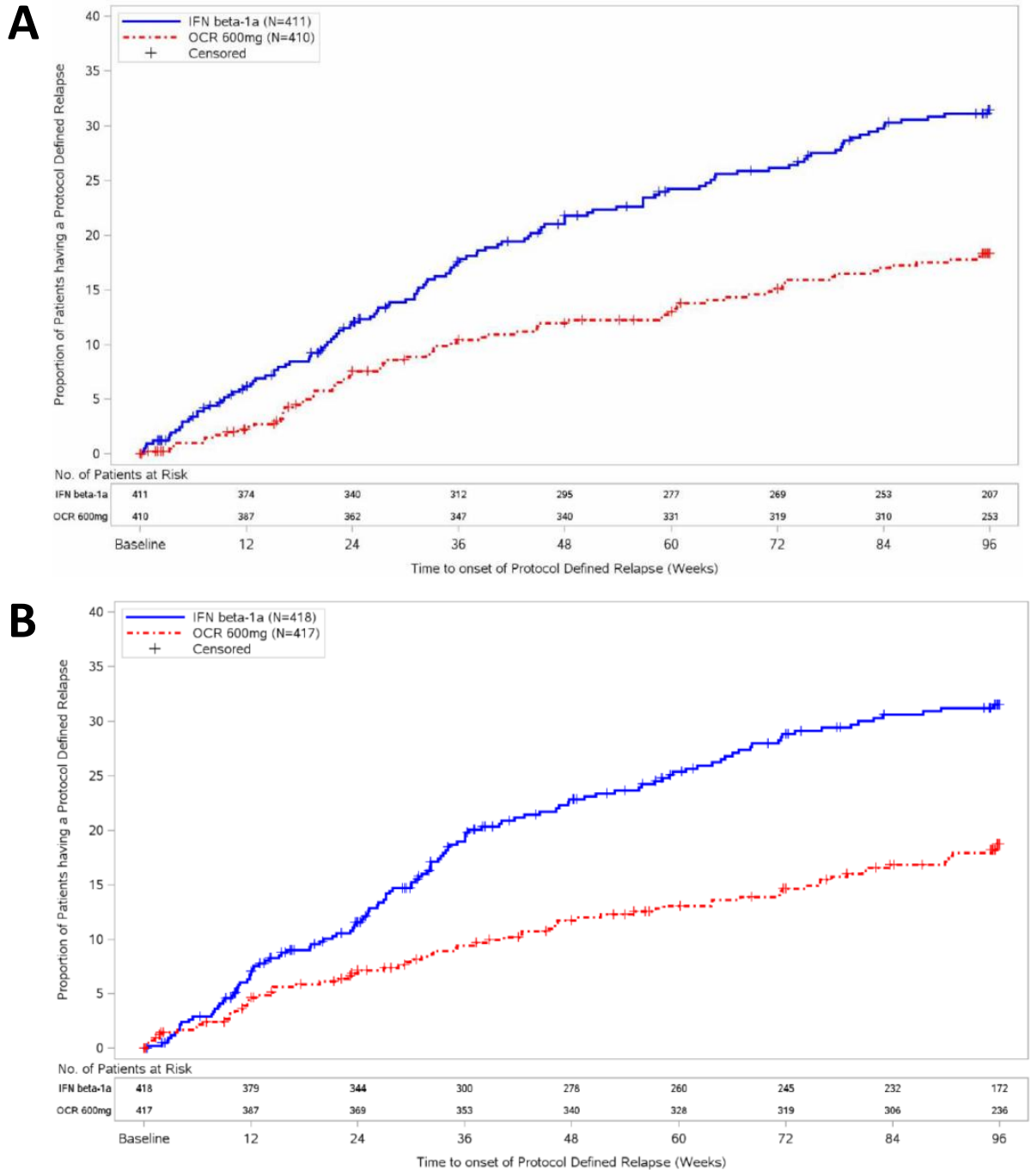


ARR = adjusted annualized relapse rate; CI = confidence interval; IFN = interferon beta-1a; OCR = ocrelizumab.

Time to First Relapse

The manufacturer conducted a pre-planned exploratory analysis for the proportion of patients who remained free of protocol-defined relapses during the 96-week study period. A greater proportion of ocrelizumab-treated patients remained free of relapses compared with the interferon beta-1a groups in both OPERA-I (80.4% versus 66.7%; relative risk [RR] 1.20 [95% CI, 1.10 to 1.31], $P < 0.0001$) and OPERA-II (78.9% versus 64.3%; RR 1.23 [95% CI, 1.12 to 1.35]; $P < 0.0001$). Kaplan–Meier curves for time to first protocol-defined relapse are shown in Figure 4.

Figure 4: Kaplan–Meier Curves for Time to First Relapse in OPERA-I (A) and OPERA-II (B)



IFN = interferon beta-1a; OCR = ocrelizumab.

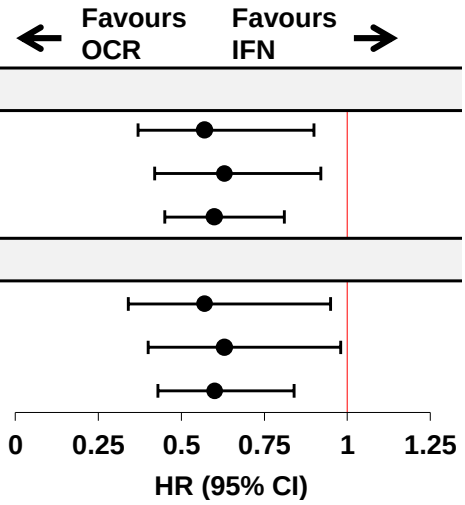
Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Confirmed Disease Progression

Figure 5 summarizes the results for time to 12-week CDP and 24-week CDP. In accordance with the pre-specified statistical testing hierarchy, both CDP at 12 weeks and 24 weeks were tested using a pooled analysis of the results from OPERA-I and OPERA-II. The pooled analysis demonstrated that ocrelizumab was associated with a statistically significant reduction in the time to CDP for both 12 weeks and 24 weeks (hazard ratio [HR] 0.60 [95% CI, 0.45 to 0.81] and HR 0.60 [95% CI, 0.43 to 0.84], respectively). The individual trial results favoured ocrelizumab over interferon beta-1a for CDP at 12 weeks and 24 weeks in both OPERA-I (HR 0.57 [95% CI, 0.37 to 0.90] and HR 0.57 [95% CI, 0.34 to 0.95], respectively) and OPERA-II (HR 0.63 [95% CI, 0.42 to 0.92] and HR 0.63 [95% CI, 0.40 to 0.98], respectively); however, these tests were outside of the statistical hierarchy and considered non-confirmatory (i.e., exploratory).[1]

Figure 5: Summary of Results for Confirmed Disease Progression

Study	Patients with CDP, n (%) IFN	Patients with CDP, n (%) OCR	OCR vs. IFN HR (95% CI)	P value
12-week CDP				
OPERA-I	50 (12.2%)	31 (7.6%)	0.57 (0.37 to 0.90)	0.0139[a]
OPERA-II	63 (15.1%)	44 (10.6%)	0.63 (0.42 to 0.92)	0.0169[a]
Pooled	113 (13.6%)	75 (9.1%)	0.60 (0.45 to 0.81)	0.0006
24-week CDP				
OPERA-I	39 (9.5%)	24 (5.9%)	0.57 (0.34 to 0.95)	0.0278[a]
OPERA-II	48 (11.5%)	33 (7.9%)	0.63 (0.40 to 0.98)	0.0370[a]
Pooled	87 (10.5%)	57 (6.9%)	0.60 (0.43 to 0.84)	0.0025

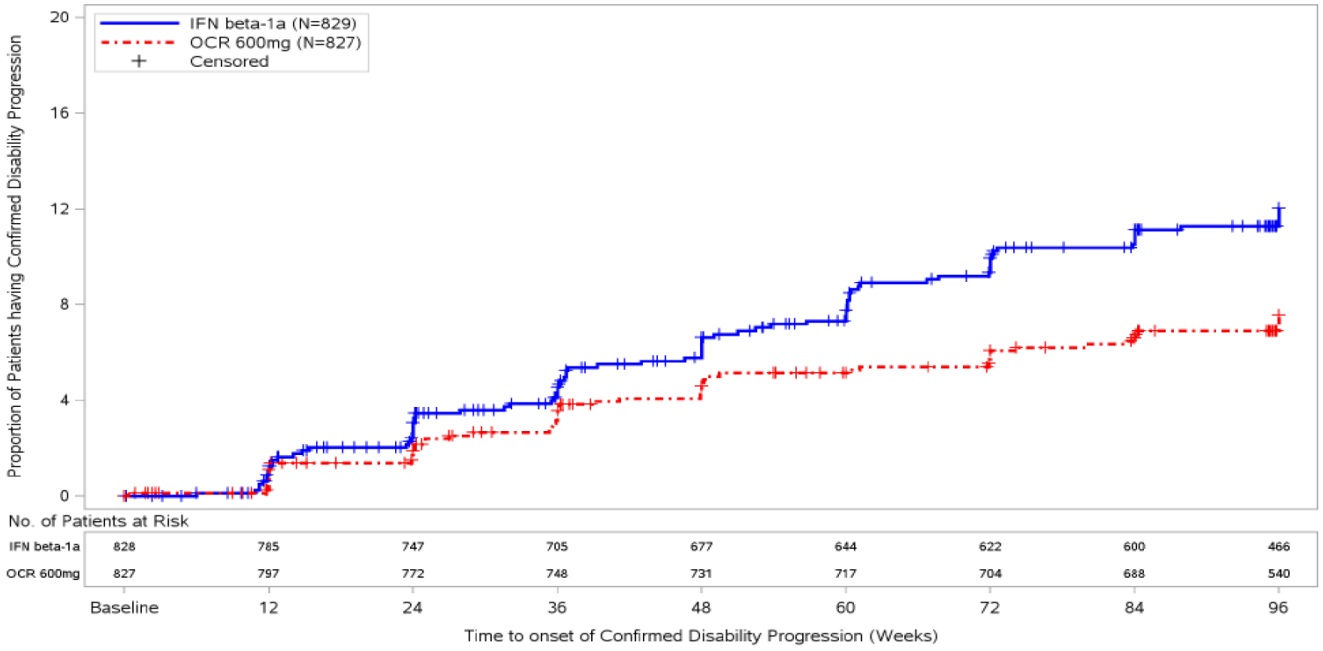


CDP = confirmed disease progression; CI = confidence interval; HR = hazard ratio; IFN = interferon beta-1a; OCR = ocrelizumab.

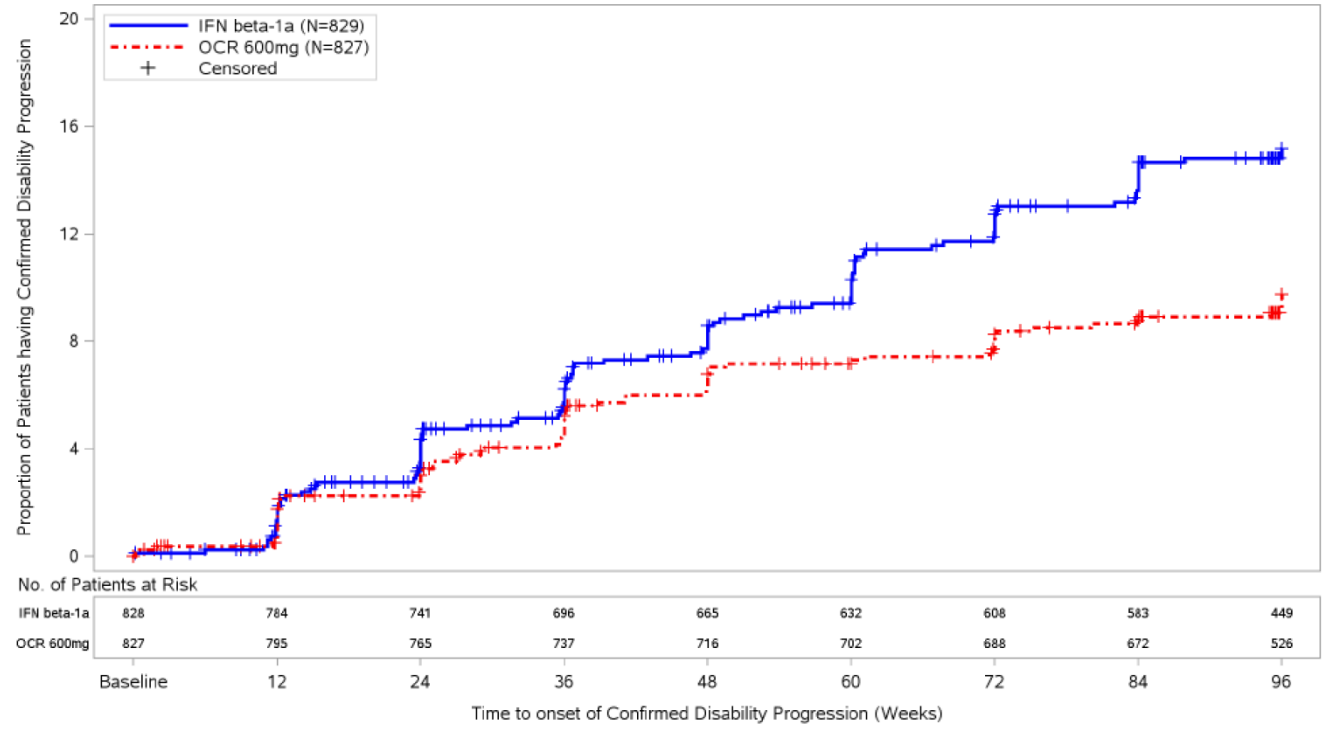
[a] These analyses were conducted outside of the statistical testing hierarchy and are non-confirmatory.

Figure 6: Time to Onset of CDP for at Least 12 Weeks (A) and 24 Weeks (B)

A



B



IFN = interferon beta 1a; OCR = ocrelizumab.

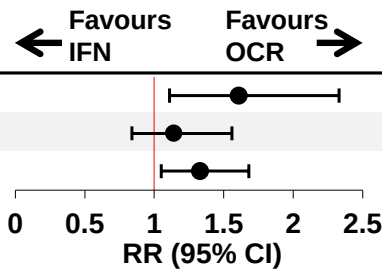
Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Confirmed Disease Improvement

Figure 7 summarizes the results for CDI for at least 12 weeks. In accordance with the pre-specified statistical testing hierarchy, CDI for at least 12 weeks was tested using a pooled analysis of the results from OPERA-I and OPERA-II. The pooled analysis demonstrated that ocrelizumab was associated with a statistically significant increase in the proportion of patients with CDI (RR 1.33 [95% CI, 1.05 to 1.68]; *P* = 0.0194). The individual trial results favoured ocrelizumab over interferon beta-1a for CDI in the OPERA-I trial (RR 1.61 [95% CI, 1.11 to 2.33]; *P* = 0.0106]), but not in the OPERA-II trial (RR 1.14 [95% CI, 0.84 to 1.56]; *P* = 0.4019).[1] These tests were outside of the statistical hierarchy and considered non-confirmatory (i.e., exploratory).

Figure 7: Summary of Results for Confirmed Disease Improvement

Study	Patients with CDI, n (%) IFN	Patients with CDI, n (%) OCR	OCR vs. IFN RR (95% CI)	P value
OPERA-I	38 (12.42)	62 (20.00)	1.61 (1.11 to 2.33)	0.0106[a]
OPERA-II	58 (18.83)	68 (21.38)	1.14 (0.84 to 1.56)	0.4019[a]
Pooled	96 (15.64)	130 (20.70)	1.33 (1.05 to 1.68)	0.0194



CDI = confirmed disease improvement; CI = confidence interval; IFN = interferon beta-1a; OCR = ocrelizumab; RR = relative risk.

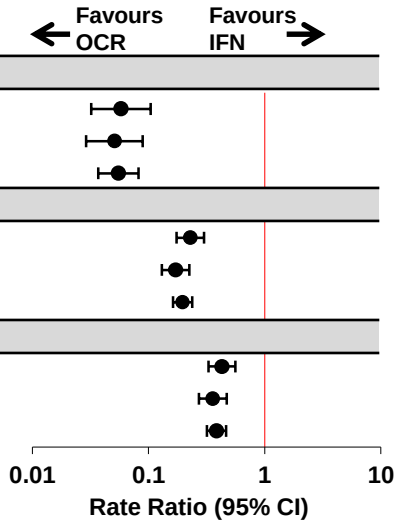
[a] These analyses were conducted outside of the statistical testing hierarchy and are non-confirmatory.

Change in Lesions on T1- and T2-Weighted Imaging

Figure 8 summarizes the results for the new or newly enlarged hyperintense lesions on T2-weighted MRI scans by week 96, new hypointense lesions by week 96, and new GdE lesions on T1-weighted scans. Ocrelizumab was associated with a statistically significant reduction in the rate of all three lesion types in both the individual trials and the pooled analysis.

Figure 8: Summary of Results for T1 and T2 Lesions

Study	Rate (95% CI) IFN	Rate (95% CI) OCR	Rate Ratio (95% CI)	P value
New T1 gadolinium-enhancing lesions				
OPERA-I	0.286 (0.200, 0.409)	0.016 (0.009, 0.030)	0.058 (0.032, 0.104)	<0.0001
OPERA-II	0.416 (0.309, 0.561)	0.021 (0.012, 0.036)	0.051 (0.029, 0.089)	<0.0001
Pooled	0.356 (0.283, 0.447)	0.020 (0.013, 0.029)	0.055 (0.037, 0.082)	<0.001[a]
New/enlarging T2 hyperintense lesions				
OPERA-I	1.413 (1.123, 1.777)	0.323 (0.256, 0.407)	0.229 (0.174, 0.300)	<0.0001
OPERA-II	1.904 (1.536, 2.359)	0.325 (0.259, 0.409)	0.171 (0.130, 0.225)	<0.0001
Pooled	1.684 (1.439, 1.971)	0.331 (0.281, 0.389)	0.196 (0.162, 0.238)	<0.001[a]
New T1 hypointense lesions				
OPERA-I	0.982 (0.780, 1.237)	0.420 (0.337, 0.524)	0.428 (0.328, 0.557)	<0.0001
OPERA-II	1.255 (1.003, 1.571)	0.449 (0.359, 0.560)	0.357 (0.272, 0.470)	<0.0001
Pooled	1.140 (0.971, 1.339)	0.437 (0.374, 0.512)	0.384 (0.317, 0.464)	<0.001[a]



CI = confidence interval; IFN = interferon beta-1a; OCR = ocrelizumab.

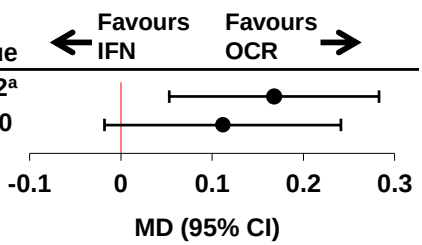
[a] These analyses were conducted outside of the statistical testing hierarchy and are non-confirmatory.

Brain Volume

Figure 9 provides a summary of the results for change in brain volume from week 24 to week 96. There was no statistically significant difference between ocrelizumab and interferon beta-1a for change in brain volume from week 24 to week 96 in the OPERA-II trial (mean difference [MD] 0.112 [95%CI, –0.018 to 0.241]; *P* = 0.0900). Failure to demonstrate a statistically significant difference for change in brain volume stopped the statistical testing hierarchy at this end point in OPERA-II (Table 12). The statistical testing hierarchy in OPERA-I had stopped at a higher-order end point; therefore, the difference favouring ocrelizumab over interferon beta-1a that was reported by the manufacturer is not considered statistically significant (MD 0.168 [95% CI, 0.053 to 0.283]; *P* = 0.0042).

Figure 9: Summary of Results for Change in Brain Volume

Study	Mean Change (SE) IFN	Mean Change (SE) OCR	OCR vs. IFN MD (95% CI)	P value
OPERA-I	-0.741% (0.046)	-0.572% (0.044)	0.168% (0.053 to 0.283)	0.0042[a]
OPERA-II	-0.750% (0.051)	-0.638% (0.049)	0.112% (-0.018 to 0.241)	0.0900



CI = confidence interval; MD = mean difference; IFN = interferon beta-1a; OCR = ocrelizumab; SE = standard error.

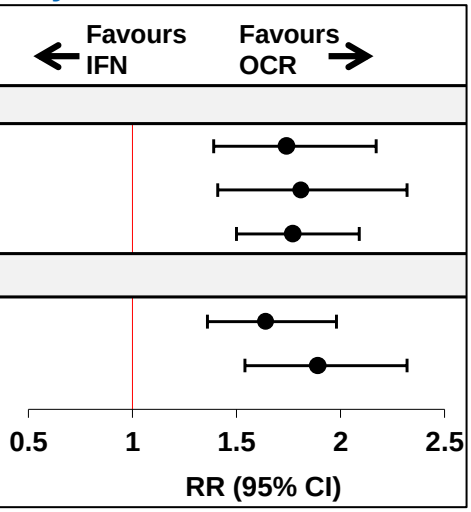
[a] This analysis was conducted outside of the statistical testing hierarchy and is non-confirmatory.

No Evidence of Disease Activity

Results for the proportion of patients with NEDA are summarized in Figure 10. The statistical testing hierarchy had been stopped before the evaluation of NEDA in both OPERA-I and OPERA-II. In both studies, a greater proportion of ocrelizumab-treated patients achieved NEDA at week 96 (43.9% to 47.4%) compared with those treated with interferon beta-1a (24.1% to 27.1%). The relative risks for NEDA were 1.74 (95% CI, 1.39 to 2.17) in OPERA-I and 1.81 (95% CI, 1.41 to 2.32) in OPERA-II. A post hoc sensitivity analysis conducted by the manufacturer that included all patients in the ITT population demonstrated results consistent with those of the analysis conducted in patients with baseline EDSS ≥ 2.0 (RR 1.64 [95% CI, 1.36 to 1.98] and 1.89 [95% CI, 1.54 to 2.32] in OPERA-I and OPERA-II, respectively).

Figure 10: Summary of Results for No Evidence of Disease Activity

Study	Patients with NEDA (n [%]) IFN	Patients with NEDA (n [%]) OCR	OCR vs. IFN RR (95% CI)	P value
Patients with baseline EDSS ≥2.0				
OPERA-I	79 (27.1)	137 (47.4)	1.74 (1.39, 2.17)	<0.0001[a]
OPERA-II	65 (24.1)	127 (43.9)	1.81 (1.41, 2.32)	<0.0001[a]
Pooled	144 (25.7)	264 (45.7)	1.77 (1.50, 2.09)	<0.0001
All patients				
OPERA-I	112 (29.2)	183 (47.9)	1.64 (1.36, 1.98)	<0.0001[b]
OPERA-II	94 (25.1)	180 (47.5)	1.89 (1.54, 2.32)	<0.0001[b]



CI = confidence interval; EDSS = Kurtzke Expanded Disability Status Scale; IFN = interferon beta-1a; NEDA = no evidence of disease activity; OCR = ocrelizumab; RR = relative risk.

[a] These *P* values are non-confirmatory due to the failure of the statistical testing hierarchy at a higher-order outcome.

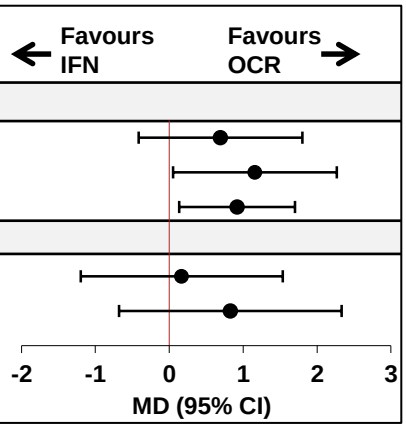
[b] This was a post hoc analysis; therefore, the *P* values are non-confirmatory.

Short Form (36) Health Survey Physical Component Summary

Results for change from baseline in the SF-36 PCS are summarized in Figure 11. In both OPERA-I and OPERA-II, the statistical testing hierarchy had been stopped before the evaluation of change from baseline in SF-36 PCS. In both studies, mean score for patients in the interferon beta-1a group showed a decrease from baseline (–0.833 to –0.657), whereas the mean scores were relatively stable in the ocrelizumab groups (0.036 to 0.326). As shown in Figure 11, the pooled analysis of the two studies suggests a greater improvement in ocrelizumab-treated patients compared with those treated with interferon beta-1a (MD 0.918 [95% CI, 0.135 to 1.702]; *P* = 0.02).

Figure 11: Summary of Results for SF-36 PCS and SF-36 MCS

Study	Mean Change (SE) IFN	Mean Change (SE) OCR	OCR vs. IFN MD (95% CI)	P value
SF-36 PCS				
OPERA-I	-0.657 (0.475)	0.036 (0.456)	0.693 (-0.414 to 1.800)	0.2193[a]
OPERA-II	-0.833 (0.472)	0.326 (0.444)	1.159 (0.051 to 2.268)	0.0404[a]
Pooled	-0.767 (0.335)	0.152 (0.319)	0.918 (0.135 to 1.702)	0.02[b]
SF-36 MCS				
OPERA-I	1.424 (0.565)	1.592 (0.540)	0.168 (-1.199, 1.534)	0.8095[b]
OPERA-II	0.961 (0.628)	1.788 (0.588)	0.827 (-0.679, 2.333)	0.2812[b]



CI = confidence interval; IFN = interferon beta-1a; MD = mean difference; OCR = ocrelizumab; SE = standard error; SF-36 MCS = Short Form (36) Health Survey mental component summary; SF-36 PCS = Short Form (36) Health Survey physical component summary.

[a] These *P* values are non-confirmatory due to the failure of the statistical testing hierarchy at a higher-order outcome.

[b] These analyses were conducted outside of the statistical testing hierarchy and are non-confirmatory.

Short Form (36) Health Survey Mental Component Summary

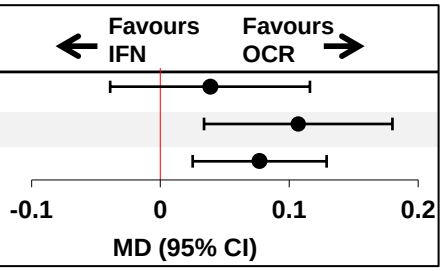
In both OPERA-I and OPERA-II, the SF-36 MCS was an exploratory end point. Neither study demonstrated a statistically significant difference between ocrelizumab and interferon beta-1a for change from baseline in the SF-36 MCS (0.168 [95% CI, −1.199 to 1.534] and 0.827 [95% CI, −0.558 to 2.212] in OPERA-I and OPERA-II, respectively).

Multiple Sclerosis Functional Composite

There was no statistically significant difference between ocrelizumab and interferon beta-1a for change from baseline in the MSFC score in OPERA-I (MD 0.039 [95% CI, –0.039 to 0.116]; *P* = 0.3261) (Figure 12). Failure to demonstrate a statistically significant difference for this end point stopped the statistical testing hierarchy at this end point in OPERA-I. In contrast, statistically significant differences favouring ocrelizumab over interferon beta-1a were observed in the OPERA-II trial (MD 0.107 [95% CI, 0.034 to 0.180]; *P* = 0.0040) and in the pooled analysis (MD 0.077 [95% CI, 0.025 to 0.129]; *P* = 0.004).

Figure 12: Results for Multiple Sclerosis Functional Composite

Study	Mean Change (SE) IFN	Mean Change (SE) OCR	OCR vs. IFN MD (95% CI)	P value
OPERA-I	0.174 (0.031)	0.213 (0.031)	0.039 (-0.039, 0.116)	0.3261
OPERA-II	0.169 (0.029)	0.276 (0.028)	0.107 (0.034, 0.180)	0.0040
Pooled	0.171 (0.021)	0.248 (0.020)	0.077 (0.025, 0.129)	0.004[a]



CI = confidence interval; IFN = interferon beta-1a; MD = mean difference; OCR = ocrelizumab; SE = standard error.

[a] This analysis was conducted outside of the statistical testing hierarchy and is non-confirmatory.

Harms

Only those harms identified in the review protocol are reported subsequently (see 2.2.1, Protocol). A summary of key adverse event data from OPERA-I, OPERA-II, and the pooled safety analysis is provided in Table 16.

Table 16: Summary of Adverse Events

Events, n (%)	OPERA-I		OPERA-II		Pooled RMS	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)	IFN (N = 826)	OCR (N = 825)
At least one AE	331 (80.9)	327 (80.1)	357 (85.6)	360 (86.3)	688 (83.3)	687 (83.3)
Serious AE	32 (7.8)	28 (6.9)	40 (9.6)	29 (7.0)	72 (8.7)	57 (6.9)
WDAE	26 (6.4)	13 (3.2)	25 (6.0)	16 (3.8)	51 (6.2)	29 (3.5)
WDSAE	4 (1.0)	3 (0.7)	5 (1.2)	3 (0.7)	9 (1.1)	6 (0.7)
Serious infection	12 (2.9)	5 (1.2)	12 (2.9)	6 (1.4)	24 (2.9)	11 (1.3)
Infections	222 (54.3)	232 (56.9)	219 (52.5)	251 (60.2)	441 (53.4)	483 (58.5)
AE leading to dose modification/interruption	31 (7.6)	20 (4.9)	54 (12.9)	18 (4.3)	85 (10.3)	38 (4.6)

AE = adverse event; IFN = interferon; OCR = ocrelizumab; RMS = relapsing multiple sclerosis; WDAE = withdrawal due to adverse event; WDSAE = withdrawal due to serious adverse event.

Source: Common Technical Document 2.7.3[1] and 2.7.4.[2]

Adverse Events

Table 17 provides a summary of adverse events reported in at least 5% of patients in either the ocrelizumab or interferon beta-1a groups in the OPERA-I and OPERA-II trials. An additional pooled analysis of adverse events is provided in Table 27. In both studies, infusion-related reactions were more commonly reported in the ocrelizumab groups (30.9% and 37.65%) than in the interferon beta-1a group (7.3% and 12.0%). Similarly, injection-site erythema was more commonly reported in the interferon beta-1a groups (12.7% and 18.1%) than in the ocrelizumab groups (0% to 0.2%). Influenza-like illness was reported for a greater proportion of patients in the interferon beta-1a groups (20.8% and 22.1%) compared with the ocrelizumab groups (3.75% and 5.5%). In both studies, a greater proportion of ocrelizumab-treated patients experienced at least one upper respiratory tract infection compared with the interferon beta-1a groups (14.5% and 15.8% versus 8.6% and 12.5%).

Table 17: Adverse Events Reported for 5% or More of Patients in Either Treatment Group

Adverse Events, n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
Infusion-related reaction	30 (7.3)	126 (30.9)	50 (12.0)	157 (37.6)
Urinary tract infection	57 (13.9)	52 (12.7)	43 (10.3)	44 (10.6)
Influenza-like illness	85 (20.8)	15 (3.7)	92 (22.1)	23 (5.5)
Upper respiratory tract infection	35 (8.6)	59 (14.5)	52 (12.5)	66 (15.8)
Headache	54 (13.2)	33 (8.1)	70 (16.8)	60 (14.4)
Nasopharyngitis	43 (10.5)	43 (10.5)	41 (9.8)	79 (18.9)
Injection-site erythema	74 (18.1)	0	53 (12.7)	1 (0.2)
Depression	24 (5.9)	30 (7.4)	30 (7.2)	34 (8.2)
Arthralgia	28 (6.8)	25 (6.1)	23 (5.5)	21 (5.0)

Adverse Events, n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
Fatigue	28 (6.8)	21 (5.1)	36 (8.6)	43 (10.3)
Back pain	20 (4.9)	25 (6.1)	17 (4.1)	28 (6.7)
Sinusitis	25 (6.1)	19 (4.7)	20 (4.8)	27 (6.5)
Insomnia	15 (3.7)	21 (5.1)	23 (5.5)	25 (6.0)
Influenza	< 5%		20 (4.8)	24 (5.8)
Dizziness			23 (5.5)	16 (3.8)
Myalgia			27 (6.5)	12 (2.9)
Pyrexia			24 (5.8)	15 (3.6)
Bronchitis			13 (3.1)	22 (5.3)
Injection-site reaction			28 (6.7)	2 (0.5)

IFN = interferon beta-1a; OCR = ocrelizumab.

Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Serious Adverse Events

Table 18 provides a summary of the serious adverse events that were reported in the OPERA-I and OPERA-II trials. The proportion of ocrelizumab-treated patients who experienced at least one serious adverse event was similar in the OPERA-I and OPERA-II trials (6.9% [39 events] and 7.0% [39 events], respectively). The proportion of patients treated with interferon beta-1a with at least one serious adverse event was 7.8% (38 events) in OPERA-I and 9.6% (50 events) in OPERA-II. The most commonly reported classes of serious adverse events across both studies were infections and infestations (1.3% with ocrelizumab and 2.9% with interferon beta-1a); nervous system disorders (1.0% with ocrelizumab and 1.3% with interferon beta-1a); and injury, poisoning, and procedural complications (0.7% with ocrelizumab and 1.2% with interferon beta-1a). There were more reports of serious hepatobiliary disorders in the ocrelizumab groups (six patients) compared with the interferon groups (three patients). There were fewer infections and infestations in the ocrelizumab groups (11 patients) than in the interferon beta-1a groups (24 patients). Serious events classified as injury, poisoning, and procedural complications were also lower in the ocrelizumab groups (six patients) compared with the interferon beta-1a group (10 patients).

Table 18: Serious Adverse Events

Serious Adverse Events, n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
At least one serious adverse events	32 (7.8)	28 (6.9)	40 (9.6)	29 (7.0)
Infections and infestations				
Cellulitis	1 (0.2)	2 (0.5)	0	0
Anal abscess	0	0	1 (0.2)	0
Abscess limb	2 (0.5)	0	0	0
Appendicitis	2 (0.5)	0	1 (0.2)	3 (0.7)
Acute tonsillitis	1 (0.2)	0	0	0
Biliary sepsis	0	1 (0.2)	0	0
Cholecystitis infective	0	0	1 (0.2)	0
Cystitis	0	0	1 (0.2)	0

Serious Adverse Events, n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
Device-related infection	0	1 (0.2)	0	0
Enterocolitis, infectious	1 (0.2)	0	0	0
Gastritis, viral	0	0	1 (0.2)	0
Gastroenteritis	1 (0.2)	0	0	0
Herpes simplex	0	1 (0.2)	0	0
Injection-site cellulitis	1 (0.2)	0	1 (0.2)	0
Perirectal abscess	1 (0.2)	0	0	0
Pneumonia	0	0	2 (0.5)	1 (0.2)
Pyelonephritis	0	0	0	2 (0.5)
Septic arthritis staphylococcal	1 (0.2)	0	0	0
Staphylococcal sepsis	0	0	1 (0.2)	0
Tooth infection	0	0	1 (0.2)	0
Urinary tract infection	1 (0.2)	0	1 (0.2)	0
Upper respiratory tract infection	0	0	0	1 (0.2)
Viral infection	0	0	1 (0.2)	0
Viral pericarditis	0	0	1 (0.2)	0
Injury/poisoning/procedural complications				
Ankle fracture	1 (0.2)	0	0	0
Craniocerebral injury	0	1 (0.2)	0	0
Hand fracture	1 (0.2)	0	0	0
Humerus fracture	0	1 (0.2)	0	0
Infusion-related reaction	0	1 (0.2)	1 (0.2)	0
Multiple injuries	1 (0.2)	0	0	0
Overdose	1 (0.2)	0	0	0
Post-procedural hematoma	1 (0.2)	0	0	0
Procedural pain	0	1 (0.2)	0	0
Tibia fracture	1 (0.2)	0	0	0
Accidental overdose	0	0	1 (0.2)	0
Cartilage injury	0	0	1 (0.2)	0
Jaw fracture	0	0	1 (0.2)	0
Lower limb fracture	0	0	0	1 (0.2)
Meniscus injury	0	0	0	1 (0.2)
Skull fracture	0	0	0	1 (0.2)
Nervous system disorders				
Multiple sclerosis relapse	3 (0.7)	0	2 (0.5)	1 (0.2)
Epilepsy	1 (0.2)	1 (0.2)	1 (0.2)	0
Seizure	0	2 (0.5)	1 (0.2)	2 (0.5)
Aphasia	1 (0.2)	0	0	0
Dizziness	0	1 (0.2)	0	0
Dysarthria	1 (0.2)	0	0	0
Ruptured cerebral aneurysm	1 (0.2)	0	0	0
Sciatica	0	1 (0.2)	0	0
Cerebral infarction	0	0	0	1 (0.2)
Head discomfort	0	0	0	1 (0.2)
Hydrocephalus	0	0	0	1 (0.2)

Serious Adverse Events, n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
Presyncope	0	0	1 (0.2)	0
VIIth nerve paralysis	0	0	1 (0.2)	0
Neoplasms (benign, malignant, and unspecified)				
Invasive ductal breast carcinoma	0	2 (0.5)	0	0
Uterine leiomyoma	2 (0.5)	0	0	0
Mantle cell lymphoma	1 (0.2)	0	0	0
Renal cancer	0	1 (0.2)	0	0
Salivary gland adenoma	1 (0.2)	0	0	0
Thyroid adenoma	0	0	0	2 (0.5)
Malignant melanoma	0	0	0	1 (0.2)
Hepatobiliary disorders				
Cholelithiasis	0	2 (0.5)	1 (0.2)	0
Cholecystitis	0	1 (0.2)	0	1 (0.2)
Cholecystitis, acute	0	0	1 (0.2)	1 (0.2)
Cholecystitis, chronic	0	1 (0.2)		
Hepatitis, acute	0	0	1 (0.2)	0
Psychiatric disorders				
Depression	0	2 (0.5)	0	0
Depression, suicidal	0	0	2 (0.5)	0
Anxiety	0	1 (0.2)	1 (0.2)	0
Completed suicide	1 (0.2)	0	0	1 (0.2)
Suicide attempt	0	1 (0.2)	0	0
Apathy	0	0	1 (0.2)	0
Stress	0	0	1 (0.2)	0
Suicidal ideation	0	0	1 (0.2)	0
Cardiac disorders				
Atrial flutter	0	1 (0.2)	0	0
Cardiac failure congestive	0	1 (0.2)	0	0
Acute myocardial infarction	0	0	1 (0.2)	1 (0.2)
Angina, unstable	0	0	1 (0.2)	0
Atrioventricular block, second-degree	0	0	1 (0.2)	0
Gastrointestinal disorders				
Abdominal pain	0	0	1 (0.2)	0
Gastritis	0	1 (0.2)	0	1 (0.2)
Pancreatitis	0	1 (0.2)	0	0
Pancreatitis, acute	0	1 (0.2)	0	0
Gastrointestinal inflammation	0	0	0	1 (0.2)
Ileus, paralytic	0	0	0	1 (0.2)
Inguinal hernia	0	0	1 (0.2)	0
Mechanical ileus	0	0	1 (0.2)	0
Esophagitis	0	0	1 (0.2)	0
General disorders and administration-site conditions				
Chest pain	0	2 (0.5)	0	1 (0.2)
Immune system disorders				
Drug hypersensitivity	1 (0.2)	1 (0.2)	0	0

Serious Adverse Events, n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
Musculoskeletal and connective tissue disorders				
Muscle spasms	0	1 (0.2)	0	0
Rheumatoid arthritis	1 (0.2)	0	0	0
Arthritis	0	0	0	1 (0.2)
Osteoarthritis	0	0	1 (0.2)	0
Vertebral osteophyte	0	0	0	1 (0.2)
Metabolism and nutrition disorders				
Dehydration	0	0	0	1 (0.2)
Hypertriglyceridemia	0	0	1 (0.2)	0
Hypoglycemia	0	0	0	1 (0.2)
Hypokalemia	0	0	0	1 (0.2)
Renal and urinary disorders				
Nephrolithiasis	0	0	2 (0.5)	0
Reproductive system and breast disorders				
Endometriosis	0	1 (0.2)	0	0
Menorrhagia	0	1 (0.2)	1 (0.2)	0
Ovarian cyst	1 (0.2)	0	1 (0.2)	0
Dysmenorrhea	0	0	0	1 (0.2)
Menometrorrhagia	0	0	0	1 (0.2)
Uterine polyp	0	0	1 (0.2)	0
Respiratory, thoracic, and mediastinal disorders				
Hyperventilation	1 (0.2)	0	0	0
Sinus congestion	1 (0.2)	0	0	0
Asthma	0	0	0	1 (0.2)
Pneumonia aspiration	0	0	0	1 (0.2)
Pulmonary embolism	0	0	1 (0.2)	0
Blood and lymphatic system disorders				
Leukopenia	1 (0.2)	0	0	0
Spontaneous hematoma	0	0	1 (0.2)	0
Skin and subcutaneous tissue disorders				
Dermatitis, bullous	0	0	0	1 (0.2)
Urticaria	0	0	1 (0.2)	0
Eye disorders				
Retinal artery occlusion	1 (0.2)	0	0	0
Surgical and medical procedures				
Mammoplasty	1 (0.2)	0	0	0
Vascular disorders				
Peripheral venous disease	0	0	0	1 (0.2)
Varicose vein	0	0	1 (0.2)	0

IFN = interferon beta-1a; OCR = ocrelizumab.

Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Withdrawals Due to Adverse Events

Table 19 provides a summary of adverse events that led to withdrawal in the OPERA-I and OPERA-II trials. In both studies, withdrawals as a result of adverse events were reported more frequently in the interferon beta-1a groups (6.0% to 6.4%) compared with the ocrelizumab groups (3.2% to 3.8%). Infusion-related reactions led to the withdrawal of 11 ocrelizumab-treated patients (1.2% to 1.5%) compared with no patients who received the placebo infusion. Adverse events associated with injection sites were more commonly cited as reasons for discontinuation in the interferon beta-1a groups. These included injection-site erythema (0.2%), injection-site inflammation (0.2%), injection-site reaction, and injection-site pain (0.2%). Influenza-like illness was more commonly cited as a reason for discontinuation from the interferon beta-1a groups (1.0% to 2.0%) compared with the ocrelizumab groups (0% to 0.2%). Withdrawals due to neutropenia or leukopenia were reported for a total of four patients treated with interferon beta-1a and for no ocrelizumab-treated patients.

Table 19: Summary of Withdrawals Due to Adverse Events

WDAEs, n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
Total WDAEs	26 (6.4)	13 (3.2)	25 (6.0%)	16 (3.8%)
General disorders and administration-site conditions				
Influenza-like illness	8 (2.0)	0	4 (1.0)	1 (0.2)
Fatigue	1 (0.2)	0	0	1 (0.2)
Injection-site erythema	1 (0.2)	0	0	0
Injection-site inflammation	1 (0.2)	0	0	0
Injection-site reaction	1 (0.2)	0	1 (0.2)	0
Injection-site pain	0	0	1 (0.2)	0
Chest pain	0	0	0	1 (0.2)
Chills	0	0	0	1 (0.2)
Injury, poisoning, and procedural complications				
Infusion-related reaction	0	6 (1.5)	0	5 (1.2)
Injection related reaction	1 (0.2)	0	0	0
Investigations				
Liver function test abnormal	2 (0.5)	0	0	0
Alanine aminotransferase increased	1 (0.2)	0	3 (0.7)	0
Blood creatine phosphokinase increased	1 (0.2)	0	0	0
Transaminases increased	1 (0.2)	0	0	0
Alanine aminotransferase abnormal	0	0	1 (0.2)	0
Amylase increased	0	0	1 (0.2)	0
Aspartate aminotransferase abnormal	0	0	1 (0.2)	0
Gamma-glutamyltransferase increased	0	0	1 (0.2)	0
Lipase increased	0	0	1 (0.2)	0
Platelet count abnormal	0	0	1 (0.2)	0
Abnormal white blood cell count	0	0	1 (0.2)	0
Musculoskeletal and connective tissue disorders				
Muscle rigidity	0	1 (0.2)	0	0
Musculoskeletal stiffness	1 (0.2)	0	0	0
Osteonecrosis	0	1 (0.2)	0	0

WDAEs, n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
Psoriatic arthropathy	0	1 (0.2)	0	0
Pain in extremity	0	0	0	1 (0.2)
Blood and lymphatic system disorders				
Neutropenia	2 (0.5)	0	0	0
Leukopenia	1 (0.2)	0	1 (0.2)	0
Lymphocytosis	0	0	0	1 (0.2)
Spontaneous hematoma	0	0	1 (0.2)	0
Infections and infestations				
Cellulitis	0	1 (0.2)	0	0
Urinary tract infection	0	1 (0.2)	0	0
Neoplasms (benign, malignant, and unspecified)				
Invasive ductal breast carcinoma	0	1 (0.2)	0	0
Mantle cell lymphoma	1 (0.2)	0	0	0
Nervous system disorders				
Multiple sclerosis relapse	1 (0.2)	0	0	0
Ruptured cerebral aneurysm	1 (0.2)	0	0	0
Headache	0	0	0	1 (0.2)
Hydrocephalus	0	0	0	1 (0.2)
Psychiatric disorders				
Anxiety	0	1 (0.2)	1 (0.2)	0
Insomnia	0	1 (0.2)	0	0
Suicide attempt	0	1 (0.2)	0	0
Depression	0	0	4 (1.0)	0
Depression, suicidal	0	0	1 (0.2)	0
Suicidal ideation	0	0	0	1 (0.2)
Vascular disorders				
Susac's syndrome	1 (0.2)	0	0	0
Skin and subcutaneous tissue disorders				
Cutaneous lupus erythematosus	0	0	1 (0.2)	0
Dermatitis bullous	0	0	0	1 (0.2)
Erythema nodosum	0	0	0	1 (0.2)
Rash	0	0	1 (0.2)	0
Urticaria	0	0	1 (0.2)	0
Cardiac disorders				
Angina, unstable	0	0	1 (0.2)	0
Ear and labyrinth disorders				
Vertigo	0	0	0	1 (0.2)
Gastrointestinal disorders				
Gastritis	0	0	0	1 (0.2)
Hepatobiliary disorders				
Hepatitis, acute	0	0	1 (0.2)	0
Metabolism and nutrition disorders				
Diabetes mellitus, inadequate control	0	0	0	1 (0.2)

IFN = interferon beta-1a; OCR = ocrelizumab; WDAE = withdrawal due to adverse events.

Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Mortality

There were three deaths reported in the OPERA-I and OPERA-II trials. Two patients who were treated with interferon beta-1a died (one due to suicide and one due to mechanical ileus), and one patient who was treated with ocrelizumab died (due to suicide).[31,32]

Adverse Events of Special Interest

Serious Infections

Table 20 provides a summary of serious infections and infections that required treatment with an anti-infective treatment administered IV. In both studies and in the pooled analysis, serious infections were more commonly reported for patients who received treatment with interferon beta-1a (3.8% [34 events]) compared with the ocrelizumab group (1.8% [18 events]). When adjusted for exposure, the event rate for serious infections in the ocrelizumab group was 0.83 per 100 patient-years (PY) (95% CI, 0.43 to 1.45) compared with 1.79 per 100 PY (95% CI, 1.16 to 2.64). The manufacturer reported that most of the serious infections in both the ocrelizumab and interferon beta-1a groups were bacterial and all resolved following treatment with antibiotics.[2]

Table 20: Serious Infections and Infections Requiring Anti-infective Treatments Administered Intravenously

Infections and Infestations n (%)	OPERA-I		OPERA-II		Pooled RMS	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)	IFN (N = 826)	OCR (N = 825)
At least one event	16 (3.9)	7 (1.7)	15 (3.6)	8 (1.9)	31 (3.8)	15 (1.8)
Events	16	8	18	10	34	18
Urinary tract infection	2 (0.5)	1 (0.2)	2 (0.5)	1 (0.2)	4 (0.5)	3 (0.4)
Appendicitis	1 (0.2)	0	1 (0.2)	3 (0.7)	3 (0.4)	3 (0.4)
Cellulitis	1 (0.2)	0	1 (0.2)	0	3 (0.4)	2 (0.2)
Pneumonia	0	1 (0.2)	1 (0.2)	0	2 (0.2)	2 (0.2)
Abscess limb	1 (0.2)	0	0	0	2 (0.2)	0
Injection-site cellulitis	1 (0.2)	0	1 (0.2)	0	2 (0.2)	0
Pyelonephritis	0	0	0	2 (0.5)	0	2 (0.2)
URTI	0	0	1 (0.2)	0	1 (0.1)	1 (0.1)
Acute sinusitis	0	0	1 (0.2)	0	1 (0.1)	0
Acute tonsillitis	1 (0.2)	0	0	0	1 (0.1)	0
Anal abscess	0	0	1 (0.2)	0	1 (0.1)	0
Biliary sepsis	0	1 (0.2)	0	0	0	1 (0.1)
Cholecystitis, infective	0	0	1 (0.2)	0	1 (0.1)	0
Cystitis	0	0	1 (0.2)	0	1 (0.1)	0
Device-related infection	0	1 (0.2)	0	0	0	1 (0.1)
Enterocolitis, infectious	1 (0.2)	0	0	0	1 (0.1)	0
Gastritis viral	0	0	1 (0.2)	0	1 (0.1)	0
Gastroenteritis	1 (0.2)	0	0	0	1 (0.1)	0
Herpes simplex	0	1 (0.2)	0	0	0	1 (0.1)
Nasopharyngitis	0	0	1 (0.2)	0	1 (0.1)	0
Perirectal abscess	1 (0.2)	0	0	0	1 (0.1)	0
Pneumonia, viral	0	0	0	1 (0.2)	0	1 (0.1)
Septic arthritis, staphylococcal	1 (0.2)	0	0	0	1 (0.1)	0

Infections and Infestations n (%)	OPERA-I		OPERA-II		Pooled RMS	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)	IFN (N = 826)	OCR (N = 825)
Staphylococcal infection	1 (0.2)	0	0	0	1 (0.1)	0
Staphylococcal sepsis	0	0	1 (0.2)	0	1 (0.1)	0
Tooth infection	0	0	1 (0.2)	0	1 (0.1)	0
Viral infection	0	0	1 (0.2)	0	1 (0.1)	0
Viral pericarditis	0	0	1 (0.2)	0	1 (0.1)	0

IFN = interferon; OCR = ocrelizumab; URTI = upper respiratory tract infection.

Source: Common Technical Document 2.7.4[2] and Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Opportunistic Infections

The proportion of patients who experienced at least one adverse event that was classified as an opportunistic infection was greater in the ocrelizumab group (7.0%) than in the interferon beta-1a group (4.1%). The manufacturer reported that this imbalance was primarily due to an increase in herpes infections in the ocrelizumab groups compared with the interferon groups. These herpes infections included including oral herpes (2.9% versus 2.1%), herpes zoster (2.1% versus 1.0%), and herpes simplex (0.8% versus 0.2%). The overall event rate for opportunistic infections was 5.25 per 100 PY (95% CI, 4.14 to 6.57) in the ocrelizumab group and 2.79 (95% CI, 1.98 to 3.81) in the interferon beta-1a group.[2] No cases of PML were reported in patients who have been treated with ocrelizumab.

Infusion-Related Reactions

Table 21 provides a summary of the frequency, severity, and timing of infusion-related adverse events reported in OPERA-I, OPERA-I, and the pooled safety analysis. Infusion-related reactions were the most commonly reported adverse event in both of the pivotal trials, occurring at a greater frequency in the ocrelizumab groups than in the interferon beta-1a groups (34.3% versus 9.7% in the pooled analysis). The most commonly reported symptoms associated with infusion-related adverse events in the ocrelizumab groups were pruritus, rash, throat irritation, and flushing. The first 300 mg dose of ocrelizumab was associated with the highest proportions of patients with an infusion-related event (27.5%), and that proportion decreased to 4.7% at the second 300 mg infusion (day 15). At the first infusion of the full 600 mg ocrelizumab dose, 13.7% of patients reported at least one infusion-related event. This proportion subsequently decreased at third and fourth doses (9.6% and 7.8%, respectively).[2]

Nearly all of the infusion-related adverse events were mild or moderate in severity (93% in the ocrelizumab group and 99% in the interferon beta-1a group were grade 1 or 2 events).[2] Grade 3 infusion-related adverse events were reported in 20 ocrelizumab-treated of patients (2.4%) compared with one (0.1%) patient in the interferon beta-1a group. There was one grade 4 event (bronchospasm) reported for an ocrelizumab-treated patient at the time of first 300 mg infusion.[2] Eleven ocrelizumab-treated patients withdrew from the study as a result of infusion-related adverse events (1.3%). All of these patients were withdrawn after receiving one infusion of ocrelizumab (i.e., 300 mg). There were no events of anaphylaxis reported in the studies.

Table 21: Summary of Infusion-Related Adverse Events

Dose	Scale	OPERA-I		OPERA-II		Pooled RMS Population	
		IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)	IFN (N = 826)	OCR (N = 825)
Total	n (%)	30 (7.3)	126 (30.9)	50 (12.0)	157 (37.6)	80 (9.7)	283 (34.3)
	Events	46	235	64	270	110	505
	Grade 1	22 (5.4)	73 (17.9)	35 (8.4)	106 (25.4)	57 (6.9)	179 (21.7)
	Grade 2	8 (2.0)	38 (9.3)	14 (3.4)	45 (10.8)	22 (2.7)	83 (10.1)
	Grade 3	0	14 (3.4)	1 (0.2)	6 (1.4)	1 (0.1)	20 (2.4)
	Grade 4	0	1 (0.2)	0	0	0	1 (0.1)
	Grade 5	0	0	0	0	0	0
Dose 1, Day 1	N	409	408	416	417	825	825
	n (%)	19 (4.6)	104 (25.5)	35 (8.4)	123 (29.5)	54 (6.5)	227 (27.5)
	Events	19	105	35	123	54	228
	Grade 1	14 (3.4)	64 (15.7)	28 (6.7)	87 (20.9)	42 (5.1)	151 (18.3)
	Grade 2	5 (1.2)	27 (6.6)	6 (1.4)	34 (8.2)	11 (1.3)	61 (7.4)
	Grade 3	0	12 (2.9)	1 (0.2)	2 (0.5)	1 (0.1)	14 (1.7)
	Grade 4	0	1 (0.2)	0	0	0	1 (0.1)
	Grade 5	0	0	0	0	0	0
Dose 1, Day 15	N	404	399	411	407	815	806
	n (%)	6 (1.5)	20 (5.0)	15 (3.6)	18 (4.4)	21 (2.6)	38 (4.7)
	Events	6	20	15	18	21	38
	Grade 1	6 (1.5)	14 (3.5)	8 (1.9)	15 (3.7)	14 (1.7)	29 (3.6)
	Grade 2	0	6 (1.5)	7 (1.7)	3 (0.7)	7 (0.9)	9 (1.1)
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
Dose 2	N	375	388	376	391	751	779
	n (%)	11 (2.9)	49 (12.6)	4 (1.1)	58 (14.8)	15 (2.0)	107 (13.7)
	Events	11	50	4	58	15	108
	Grade 1	8 (2.1)	38 (9.8)	3 (0.8)	46 (11.8)	11 (1.5)	84 (10.8)
	Grade 2	3 (0.8)	10 (2.6)	1 (0.3)	10 (2.6)	4 (0.5)	20 (2.6)
	Grade 3	0	1 (0.3)	0	2 (0.5)	0	3 (0.4)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
Dose 3	N	360	380	342	379	702	759
	n (%)	4 (1.1)	33 (8.7)	4 (1.2)	40 (10.6)	8 (1.1)	73 (9.6)
	Events	4	33	4	40	8	73
	Grade 1	3 (0.8)	24 (6.3)	4 (1.2)	32 (8.4)	7 (1.0)	56 (7.4)
	Grade 2	1 (0.3)	8 (2.1)	0	6 (1.6)	1 (0.1)	14 (1.8)
	Grade 3	0	1 (0.3)	0	2 (0.5)	0	3 (0.4)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
Dose 4	N	346	367	317	365	663	732
	n (%)	6 (1.7)	26 (7.1)	6 (1.9)	31 (8.5)	12 (1.8)	57 (7.8)
	Events	6	27	6	31	12	58
	Grade 1	5 (1.4)	22 (6.0)	4 (1.3)	22 (6.0)	9 (1.4)	44 (6.0)
	Grade 2	1 (0.3)	4 (1.1)	2 (0.6)	9 (2.5)	3 (0.5)	13 (1.8)

Dose	Scale	OPERA-I		OPERA-II		Pooled RMS Population	
		IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)	IFN (N = 826)	OCR (N = 825)
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0

IFN = interferon; OCR = ocrelizumab; RMS = relapsing multiple sclerosis.

Source: Common Technical Document 2.7.4[2] and Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Malignancies

Across OPERA-I and OPERA-II, malignancy was reported for four ocrelizumab-treated patients and two interferon beta-1a treated patients. The malignancy events in the ocrelizumab group included two invasive ductal breast carcinomas, one renal cancer, and one malignant melanoma. Those in the interferon beta-1a group included single events of squamous cell carcinoma and mantle cell lymphoma. The rate of malignancy was 0.28 per 100 PYs (95% CI, 0.08 to 0.71) for ocrelizumab and 0.14 per 100 PYs (95% CI, 0.02 to 0.52) for interferon beta-1a.[2]

Depression

Adverse events related to depression and suicide are summarized in Table 22. The proportion of patients who experienced depression was similar across the ocrelizumab and interferon beta-1a groups (7.8% versus 6.5%, respectively). [2]

Table 22: Depression and Suicidality

Depression and Suicidality n (%)	Pooled RMS Population	
	IFN (N = 826)	OCR (N = 825)
At least one event	65 (7.9)	70 (8.5)
Overall total number of events	76	78
Depression	54 (6.5)	64 (7.8)
Depressed mood	9 (1.1)	3 (0.4)
Suicidal ideation	4 (0.5)	2 (0.2)
Completed suicide	1 (0.1)	1 (0.1)
Depression suicidal	2 (0.2)	0
Major depression	1 (0.1)	0
Suicide attempt	0	1 (0.1)

IFN = interferon beta-1a; OCR = ocrelizumab; RMS = relapsing multiple sclerosis.

Source: Common Technical Document 2.7.4.[2]

Discussion

Summary of Available Evidence

The CDR systematic review included two identically designed, multi-centre, parallel-group, double-blind, double-dummy, active-comparator, phase III RCTs. Patients enrolled in the OPERA-I (N = 821) and OPERA-II (N = 835) studies were randomized (1:1) to receive ocrelizumab 600 mg IV once every six weeks or interferon beta-1a 44 mcg SC three times per week. The studies evaluated clinical end points (e.g., relapse), MRI end points (e.g., changes in lesions on T1- and T2-weighted scans), and patient-reported end points (e.g., SF-36 PCS). The clinical expert involved in the review noted that the baseline demographic and disease characteristics of patients enrolled in both studies were, overall, similar to those seen in clinical practice.

The Health Canada–approved indication for ocrelizumab is for the treatment of adult patients with RRMS with active disease defined by clinical and imaging features. This indication is not restricted based on prior exposure to one or more DMTs; therefore, ocrelizumab may be used in both treatment-naive and treatment-experienced patients. The majority of patients in the phase III trials (OPERA-I and OPERA-II) had no prior exposure to any MS treatments.[1] The manufacturer is currently conducting two open-label, uncontrolled, phase IIIb studies to evaluate the efficacy and safety of ocrelizumab in patients with RRMSwho have demonstrated a suboptimal response to a DMT (CHORD and CASTING).[43,44]

The OPERA-I and OPERA-II trials provided a head-to-head comparison of ocrelizumab against interferon beta-1a; however, there are numerous DMTs approved for use in Canada. Therefore, CADTH also considered the results of two network meta-analyses that compared ocrelizumab against all other available treatments.

The two controlled studies were 96 weeks in duration, with study participants eligible to enrol in an open-label extension following completion; therefore, CADTH also summarized the available data from the manufacturer's long-term extension trial, which provides additional, uncontrolled efficacy and safety data for up to an additional year of treatment.

Interpretation of Results

Efficacy

In both OPERA-I and OPERA-II, treatment with ocrelizumab was shown to be statistically superior to interferon beta-1a for reducing the risk of relapse at 96 weeks (pooled rate ratio 0.535 [95% CI, 0.435 to 0.659]). This 46.5% reduction in the ARR was considered to be clinically relevant by the FDA and by the clinical expert consulted by CADTH. Disability progression is an important clinical outcome and of major importance to patients. In both studies, ocrelizumab was shown to be statistically superior to interferon beta-1a for reducing the hazard for CDP that persisted for at least 12 or 24 weeks (pooled HR 0.60 [95% CI, 0.45 to 0.81] and HR 0.60 [95% CI, 0.43 to 0.84], respectively). This 40% reduction was also considered to be clinically relevant by the FDA and the clinical expert consulted by CADTH. However, the FDA noted that the disease progression observed in the OPERA-I and OPERA-II trials was typically reversible and not reflective of permanent disability progression.

In OPERA-I and OPERA-II, ocrelizumab was shown to be statistically superior to interferon beta-1a for the following MRI end points: number of new and enlarging hyperintense lesions on T2-weighted imaging; number of hypointense lesions on T1-weighted imaging; and number of GdE lesions. These are conventional MRI outcomes that are widely used to monitor treatment effects in clinical trials of MS. Their roles as a surrogate for clinical outcomes such as relapses and disability progression in RRMS have been investigated in previous research, but inconsistent conclusions were drawn. Moreover, there was a sizable proportion of missing data for these outcome measures. For example, data for change in brain volume were missing for approximately 20% to 30% of randomized patients (i.e., the ITT population) by week 48 and, in certain instances, the missing data differed between treatment groups (Table 24). These limitations were more pronounced by week 96. Therefore, this means that a considerable amount of data were imputed for the MRI analyses, and there is uncertainty regarding whether these analyses could still be considered comparisons based on a randomized population.

The SF-36 questionnaire was used to measure the clinical benefits of the study drug on health-related quality of life. The individual trials were inconsistent with respect to whether ocrelizumab demonstrated favourable effects on the SF-36 PCS, and the statistical testing hierarchy had stopped in both studies prior to this end point. The pooled analysis demonstrated a slight favourable effect; however, the difference was below the MCID for the SF-36. Furthermore, like the MRI outcome analyses, this analysis suffered from a large amount of missing data. The EMA's guidance to industry on the clinical investigation of medicinal products for the treatment of MS states that there is limited evidence validating patient-reported outcomes measures for the MS patient population and that "specific recommendations on specific scales cannot be made." In addition, there were no specific patient-reported outcomes directly measuring either fatigue or productivity (i.e., patients' capacity to participate in school or work). Therefore, there remains uncertainty regarding the comparative effects of ocrelizumab on health-related quality of life and other patient-reported outcomes.

Two network meta-analyses were reviewed and critically appraised by CADTH (one unpublished network meta-analysis submitted by the manufacturer and one published network meta-analysis conducted by the Institute for Clinical and Economic Review).[45,46] [redacted]

Harms

The mechanism of action for ocrelizumab involves the depletion of B cells, which can increase the risk of the adverse events associated with decreased function of the immune system. Patients treated with ocrelizumab, an immunomodulator, may be at increased risk of infections. In the OPERA-I and OPERA-II trials, serious infections were reported less frequently in the ocrelizumab groups than in the interferon beta-1a groups. The clinical expert noted that the absolute difference between the ocrelizumab and interferon beta-1a groups (approximately 2%) was unlikely to be clinically relevant.

PML is a serious condition that can develop in patients with reduced immune function as a result of infection by the John Cunningham virus. No cases of PML have been reported in patients who have been treated with ocrelizumab; however, the Canadian product

monograph for ocrelizumab contains a warning about this potential risk.[17] The product monograph recommends that patients be monitored for early signs and symptoms of PML, noting these can appear similar to an MS relapse (e.g., worsening of neurological signs or symptoms). Several other DMTs approved for use in Canada include warnings regarding the risk of PML, including natalizumab and alemtuzumab, which have black box warnings, and dimethyl fumarate and fingolimod, which have non–black box warnings. The clinical expert consulted by CADTH noted that patients treated with ocrelizumab are not likely to receive the specialized monitoring for PML that is provided to patients being treated with natalizumab.

Ocrelizumab is associated with infusion-related reactions,[17] which were the most commonly reported adverse events in both of the pivotal trials.[31,32] These events were typically mild to moderate in severity and were more likely to occur during or following the first infusion. To reduce the frequency and severity of infusion-related reactions, the product monograph recommends that patients receive: 100 mg IV methylprednisolone (or an equivalent) approximately 30 minutes before each infusion, pre-treatment with an oral or IV antihistamine approximately 30 to 60 minutes before each infusion, and optional treatment with an antipyretic drug (e.g., acetaminophen). The recommendations in the product monograph are consistent with the pre-medication protocols used in the OPERA-I and OPERA-II studies.[17,31,32] Similarly, the recommendations for pre-medication and dosage adjustment (i.e., slowing, interrupting, or stopping the infusion) in the product monograph are also consistent with the protocols used in the OPERA-I and OPERA-II study protocols. This suggests that the infusion-related adverse events observed in the pivotal trials would be similar to those observed in clinical practice. The clinical expert consulted by CADTH suggested that these infusion-related adverse events associated with ocrelizumab are similar to those observed with other DMTs that require IV administration.

Overall, the clinical expert indicated that the adverse events for ocrelizumab observed in the OPERA trials appear consistent with those observed in other available MS treatment. The expert noted that patients are generally willing to accept the risks associated with various MS treatments for the potential benefits of slowing disability progression (most notably, avoiding the need for a wheelchair).

The analysis of safety end points in the indirect treatment comparisons was limited to aggregate outcomes (i.e., serious adverse events and all-cause discontinuations), and the results suggested there were no differences between any of the DMTs included in the analyses. However, such aggregate end points cannot be used to evaluate the unique safety profiles of different DMTs.

Other Considerations

- Reviewers for the FDA noted that ocrelizumab does not meet an unmet need for the treatment of relapsing MS, due to the availability of many other therapies indicated for relapsing MS.29 However, in their input to CADTH, MS patients emphasized the need to have as many treatment options as possible.
- In their submission to CADTH, patients indicated they would prefer the dosage schedule of ocrelizumab (i.e., once every six months) compared with treatment regimens that require more frequent dosage.

Potential Place in Therapy[1]

Data from the OPERA trials suggest ocrelizumab could either be a first-line or second-line option after an inadequate response or intolerance to a previous DMT. It is difficult to determine from the OPERA-I and OPERA-II studies whether those patients who had not been exposed to a DMT in the prior two years had had any treatments at all or were completely naive to DMT. If the latter, then ocrelizumab could be considered a first-line therapy; if the former, then it would be more appropriate as a second-line therapy.

In terms of unmet need, the current first-line therapies are of moderate effectiveness and have inconvenient dosage schedules and/or inconvenient administration. Ocrelizumab was shown to be more efficacious than interferon beta-1a SC in the OPERA-I and OPERA-II trials; it could be considered equivalent to alemtuzumab with potentially fewer side effects and less monitoring, although there is no direct comparative evidence and indirect treatment comparisons were not statistically significant, making it difficult to draw a concrete conclusion on this comparison.

The OPERA-I and OPERA-II studies were conducted only in patients with relapsing forms of MS; there should not be any difficulty identifying these patients in clinical practice, including those who are naive or experienced with DMTs. Specialized testing prior to exposure to ocrelizumab may include immunization status (or ensuring that immunization status is current). The studies do not suggest a need for assessing John Cunningham virus antibody status, varicella zoster status, or cardiac status. There does not appear to be any need for specialized monitoring during infusions, except for possible anaphylaxis.

Conclusions

Two double-blind phase III RCTs (OPERA-I and OPERA-II) demonstrated that ocrelizumab was superior to interferon beta-1a for reducing the ARR and the HR for disability progression for three and six months. This was considered clinically relevant by both regulatory authorities and the clinical expert consulted by CADTH. Treatment with ocrelizumab was also associated with an increase in the proportion of patients with disability improvement and an increase in the proportion of patients with NEDA at 96 weeks. Evaluations using MRI suggest that lower proportions of ocrelizumab-treated patients developed new or newly enlarging hyperintense lesions on T2-weighted scans, new hypointense lesions on T1-weighted scans, and new GdE lesions on T1-weighted scans. Two NMAs suggested that [redacted]

The clinical expert consulted by CADTH indicated that the adverse event profile for ocrelizumab is consistent with other available MS treatments. The proportion of patients with at least one serious adverse event ranged from 6.9% to 7.0% with ocrelizumab and 7.8% to 9.6% with interferon beta-1a. Serious infections were more commonly reported for patients who received treatment with interferon beta-1a than for patients in the ocrelizumab group; however, opportunistic infections were more commonly reported in the ocrelizumab

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

group. Withdrawals due to adverse events were reported more frequently in the interferon beta-1a groups than in the ocrelizumab groups. Infusion-related reactions were the most commonly reported adverse events in both of the pivotal trials and occurred at a greater frequency in the ocrelizumab groups. Nearly all of the infusion-related adverse events were mild or moderate in severity, and the proportion of ocrelizumab-treated patients who experienced infusion-related reactions tended to decrease over the course of the trial. Indirect treatment comparisons of safety end points were restricted to aggregate end points that cannot evaluate the unique adverse event profiles of the different drugs.

Appendix 1: Patient Input Summary

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

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

One patient group supplied input for this submission.

The Multiple Sclerosis Society of Canada (MS Society) is a national voluntary organization that supports multiple sclerosis (MS) research and provides services related to MS for patients and their families/caregivers. Between 2016 and 2017, the MS Society received educational grants from the following companies: Bayer, Biogen, EMD Serono, Novartis, Roche, Pfizer, Sanofi Genzyme, Allergan, and Teva Neuroscience. The contributions totalled less than 2% of the MS Society's overall revenue and are subject to strict policies that prevent any control or influence by the donor on MS Society decision-making.

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

2. Condition-Related Information

Information was obtained from publicly available information and from a bilingual (English and French) online survey using social media. A total of 109 people responded to the survey: 77% were female; 91% were MS patients and the remainder were caregivers; 69% had relapsing-remitting MS, 14% had secondary-progressive MS, 11% had primary-progressive MS, and a small percentage of patients were unsure what type of MS they had. The ages of respondents ranged from 25 years to 65 and older. Time since diagnosis ranged from less than two years to more than 20 years, with the highest number diagnosed between five and 10 years ago.

MS is an unpredictable and often disabling disease of the central nervous system in which the myelin sheath surrounding the axons is damaged, and there is an interrupted or loss of normal nerve impulse flow along the axons. The most commonly diagnosed form of MS is the relapse-remitting form (85% to 90% of patients), which is characterized by attacks of bouts of inflammation in the central nervous system followed by full or near-full recovery. About 50% of these patients will develop secondary-progressive MS within 10 to 20 years of initial diagnosis, and this form is characterized by fewer or no attacks but advanced disability. The remaining 10% to 15% patients have primary-progressive MS, which is characterized by steady worsening of disease and is not preceded by the relapse-remitting form. MS is most commonly diagnosed between the ages of 15 and 40 but can occur at any age. It is more common in women than men and is more prevalent in countries located in the northern hemisphere, with the highest prevalence in Canada.

Patients with MS most commonly experience fatigue, difficulty walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain. Other symptoms may include issues with balance, sexual dysfunction, spasticity, tremor, weakness, and difficulty speaking and swallowing. Depending on the type and severity of the symptom, an individual's quality of life can be greatly affected. The episodic nature of MS creates unique employment issues; many people are unable to maintain stable jobs or remain in the workplace due to relapses, symptoms, medication side effects, and disability progression. In addition to hindering employment, MS can interfere with or pose a barrier to education,

physical activity, family commitments, interpersonal relationships, and social and recreational life.

Caregivers can also be greatly affected and, in most instances, must provide extensive care to their loved ones affected by MS. Such care can range from emotional support and assistance with medication administration to helping with activities of daily living such as personal care, feeding, and transportation to and from appointments. MS treatments make it more possible for those affected by MS to make family and social commitments and to remain in the workplace. These factors greatly improve quality of life for both patients with MS and their caregivers.

3. Current Therapy-Related Information

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

While DMTs are generally well tolerated, some patients will need to switch to another therapy class because they are unable to tolerate specific side effects or because their MS is unresponsive to the therapy. Patients highlighted the value of having more DMT options available so they can find one that best suits them and their disease course. Also, it is a common theme for one drug to work well with one patient but not with another. This emphasizes the need to have as many treatment options as possible to provide the best benefit for MS patients and to increase their quality of life.

4. Expectations About the Drug Being Reviewed

While only three respondents had direct experience with ocrelizumab during clinical trials, most patients expect that monoclonal antibodies such as ocrelizumab will be highly effective in managing aggressive forms of relapsing MS when other therapies have not had clinical benefit; however, patients acknowledge that these biologics also carry a higher risk of adverse events. Patients also prefer the dosage schedule of ocrelizumab, which is administered only once every six months.

Overall, patients expect ocrelizumab to have serious adverse events only rarely. It was noted that there had been one death due to brain edema during the clinical trials and one case of progressive multifocal leukoencephalopathy recorded in Europe during post-marketing surveillance.[2] Thirty respondents stated they would be willing to risk experiencing the adverse side effects of ocrelizumab for the perceived benefits of the drug, while 24 said they would not be willing to take such risk, and 31 stated they did not know whether they would be willing to take the risk.

"Anything that can help bring quality of life with this disease is worth trying . . . It gives hope."

[2] The manufacturer reported to CADTH that the physician and Roche assessed this event of PML as unrelated to ocrelizumab treatment.[47]

Patients expect that, when first-line therapies are no longer effective or tolerated, they will have a wider choice of therapeutic options to control their MS. Such treatments should be amenable to an individual's lifestyle and have tolerable side effects. Based on promising results, patients feel that ocrelizumab would be a welcome addition to the current suite of therapeutic options for MS.

Appendix 2: Literature Search Strategy

Overview	
Interface:	Ovid
Databases:	Embase 1974 to present Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 13 2017
Alerts:	Weekly search updates until October 18 2017
Limits:	No date or language limits were used Conference abstracts were excluded

Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) **1946 to Present**
oemezd	Ovid database code; Embase 1974 to present, updated daily

Multi-Database Strategy	
1.	(ocrevus* or ocrelizumab* or PR070769 or PR0-70769 or R1594 or R-1594 or PRO70769 or PRO-70769 or A10SJL62JY or 637334-45-3).ti,ab,kf,ot,hw,rn,nm.
2.	1 use ppez
3.	*ocrelizumab/
4.	(ocrevus* or ocrelizumab* or PR070769 or PR0-70769 or R1594 or R-1594 or PRO70769 or PRO-70769 or A10SJL62JY or 637334-45-3).ti,ab,kw.
5.	3 or 4
6.	5 use oemezd
7.	2 or 6

Multi-Database Strategy
8. remove duplicates from 7
9. conference abstract.pt.
10. 8 not 9

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

Grey Literature

Dates for Search:	June 5 – June 9
Keywords:	Ocrevus
Limits:	No date or language limits used

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

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- databases (free)
- Internet search.

Appendix 3: Detailed Outcome Data

Table 23: Summary of Efficacy Outcomes

Time Point	Parameters	OPERA-I		OPERA-II	
		IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)
Multiple Sclerosis Functional Composite					
Baseline	n	359	360	342	358
	Mean (SE)	0.028 (0.034)	–0.012 (0.040)	–0.001 (0.033)	0.026 (0.034)
Week 96	n	308	322	269	308
	Mean change (SE)	0.174 (0.031)	0.213 (0.031)	0.169 (0.029)	0.276 (0.028)
	MD (95% CI)	0.039 (–0.039 to 0.116)		0.107 (0.034 to 0.180)	
	P value	0.3261		0.0040	
Total Number of T1 Gadolinium−Enhancing Lesions					
Baseline to week 96	n	377	388	375	389
	Total GdE lesions	337	21	465	21
	Number MRI scans	1,064	1,118	1,017	1,117
	Rate (95% CI)	0.286 (0.200 to 0.409)	0.016 (0.009 to 0.030)	0.416 (0.309, 0.561)	0.021 (0.012, 0.036)
	Rate ratio	0.058 (0.032 to 0.104)		0.051 (0.029 to 0.089)	
	P value	< 0.0001		< 0.0001	
Week 24	n	372	382	372	385
	Total GdE lesions	106	12	143	10
	Rate	0.155	0.014	0.302	0.023
	Rate ratio	0.092 (0.042 to 0.199)		0.077 (0.036 to 0.164)	
	P value	< 0.0001		< 0.0001	
Week 48	n	357	377	334	373
	Total GdE lesions	82	2	154	6
	Rate	0.182	0.004	0.327	0.015
	Rate ratio	0.023 (0.005 to 0.101)		0.044 (0.018 to 0.112)	
	P value	< 0.0001		< 0.0001	
Week 96	n	335	359	311	359
	Total GdE lesions	149	7	168	5
	Rate	0.407	0.019	0.539	0.015
	Rate ratio	0.046 (0.018 to 0.116)		0.028 (0.010 to 0.077)	
	P value	< 0.0001		< 0.0001	
Total number of New and Enlarging T2 Lesions					
Baseline to week 96	n	378	390	376	390
	Total T2 lesions	1,916	430	2,103	380
	Number MRI scans	1,066	1,123	1,025	1,123
	Rate (95% CI)	1.413 (1.123 to 1.777)	0.323 (0.256 to 0.407)	1.904 (1.536 to 2.359)	0.325 (0.259 to 0.409)
	Rate ratio	0.229 (0.174 to 0.300)		0.171 (0.130 to 0.225)	
	P value	< 0.0001		< 0.0001	
Week 24	n	373	385	374	387
	Total T2 lesions	739	392	800	327
	Rate	1.338	0.788	1.886	0.742
	Rate ratio	0.589 (0.444 to 0.780)		0.393 (0.294 to 0.526)	
	P value	0.0002		< 0.0001	

Time Point	Parameters	OPERA-I		OPERA-II	
		IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)
Week 48	n	357	378	337	376
	Total T2 lesions	343	23	458	23
	Rate	0.764	0.047	1.055	0.047
	Rate ratio	0.061 (0.034 to 0.111)		0.044 (0.025 to 0.079)	
	P value	< 0.0001		< 0.0001	
Week 96	n	336	360	314	360
	Total T2 lesions	834	15	845	30
	Rate	1.961	0.033	2.329	0.072
	Rate ratio	0.017 (0.009 to 0.032)		0.031 (0.018 to 0.053)	
	P value	< 0.0001		< 0.0001	
New T1 Hypointense Lesions					
Baseline to week 96	n	377	388	375	389
	Total T1 hypointense lesions	1,307	564	1,484	567
	Number MRI scans	1,064	1,116	1,016	1,115
	Rate	0.982	0.420	1.255	0.449
	Rate ratio	0.428 (0.328 to 0.557)		0.357 (0.272 to 0.470)	
	P value	< 0.0001		< 0.0001	
Week 24	n	372	381	372	385
	Mean (SD)	1.98 (5.25)	1.44 (3.73)	2.06 (4.80)	1.38 (3.68)
Week 48	n	357	377	334	373
	Mean (SD)	0.55 (1.78)	0.03 (0.30)	0.84 (2.94)	0.04 (0.27)
Week 96	n	335	358	310	357
	Mean (SD)	1.11 (2.93)	0.01 (0.12)	1.41 (3.78)	0.06 (0.59)
Brain Volume					
Baseline (Week 24)	n	309	328	294	336
	Mean (SE)	1,488.325 (4.959)	1,492.170 (4.641)	1,492.984 (5.453)	1,497.599 (5.048)
Week 24 to week 48	n	305	319	290	332
	Mean change (SE)	–0.294 (0.033)	–0.248 (0.032)	–0.306 (0.035)	–0.267 (0.032)
	MD (95% CI)	0.046 (–0.030 to 0.123)		0.039 (–0.039 to 0.117)	
Week 24 to week 96	n	267	281	259	287
	Mean change (SE)	–0.741 (0.046)	–0.572 (0.044)	–0.750 (0.051)	–0.638 (0.049)
	MD (95% CI)	0.168 (0.053 to 0.283)		0.112 (–0.018 to 0.241)	
	P value	0.0042		0.0900	
SF-36 PCS					
Baseline	n	338	357	319	355
	Mean (SE)	45.399 (0.529)	45.065 (0.507)	44.552 (0.544)	44.307 (0.541)
Baseline to week 48	n	332	346	307	337
	Mean change (SE)	–0.731 (0.442)	–0.026 (0.428)	–0.844 (0.435)	0.268 (0.413)
	MD (95% CI)	0.705 (–0.300 to 1.710)		1.112 (0.111 to 2.113)	
Baseline to week 96	n	309	331	276	315
	Mean change (SE)	–0.657 (0.475)	0.036 (0.456)	–0.833 (0.472)	0.326 (0.444)
	MD (95% CI)	0.693 (–0.414 to 1.800)		1.159 (0.051 to 2.268)	
	P value	0.2193		0.0404	
SF-36 MCS					
Baseline	n	338	357	319	355

Time Point	Parameters	OPERA-I		OPERA-II	
		IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)
	Mean (SE)	45.399 (0.529)	45.065 (0.507)	45.586 (0.572)	45.855 (0.571)
Baseline to week 48	n	332	346	307	337
	Mean change (SE)	–0.731 (0.442)	–0.026 (0.428)	0.699 (0.538)	1.053 (0.509)
	MD (95% CI)	0.705 (–0.300 to 1.710)		0.355 (–0.924 to 1.633)	
Baseline to week 96	n	309	331	276	315
	Mean change (SE)	–0.657 (0.475)	0.036 (0.456)	0.851 (0.577)	1.678 (0.541)
	MD (95% CI)	0.693 (–0.414 to 1.800)		0.827 (–0.558 to 2.212)	
	P value	0.2193		0.2413	
No Evidence of Disease Activity					
Week 96	NEDA, n (%)	79 (27.1%)	137 (47.4%)	65 (24.1%)	127 (43.9%)
	RD (95% CI)	20.3 (12.56 to 27.95)		19.9 (12.21 to 27.54)	
	RR (95% CI)	1.74 (1.39 to 2.17)		1.81 (1.41 to 2.32)	
	P value	< 0.0001		0.0001	

CI = confidence interval; GdE = gadolinium-enhancing; IFN = interferon beta-1a; MD = mean difference; MRI = magnetic resonance imaging; NEDA = no evidence of disease activity; OCR = ocrelizumab; RD = risk difference; RR = relative risk; SD = standard deviation; SE = standard error; SF-36 MCS = Short Form (36) Health Survey mental component summary; SF-36 PCS = Short Form (36) Health Survey physical component summary.

Table 24: Missing Data for Continuous Variables

Time Point	Number of Patients				Percentage of Randomized Patients			
	OPERA-I		OPERA-II		OPERA-I		OPERA-II	
	IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)	IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)
Multiple Sclerosis Functional Composite								
Baseline	359	360	342	358	87	88	82	86
Week 96	308	322	269	308	75	78	64	74
Total Number of T1 Gadolinium−Enhancing Lesions								
Baseline to week 96	377	388	375	389	92	94	90	93
Week 24	372	382	372	385	91	93	89	92
Week 48	357	377	334	373	87	92	80	89
Week 96	335	359	311	359	82	87	74	86
Total Number of New and Enlarging T2 Lesions								
Baseline to week 96	378	390	376	390	92	95	90	94
Week 24	373	385	374	387	91	94	89	93
Week 48	357	378	337	376	87	92	81	90
Week 96	336	360	314	360	82	88	75	86
Total Number of New T1 Hypointense Lesions								
Baseline to week 96	377	388	375	389	92	94	90	93
Week 24	372	381	372	385	91	93	89	92
Week 48	357	377	334	373	87	92	80	89
Week 96	335	358	310	357	82	87	74	86
Brain Volume								
Baseline (Week 24)	309	328	294	336	75	80	70	81
Week 24 to week 48	305	319	290	332	74	78	69	80
Week 24 to week 96	267	281	259	287	65	68	62	69

Time Point	Number of Patients				Percentage of Randomized Patients			
	OPERA-I		OPERA-II		OPERA-I		OPERA-II	
	IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)	IFN (N = 411)	OCR (N = 410)	IFN (N = 418)	OCR (N = 417)
SF-36 PCS								
Baseline	338	357	319	355	82	87	76	85
Baseline to week 48	332	346	307	337	81	84	73	81
Baseline to week 96	309	331	276	315	75	81	66	76
SF-36 MCS								
Baseline	338	357	319	355	82	87	76	85
Baseline to week 48	332	346	307	337	81	84	73	81
Baseline to week 96	309	331	276	315	75	81	66	76

IFN = interferon beta-1a; OCR = ocrelizumab; SF-36 MCS = Short Form (36) Health Survey mental component summary; SF-36 PCS = Short Form (36) Health Survey physical component summary.

Table 25: Concomitant Use of Corticosteroids in OPERA-I and OPERA-II

Concomitant Corticosteroids n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
Corticosteroids	167 (40.8)	140 (34.3)	168 (40.3)	142 (34.1)
Methylprednisolone	125 (30.6)	88 (21.6)	123 (29.5)	95 (22.8)
Prednisone	23 (5.6)	25 (6.1)	24 (5.8)	18 (4.3)
Hydrocortisone	8 (2.0)	15 (3.7)	6 (1.4)	13 (3.1)
Dexamethasone	8 (2.0)	10 (2.5)	7 (1.7)	7 (1.7)
Methylprednisolone aceponate	9 (2.2)	1 (0.2)	2 (0.5)	1 (0.2)
Mometasone	6 (1.5)	4 (1.0)	5 (1.2)	7 (1.7)
Fluticasone/mometasone	5 (1.2)	2 (0.5)	1 (0.2)	2 (0.5)
Prednisolone	3 (0.7)	4 (1.0)	5 (1.2)	1 (0.2)
Fluticasone	3 (0.7)	2 (0.5)	4 (1.0)	3 (0.7)
Betamethasone	1 (0.2)	3 (0.7)	2 (0.5)	8 (1.9)
Budesonide	1 (0.2)	3 (0.7)	1 (0.2)	5 (1.2)
Triamcinolone	3 (0.7)	1 (0.2)	0	6 (1.4)
Cortisone	2 (0.5)	1 (0.2)	3 (0.7)	3 (0.7)
Hydrocortisone sodium succinate	0	3 (0.7)	0	1 (0.2)
Beclometasone	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.2)
Betamethasone dipropionate	1 (0.2)	1 (0.2)	0	1 (0.2)
Clobetasol	1 (0.2)	1 (0.2)	0	5 (1.2)
Fluocinolone acetonide	1 (0.2)	1 (0.2)	NR	NR
Betamethasone dipropionate/ betamethasone sodium phosphate	1 (0.2)	0	1 (0.2)	0
Ciclesonide	1 (0.2)	0	1 (0.2)	2 (0.5)
Cortivazol	1 (0.2)	0		
Desonide	1 (0.2)	0	1 (0.2)	0
Fluocinonide	0	1 (0.2)	0	1 (0.2)
Fluorometholone	1 (0.2)	0	0	1 (0.2)
Fluprednidene acetate	0	1 (0.2)	NR	NR
Fluticasone furoate	1 (0.2)	0	NR	NR

Concomitant Corticosteroids n (%)	OPERA-I		OPERA-II	
	IFN (N = 409)	OCR (N = 408)	IFN (N = 417)	OCR (N = 417)
Methylprednisolone sodium succinate	1 (0.2)	0	1 (0.2)	0
Prednisolone acetate	1 (0.2)	0	1 (0.2)	0
Prednisolone hemisuccinate	1 (0.2)	0	0	2 (0.5)
Prednisolone sodium metasulfobenzoate	0	1 (0.2)	2 (0.5)	0
Prednisolone sodium succinate	1 (0.2)	0	NR	NR
Methylprednisolone acetate	NR	NR	2 (0.5)	2 (0.5)
Triamcinolone	NR	NR	2 (0.5)	1 (0.2)
Betamethasone valerate	NR	NR	0	2 (0.5)
Loteprednol	NR	NR	1 (0.2)	1 (0.2)
Corticosteroid NOS	NR	NR	0	1 (0.2)
Deflazacort	NR	NR	1 (0.2)	0
Dexamethasone acetate	NR	NR	1 (0.2)	0
Dexamethasone sodium phosphate	NR	NR	0	1 (0.2)
Hydrocortisone acetate	NR	NR	1 (0.2)	0
Hydrocortisone butyrate	NR	NR	0	1 (0.2)
Meprednisone	NR	NR	0	1 (0.2)
Steroid NOS	NR	NR	1 (0.2)	0

IFN = interferon beta-1a; NOS = not otherwise specified; NR = none reported; OCR = ocrelizumab.

Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Table 26: Sensitivity Analyses for Annualized Relapse Rate

Analysis	OPERA-I		OPERA-II	
	Rate Ratio (95% CI)	*P* value	Rate Ratio (95% CI)	*P* value
ITT analysis	0.536 (0.400 to 0.719)	< 0.0001	0.532 (0.397 to 0.714)	< 0.0001
PP population	0.514 (0.380 to 0.696)	< 0.0001	0.528 (0.391 to 0.712)	< 0.0001
Safety population	0.537 (0.400 to 0.719)	< 0.0001	0.532 (0.397 to 0.714)	< 0.0001
Additional covariates	0.541 (0.405 to 0.723)	< 0.0001	0.547 (0.409 to 0.732)	< 0.0001
Poisson model	0.552 (0.432 to 0.706)	< 0.0001	0.545 (0.427 to 0.697)	< 0.0001
50% imputation	0.538 (0.402 to 0.718)	NA	0.516 (0.390 to 0.684)	N/A
100% imputation	0.537 (0.411 to 0.701)	< 0.0001	0.507 (0.397 to 0.647)	< 0.0001

CI = confidence interval; ITT = intention-to-treat; NA = not applicable; PP = per-protocol.

Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Table 27: Adverse Events Reported in 2% or More of Patients

Adverse Events, n (%)	Pooled RMS Population	
	IFN (N = 826)	OCR (N = 825)
At least one adverse event	603 (73.0)	620 (75.2)
Infusion-related reaction	80 (9.7)	283 (34.3)
Headache	124 (15.0)	93 (11.3)
Influenza-like illness	177 (21.4)	38 (4.6)
Upper respiratory tract infection	87 (10.5)	125 (15.2)
Nasopharyngitis	84 (10.2)	122 (14.8)

Adverse Events, n (%)	Pooled RMS Population	
	IFN (N = 826)	OCR (N = 825)
Urinary tract infection	100 (12.1)	96 (11.6)
Fatigue	64 (7.7)	64 (7.8)
Injection-site erythema	127 (15.4)	1 (0.1)
Depression	54 (6.5)	64 (7.8)
Arthralgia	51 (6.2)	46 (5.6)
Sinusitis	45 (5.4)	46 (5.6)
Back pain	37 (4.5)	53 (6.4)
Insomnia	38 (4.6)	46 (5.6)
Influenza	38 (4.6)	38 (4.6)
Pain in extremity	35 (4.2)	39 (4.7)
Bronchitis	29 (3.5)	42 (5.1)
Dizziness	35 (4.2)	28 (3.4)
Pyrexia	38 (4.6)	23 (2.8)
Muscle spasms	30 (3.6)	30 (3.6)
Pharyngitis	33 (4.0)	25 (3.0)
Nausea	28 (3.4)	28 (3.4)
Anxiety	27 (3.3)	28 (3.4)
Myalgia	35 (4.2)	20 (2.4)
Paresthesia	27 (3.3)	24 (2.9)
Diarrhea	21 (2.5)	28 (3.4)
Hypoesthesia	29 (3.5)	19 (2.3)
Injection-site reaction	45 (5.4)	2 (0.2)
Rash	25 (3.0)	22 (2.7)
Gastroenteritis	19 (2.3)	25 (3.0)
Musculoskeletal pain	24 (2.9)	18 (2.2)
Migraine	16 (1.9)	25 (3.0)
Oral herpes	17 (2.1)	24 (2.9)
Viral infection	23 (2.8)	18 (2.2)
Constipation	17 (2.1)	23 (2.8)
Hypertension	23 (2.8)	17 (2.1)
Vertigo	22 (2.7)	17 (2.1)
Cough	12 (1.5)	25 (3.0)
Cystitis	18 (2.2)	18 (2.2)
Respiratory tract infection	17 (2.1)	19 (2.3)
Alanine aminotransferase increased	24 (2.9)	9 (1.1)
Contusion	12 (1.5)	18 (2.2)
Leukopenia	22 (2.7)	8 (1.0)
Chills	21 (2.5)	8 (1.0)
Vomiting	11 (1.3)	17 (2.1)
Anemia	17 (2.1)	8 (1.0)
Hepatic enzyme increased	22 (2.7)	3 (0.4)
Herpes zoster	8 (1.0)	17 (2.1)
Pruritus	6 (0.7)	17 (2.1)

IFN = interferon beta-1a; OCR = ocrelizumab; RMS = relapsing multiple sclerosis.

Source: Common Technical Document 2.7.4.[2]

Appendix 4: Validity of Outcome Measures

Aim

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

- Kurtzke Expanded Disability Status Scale (EDSS)
- Multiple Sclerosis Functional Composite (MSFC) score
- Short Form (36) Health Survey (SF-36)
- magnetic resonance imaging (MRI) outcomes.

Findings

Kurtzke Expanded Disability Status Scale

The EDSS is an ordinal scale used to measure disability in MS. It addresses disability in eight functional systems (FSs): pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. The EDSS score is a composite ranging from 0 to 10 (in increments of 0.5) that incorporates FS grades as well as the degree of functional disability and ambulation (Table 28).[36] Scores from 0 to 4.5 represent normal ambulation, while scores of 5 and higher represent a progressive loss of ambulatory ability.

The distribution of EDSS scores among MS patients is typically biphasic, accumulating around two to three points, and six to seven points, indicating that patients do not stay at each step of the scale for equally long periods. There are many criticisms of the EDSS, including the fact that it has moderate intra-rater reliability (kappa values from 0.32 to 0.76 for overall EDSS and from 0.23 to 0.58 for the individual FSs have been reported);[36] it has poor assessment of upper-limb and cognitive function, and it lacks a linear relationship between score difference and clinical severity.[48-51] Another limitation is that it relies heavily on the evaluation of motor function and the ability to walk. As a result, a patient who might not be able to walk but who maintains full dexterity is classified toward the severe end of the scale.

In published literature,[52] the MCID was determined to be a 1.0 point change when the EDSS score was less than 5.5, and a 0.5 point change when the EDSS score was from 5.5 to 8.5.

Table 28: Scoring of Expanded Disability Status Scale

	Normal neurological exam (all grade 0 in functional systems; cerebral grade 1 acceptable)
1	No disability, minimal signs in one FS (i.e., grade 1, excluding cerebral grade 1)
1.5	No disability, minimal signs in more than one FS (more than one grade 1, excluding cerebral grade 1)
2.0	Minimal disability in one FS (one FS grade 2; other 0 or 1)
2.5	Minimal disability in two FSs (two FS grade 2; others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3; others 0 or 1) or mild disability in three or four FSs (three/four FSs grade 2; others 0 or 1) although fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FSs grade 2; or two FSs grade 3; or five FSs grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relative severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps; able to walk without

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

FS = functional system; MS = multiple sclerosis.

Multiple Sclerosis Functional Composite

The MSFC is a measure of MS disability developed in 1994 by a task force convened by the US National Multiple Sclerosis Society.[53,54] The MSFC assesses different clinical dimensions: arm (9-Hole Peg Test [9-HPT] = time to insert and remove nine pegs), leg (timed 25-foot walk [T25FW]), and cognition (Paced Auditory Serial Addition Test [PASAT] 3 = number of correct additions). The raw scores for each item are transformed into z scores to achieve a common metric in standard deviation [SD] units (i.e., mean of 0 and SD of 1). A z score represents the number of SDs a patient's test result is higher ($z > 0$) or lower ($z < 0$) than the average test result ($z = 0$) of the reference population. The mean and SD from test results at the baseline visit for all patients in each study were used as the reference population values to create the z scores for each component of the composite. The z score is calculated by subtracting the mean of the reference population from the test result and then dividing this by the SD of the reference population. For the T25FW and 9-HPT, a higher test result means the patient worsened from baseline. For PASAT3, a higher test result means the patient improved from baseline. To ensure that all measures are in the same direction, a transformation is necessary. In creating the composite outcome measure, it was decided that a higher test result would indicate improvement from baseline.[54] Psychometric properties and MCID in MS patients are provided below:

Test–retest reliability: In a study of a small cohort of patients (10 patients) in which the MSFC was administered to each patient twice over a two-week period for a total of six assessments, inter-examiner reliability and intra-class coefficients were reported to be 0.98 and 0.96, respectively.[35,36]

Construct validity: Scores were lower in more disabled patients (–0.4 in primary-progressive MS, –0.3 in secondary-progressive MS, and +0.42 in relapsing-remitting MS).[53]

Convergent validity (correlation with EDSS): A study by Ozakbas et al. (N = 38) found a moderate-to-strong correlation between EDSS and MSFC. In looking at individual components, the EDSS had the lowest correlation (r = 0.31) with the PASAT3, and the authors suggested this might confirm the observation of poor assessment of cognitive function by EDSS. The strongest correlation was between EDSS and T25WT (r = 0.84) followed by 9-HPT (r = 0.51 [moderately correlated]); again, consistent with the observation of poor assessment of upper-limb function by EDSS. A systematic review of MSFC found the correlation with EDSS ranged from –0.41 to –0.83.[36]

MCID: A 20% change in T25FW and 9HPT scores, and a 0.5 SD change in PASAT3 scores, are considered clinically meaningful; however, a clinically meaningful value for overall MSFC score has not been determined.[53]

Short Form (36) Health Survey

The SF-36 is a generic health assessment questionnaire that is used to study the impact of chronic disease on health-related quality of life. The multi-item questionnaire contains eight dimensions: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS), which are created by aggregating the eight domains according to a scoring algorithm. The PCS and MCS and eight dimensions are each measured on a scale of 0 to 100, which are T scores (mean of 50 and SD of 10) that have been standardized to the US general population.[37] Thus, a score of 50 on any scale would be at the average or norm of the general US population, and a score 10 points lower (i.e., 40) would be one SD below the norm.[37] An increase in score indicates improvement in health status on any scale. In general use, a change of two points in the SF-36 PCS and three points in the SF-36 MCS indicates a clinically meaningful improvement, as determined by the patient.

Summary scores of SF-36 in the MS patient population should be reported and interpreted with caution. This is the result of the inability to explain variability in the social functioning and SF-36 component scores. As well, orthogonal factor rotations are used to generate weighting coefficient for summary scores.[55] In addition, the SF-36 has been reported to overestimate the mental health of MS patients on the mental health summary scale.[56]

Magnetic Resonance Imaging Outcomes

MRI techniques play an important role in the diagnosis of multiple sclerosis. In addition, they are valuable in monitoring treatment response and predicting disease progression. However, the correlation between the burden of lesions observed on MRI scans and the clinical manifestations of the disease remains controversial.[57-59]

In CARE-MS II,[60] the following MRI outcomes were measured between treatment groups: number of new and enlarging hyperintense lesions on T2-weighted images, number of

hyperintense lesions on T2-weighted images, and number of gadolinium-enhancing lesions. These conventional MRI outcomes are widely used to monitor treatment effects in clinical trials of MS. Their roles as a surrogate for clinical outcomes such as relapses and disability progression in relapsing-remitting MS have been investigated in previous research. Findings from systematic reviews and large randomized controlled trials reporting the correlations between the treatment effect on relapses and disability progression and the treatment effect on MRI lesions are presented in Table 29. In these studies, patients with relapsing-remitting MS received interferon, cladribine, fingolimod, placebo, or no drug treatment. The correlations between MRI outcomes and clinical outcomes (relapses and disability progression) varied across studies.

Table 29: Summary of Correlations Between MRI Outcomes and Clinical Outcomes

Study	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
Sormani et al. 2013[61]	• 31 RCTs of all available DMTs for RRMS; published from 2008 to 2012	• Number of MRI lesions • ARR • MRI effect: ratio between the average number of MRI lesions per patient in the experimental arm and in the control arm • REL effect: ratio between the relapse rate in the experimental arm and in the control arm • Coefficient of determination (R^2): used to assess the goodness of fit for a regression equation in which the treatment effect on relapses was predicted by MRI results	Data from 31 RCTs were used in deriving regression equation. R^2 = 0.71, suggesting a good degree of prediction of REL effect using MRI effect.	The effect of a treatment on relapses can be accurately predicted by the effect of that therapy on MRI lesions.
Sormani et al. 2010[62]	• 3 RCTs enrolling RRMS patients (cladribine versus placebo; fingolimod versus placebo; fingolimod versus interferon) • Follow-up: 12 to 24 months	• MRI effect: ratio between the average number of new and enlarging T2 lesions per patient in the experimental arm and in control arm • REL effect: ratio between the ARR in the experimental arm and in the control arm • DIS effect: ratio between % of patients with disability progression (≥ 1 point on EDSS at month 3) in experimental and control arms • Regression equations from previous meta-analyses were used to predict the drug effect on relapse (REL effect) and disability progression (DIS effect) based on MRI effect	92% of observed effects of oral drugs (cladribine and fingolimod) on clinical outcomes were close to those predicted by MRI active lesions. From the regression lines provided in the article, 10 out of 12 observed effects on the clinical variables were very close to those predicted by the lines.	MRI markers were able to predict treatment effects on clinical end points in RRMS patients treated with novel oral drugs.

Study	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
Sormani et al. 2010[63]	• The PRISMS study enrolling 560 RRMS patients: subcutaneous interferon versus placebo • Follow-up: 2 years	• PTE on relapses that was accounted for by the effect of treatment on the MRI marker	New T2 lesions and relapses were significantly correlated: compared with placebo, interferon significantly lowered new T2 lesions by 60% over 2 years, and relapses by 30%. PTE on relapses accounted for by the effect of treatment on new T2 MRI lesions was 53% in RRMS patients. A pooled PTE of 62% was found when meta-analysis was performed on data from PRISMS and 2 other trials of DMTs.	The study provides evidence that new T2 MRI lesion count is a surrogate for relapses in MS patients treated with interferon or drugs with similar mechanism of action.
Kappos et al. 1999[64]	• Patients in natural-course studies or treated with placebo or observed in the pre-treatment phase of controlled clinical trials • 77% of the patients had RRMS; 23% had secondary-progressive MS • Follow-up: 6 to 24 months	• Change in disability: assessed by EDSS • Relapse • MRI data	Relapse rate in the first year was predicted with moderate ability by mean number of GdE lesions: RR 1.13, *P* = 0.023 The mean of GdE lesion counts in the first 6 monthly scans was weakly predictive of EDSS change after 1 year: OR 1.34, *P* = 0.082; and 2 years: OR 1.65, *P* = 0.049.	GdE MRI was not a strong predictor of the development of cumulative impairment or disability.

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

Conclusion

A summary of the characteristics of five instruments was provided: two measuring disability (EDSS and MSFC) and one measuring health-related quality of life (SF-36). In addition, the correlation between MRI outcomes and clinical outcomes such as relapses and progression in disability in MS patients with relapsing-remitting MS were examined.

With respect to the reliability and validity of the instruments:

- EDSS had moderate reliability and a published MCID of 1.0-point change when the score was below 5.5, and a 0.5-point change when the score was between 5.5 to 8.5.
- MSFC shows good construct validity but is only moderately correlated with EDSS.
- SF-36 reporting should be detailed by domain, as summary reporting may have unexplainable variability and is known to overestimate mental health of MS patients.

No MCID was available for the SF-36 with regard to patients with MS. A 20% change in T25FW and 9HPT scores, and a 0.5 SD change in PASAT3 scores are considered clinically meaningful in MSFC; however, an MCID for the overall MSFC score has not been determined.

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

Appendix 5: Summary of Extension Study

Aim

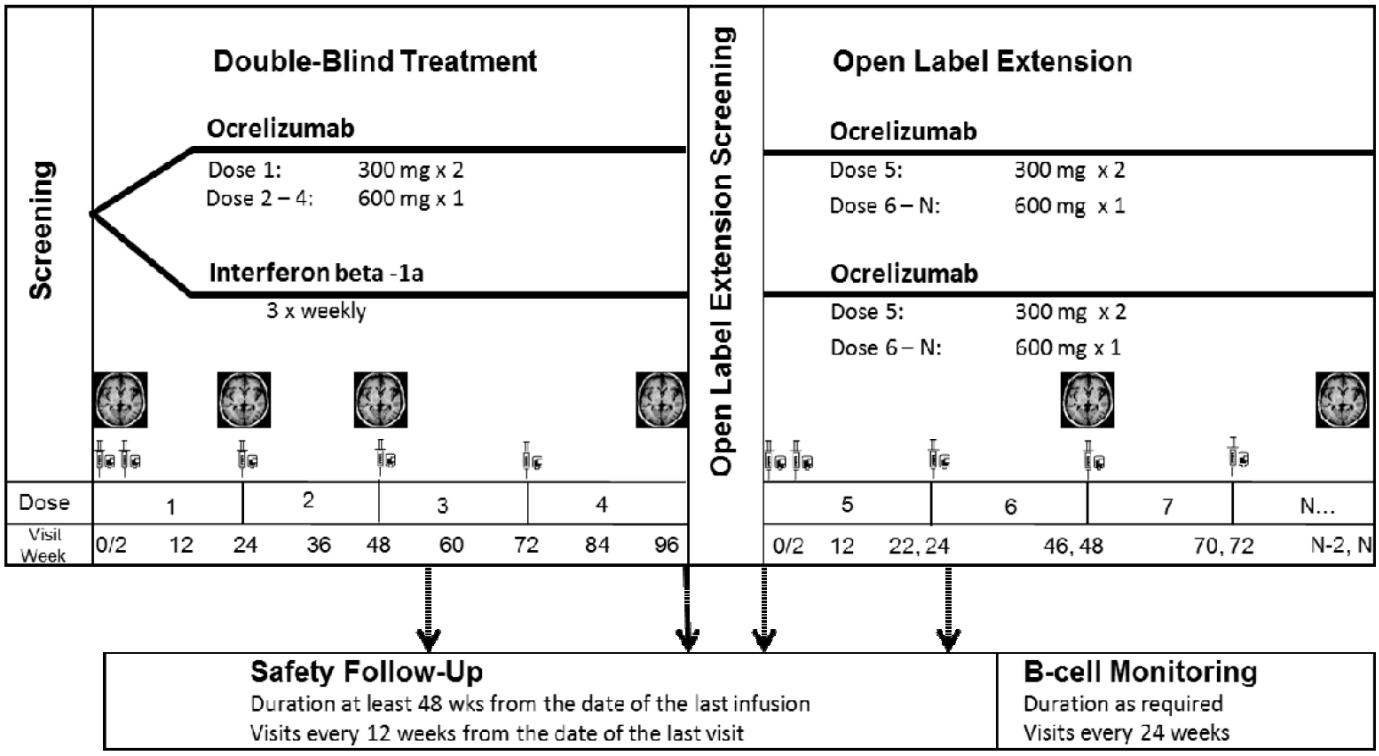
To summarize results of the OPERA-I and OPERA-II open-label extension (OLE) phases.

Study Design

OPERA-I and OPERA-II were identically designed multi-centre, parallel-group, double-blind, double-dummy, active-comparator studies, and both included an OLE phase at the end of the 96-week double-blind treatment period. To be eligible to enter the OLE phase, patients had to complete the 96-week double-blind treatment period and be willing to continue treatment with ocrelizumab (OCR). Patients had a four-week screening period if they were willing to move to the OLE phase. Otherwise, patients unwilling to enter the OLE phase had a safety follow-up for 48 weeks. To be included, the investigator had to deem the patient likely to benefit from OCR treatment. The OLE phase continued until OCR became available in the country of the patient, or until four years following the last visit in the double-blind treatment period. OCR was given to all enrolled patients according to the same dosage schedule as during the double-blind treatment phase (initial dose at two 300 mg injections 15 days apart, subsequent doses of one 600 mg injection every 24 weeks). Original treatment assignment remained unknown. Figure 13 provides a schematic showing the design of the OPERA-I and OPERA-II trials as well as the OLE study.

The OLE phase of both studies aimed to describe the long-term safety and tolerability of OCR. Both extension phases of OPERA-I and OPERA-II were descriptive in nature, with no comparison group. All results were reported using general descriptive statistics (e.g., mean, median, standard deviation, range, etc.). Missing or incomplete data were not imputed. These extension phases are still currently running. Interim safety results were reported in the clinical study report and are presented here. Results represented all ongoing patients at varying time periods (up to two years).

Figure 13: Flow Diagram of OPERA-I and OPERA-II



Source: Common Technical Document 2.7.3.[1]

Patient Disposition

The OLE phase of OPERA-I included 678 (96%) of 706 patients who had completed the 96-week double-blind treatment phase. In OPERA-II, 647 (95%) of 680 patients who had completed the 96-week double-blind treatment phase proceeded to the OLE phase.

Table 30: Patient Disposition

Disposition, n (%)	OPERA-I		OPERA-II	
	IFN/OCR	OCR/OCR	IFN/OCR	OCR/OCR
Randomized to double-blind treatment period (total), N	821		835	
Randomized to double-blind treatment period (arms), N	411	410	418	417
Completed to week 96 of double-blind treatment period, n (%)	340 (82.7)	44 (89.3)	320 (76.6)	360 (86.3)
Entered OLE phase, n (%)	326 (79.3)	352 (85.9)	297 (71.1)	350 (83.9)
Withdraw after OLE enrolment, n (%)	10	19	15	10
Ongoing, n (%)	316	333	282	340

IFN = interferon beta-1a; OCR = ocrelizumab; OLE = open-label extension.

Source: Common Technical Document 2.7.3[1] and Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Demographic Characteristics

Demographic characteristics of patients entering the OLE in OPERA-I and OPERA-II were not provided in the available reports.

Drug Exposure

The available interim reports for the ongoing OLE phase of OPERA-I and OPERA-II indicate that approximately 70% and 75% of OLE-enrolled patients received one or two doses in OPERA-I and OPERA-II, respectively. The mean total cumulative dose was more than 1,200 mg in OPERA-I for both arms (1,208.9 mg, standard deviation [SD] 518.7 mg, for the interferon beta-1a (IFN)/OCR arm, and 1,234.9 mg, SD 523.9, for the OCR/OCR arm). In OPERA-II, the mean total cumulative dose was 1,093.2 mg (SD 539.7) and 1,138.3 mg (526.6) for the IFN/OCR arm and the OCR/OCR arm, respectively.

Efficacy

Efficacy results of the OLE phase were reported as a pooled analysis for OPERA-I and OPERA-II OLE studies. The annualized relapse rate was reported as 0.137 in the IFN/ OCR patients, and 0.142 in the OCR/OCR group. Data on new and enlarging hyperintense lesions on T2-weighted images at week 46 of the OLE phase were available for 181 and 211 patients in the pooled IFN/OCR group and OCR/OCR groups, respectively. These show a mean of 0.34 (SD 0.89) new or enlarged lesions in the IFN/OCR group and a mean of 0.19 (SD 1.53) new or enlarged lesions in the OCR/OCR group. Table 31 provides an overview of available efficacy results.

Table 31: Available Efficacy Results in the Pooled Open-Label Extension Population of OPERA-I and OPERA-II, Pooled Intention-to-Treat Population

Efficacy Outcome	Pooled Data From OPERA-I and OPERA-II ITT Populations	
	IFN/OCR (N = 623)	OCR/OCR (N = 702)
Total number of relapses	49	59
Total patient-years followed	356.4	416.6
Unadjusted annualized relapse rate	0.137	0.142
New and/or enlarging T2 hyperintense lesions at OLE week 46		
Number of patients with MRI data at OLE week 46	181	211
Total number of lesions	61	41
Mean (SD)	0.34 (0.89)	0.19 (1.53)

IFN = interferon; ITT = intention-to-treat; MRI = magnetic resonance imaging; OCR = ocrelizumab; OLE = open-label extension; SD = standard deviation.
Source: Common Technical Document 2.7.3.[1]

Safety

A summary of available safety results is outlined in Table 32. There were no deaths recorded in either OLE study periods. Two malignancies were reported in OPERA-I, one adenocarcinoma of the colon in the IFN/OCR group, and one papillary thyroid cancer in the OCR/OCR group.

Table 32: Summary of Adverse Events From Open-Label Extension Phase of OPERA-I and OPERA-II

Adverse Events, n (%)	OPERA-I		OPERA-II	
	IFN / OCR N = 326	OCR / OCR N = 352	IFN / OCR N = 297	OCR / OCR N = 350
AE	180 (55.2)	184 (52.3)	163 (54.9)	210 (60.0)
SAE	5 (1.5)	19 (5.4)	8 (2.7)	12 (3.4)
Serious infection	1 (0.3)	5 (1.4)	3 (1.0)	3 (0.9)
WDSAE	1 (0.3)	2 (0.6)	0	2 (0.6)
SAE leading to dose modification/interruption	0	1 (0.3)	2 (0.7)	1 (0.3)
WDAE	4 (1.2)	3 (0.9)	4 (1.3)	2 (0.6)
AE leading to dose modification/interruption	5 (1.5)	1 (0.3)	5 (1.7)	1 (0.3)
Malignancies	1 (0.3)	1 (0.3)	0	0
Infections	100 (30.7)	111 (31.5)	79 (26.6)	140 (40.0)
Serious infections	3 (0.9)	5 (1.4)	4 (1.3)	3 (0.9)

AE = adverse event; IFN = interferon; OCR = ocrelizumab; SAE = serious adverse event; WDAE = withdrawal due to adverse event; WDAE = withdrawal due to serious adverse event.

Source: Clinical Study Reports for OPERA-I[31] and OPERA-II.[32]

Limitations

The OLE studies have several limitations imposed by the overall design: the lack of a randomized comparison group to provide context and control for potential confounders, and the open-label design may influence the perception of improvement by patients and clinicians. The specific limitations of these two extension studies include the following:

- an interim analysis that provides only one additional year of data to inform the tolerability of a drug indicated for a lifetime condition
- a lack of a group that would have been maintained on IFN, while another would have switched to OCR.

Because of these limitations, the OLE studies fail to provide high-quality information on the benefits of switching from IFN to OCR.

Summary

Efficacy results of the OLE phase were reported as a pooled analysis for the OPERA-I and OPERA-II OLE phases. The annualized relapse rate was reported as 0.137 in the IFN/OCR group, and 0.142 in the OCR/OCR group. Safety results were consistent with the those observed in the double-blind phase of the OPERA-I and OPERA-II studies.

Appendix 6: Summary of Indirect Treatment Comparisons

Background

Ocrelizumab has been previously compared with interferon beta-1a in two clinical trials. However, there is no head-to-head evidence comparing ocrelizumab against other relevant disease-modifying therapies (DMTs) that are used to treat relapsing-remitting multiple sclerosis (RRMS). The aim of this section is to summarize and critically appraise any indirect treatment comparisons (ITCs) that compare ocrelizumab (600 mg administered intravenously [IV] once every six months) with other DMTs for the management of RRMS.

Methods

Adult patients with a confirmed diagnosis of RRMS were evaluated in this review. The unpublished ITC submitted by the manufacturer[45] and a published ITC by the Institute for Clinical and Economic Review (ICER),[46] identified in a separate literature search, were summarized and critically appraised.

Description of Indirect Treatment Comparisons Identified

The manufacturer submitted an ITC[45] to evaluate the clinical efficacy and safety of ocrelizumab 600 mg administered every six months relative to all treatments likely to be indicated for RRMS following approval of ocrelizumab by the European Medicines Agency and the FDA (2017). The manufacturer performed a systematic review to identify relevant studies for inclusion in the ITC. While the authors of the manufacturer's ITC planned to provide results on a long list of outcomes, seven outcomes were eventually analyzed, including annualized relapse rate (ARR), confirmed disability progression (CDP) at 12 weeks, CDP at 24 weeks, proportion of patients who were free of relapses, discontinuations due to adverse events, serious adverse events, and all-cause discontinuations. Details regarding the inclusion criteria for the manufacturer-submitted ITC are presented in Table 33.

ICER performed an ITC to compare the efficacy and safety of daclizumab, glatiramer acetate, interferon beta-1a, peg-interferon beta-1a, interferon beta-1b, dimethyl fumarate, fingolimod, teriflunomide, alemtuzumab, natalizumab, and ocrelizumab for the treatment of patients with RRMS and primary-progressive multiple sclerosis (PPMS).[46] An overview of the inclusion criteria for the ICER ITC is presented in Table 33.

Table 33: Overview of Included Indirect Treatment Comparisons

	Manufacturer's ITC	ICER ITC
Patient Population	• Adults • Patients with relapsing forms of MS • Trials of mixed populations of RRMS and SPMS in which < 50% have SPMS	• Patients with RRMS or PPMS
Intervention	• Ocrelizumab (600 mg q.6.m.) • IFN beta-1a (SC 22 to 44 mcg t.i.w. or IM 30 mcg q.w.) • IFN beta-1b (250 to 500 mcg q.o.d.) • Pegylated interferon (125 mg q.2.w.) • Glatiramer acetate (20 mg q.d., 40 mg t.i.w.) • Natalizumab (300 mg q.4.w.) • Teriflunomide (7 or 14 mg q.d.) • Fingolimod (0.5 mg q.d.) • Dimethyl fumarate (240 mg b.i.d.) • Daclizumab (150 q.4.w.) • Alemtuzumab (12 mg for 5 days at start and 3 days at year-end) • Cladribine (3.5 mg/kg or 5.25 mg/kg cumulative doses)	Included the following as approved by the FDA: • Daclizumab • Glatiramer acetate • IFN beta-1a • Peg-IFN beta-1a • IFN beta-1b • Dimethyl fumarate • Fingolimod • Teriflunomide • Alemtuzumab • Natalizumab • Ocrelizumab
Comparators	• Placebo • IFN beta-1a (SC 22 to 44 mcg t.i.w. or IM 30 mcg q.w.) • IFN beta-1b (250 to 500 mcg q.o.d.) • Peg-IFN (125 mg q.2.w.) • Glatiramer acetate (20 mg q.d., 40 mg t.i.w.) • Natalizumab (300 mg q.4.w.) • Teriflunomide (7 or 14 mg q.d.) • Fingolimod (0.5 mg q.d.) • Dimethyl fumarate (240 mg b.i.d.) • Daclizumab (150 q.4.w.) • Alemtuzumab (12 mg for 5 days at start and 3 days at year-end) • Cladribine (3.5 mg/kg or 5.25 mg/kg cumulative doses)	• Best supportive care • Daclizumab • Glatiramer acetate • IFN beta-1a • Peg-IFN beta-1a • IFN beta-1b • Dimethyl fumarate • Fingolimod • Teriflunomide • Alemtuzumab • Natalizumab • Ocrelizumab
Outcomes	***Clinical Outcomes*** • Annualized relapse rate • Relapse-free proportion • Disability progression (12 week confirmed) • Disability progression (24 week confirmed) • GdE T1 lesions (number) • T2 lesions (volume) • Proportion of patients NEDA (+definition) ***Quality of Life*** • SF-36 • EQ-5D ***Safety Outcomes*** • Any adverse events • Serious adverse events • Discontinuations due to adverse events	***Clinical Outcomes*** • Relapse rates • Disability progression • Quality of life • Fatigue, mood • Cognitive function ***Safety Outcomes*** • Drug-related adverse events

	Manufacturer's ITC	ICER ITC
	• All-cause discontinuation • Mortality • Infections • Malignancies	
Study Design	Randomized controlled trials with a minimum duration of 12 weeks	Phase II or III randomized controlled trials

b.i.d. = twice daily; EQ-5D = Euro-Qol 5-Dimensions questionnaire; GdE = gadolinium-enhancing; ICER = Institute for Clinical and Economic Review; ITC = indirect treatment comparison; IFN = interferon; IM = intramuscular; MS = multiple sclerosis; NEDA = no evidence of disease activity; Peg = pegylated; PPMS = primary-progressive multiple sclerosis; q.2.w. = once every two weeks; q.4.w. = once every four weeks; q.6.m. = once every six months; q.d. = once a day; q.o.d. = every other day; q.w. = once weekly; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SF-36 = Short Form (36) Health Survey; SPMS = secondary-progressive multiple sclerosis; t.i.w. = three times per week.

Source: Manufacturer-submitted ITC[45] and ICER reports.[46]

Manufacturer-Submitted ITC

Objectives and Rationale

The rationale behind conducting the ITC was not clearly communicated. It can be assumed, however, that it was conducted because of the lack of head-to-head evidence comparing ocrelizumab (600 mg every six months) with DMTs other than interferon beta-1a.

Study Eligibility, Selection Process, and Data Extraction

The authors provided clear pre-specified eligibility criteria for the inclusion of potential studies (Table 33). In addition, a comprehensive search strategy was provided in the report. The authors of the manufacturer's ITC conducted their literature search using eight bibliographical databases. A grey literature search was also conducted. We were unable to find information regarding the screening process (e.g., whether they used two independent reviewers). Details of the methods used to extract data from the included studies were not reported.

Comparators

The authors planned to primarily compare ocrelizumab with all treatments that are likely to be indicated for RRMS at when ocrelizumab is approved by the European Medicines Agency and the FDA (2017). The list of comparators is provided in Table 33. These comparators were also considered to be appropriate in the Canadian setting, according to the clinical expert.

Outcomes

The outcomes investigated in the ITC included clinical end points, quality-of-life measurements, and adverse events (Table 33).

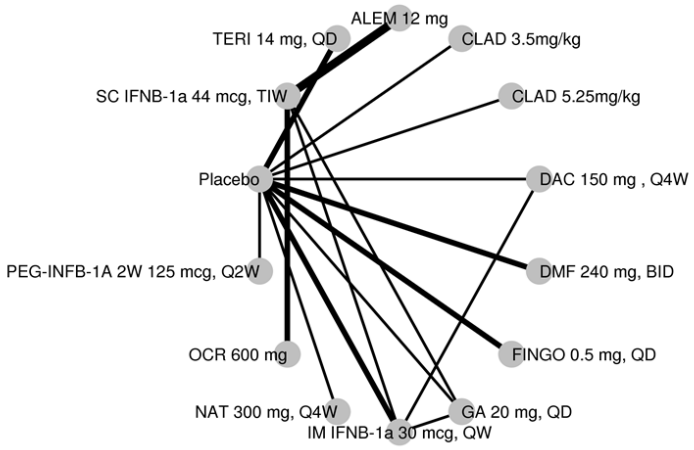
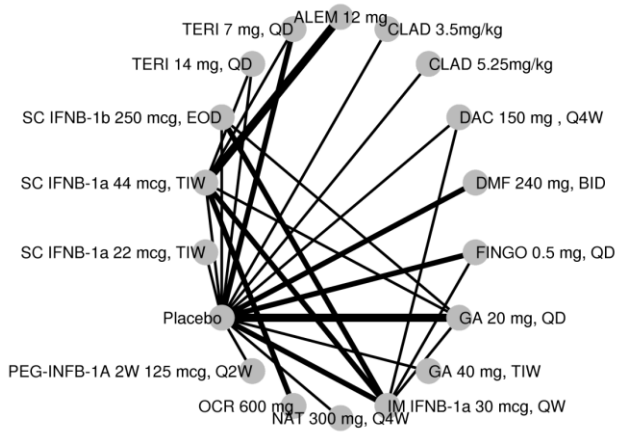
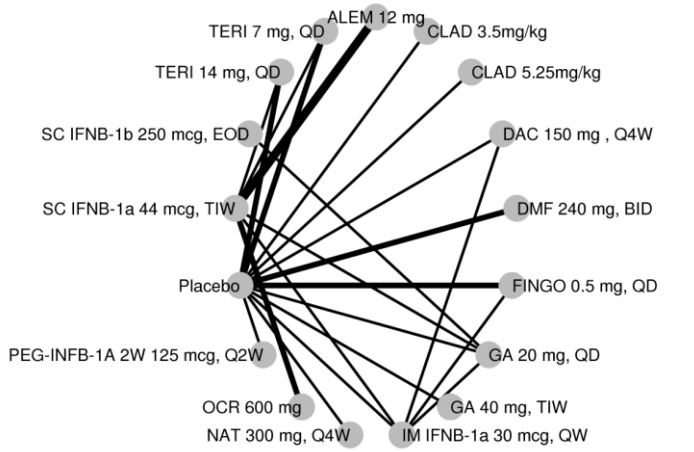
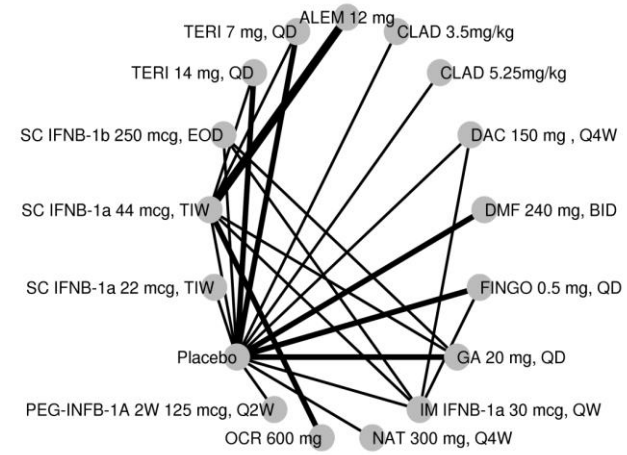
Quality Assessment of Included Studies

The authors used the Cochrane tool for assessing the risk of bias in randomized controlled studies. The results of the assessment for each individual study were reported in detail. However, the authors of the manufacturer's ITC did not provide a plan to investigate the impact of studies that were considered to be of low quality or having a high risk of bias.

Evidence Networks

The evidence networks for each end point are shown in Table 34.

Table 34: Evidence Network Diagrams

24-Week CDP	Proportion of Patients Who Were Relapse-Free
	
Serious Adverse Events	**All-Cause Discontinuation**
	

2W = two weeks; ALEM = alemtuzumab; BID = twice daily; CLAD = cladribine; DAC = daclizumab; DMF = dimethyl fumarate ; EOD = every other day; FINGO = fingolimod; GA = glatiramer acetate;; IFNB = interferon beta; IM = intramuscular; NAT = natalizumab; OCR = ocrelizumab; PEG = pegylated; Q2W = once every two weeks; Q4W = once every four weeks; QW = once every week; QD = once every day; SC = subcutaneous; TERI = teriflunomide; TIW = three times per week.

Source: Manufacturer-submitted ITC.[45]

Indirect Treatment Comparison Methods

The authors of the manufacturer-submitted ITC used a Bayesian network meta-analysis approach, based on published guidelines from the National Institute for Health and Care Excellence Decision Support Unit (NICE DSU). The analytical approach included the use of a random-effects model for the primary results, the use of vague priors, and the application of meta-regression to adjust for potential confounding factors. In addition, the authors provided separate sensitivity analyses using a fixed-effects model, using an "alternative" prior to inform between-study variance, and attempted two subgroup analyses (i.e., highly active disease, rapidly evolving severe disease). The authors conducted 400,000 iterations (with 100,000 burn-ins), which they reported have led to convergence according to Brooks–Gelman–Rubin graphs, but they provided no graphs or data. Model diagnostics, including deviance information criterion (DIC) and posterior mean residual deviance were calculated and provided. No statistical assessment of inconsistencies was attempted.

The authors analyzed and reported the results using a Poisson model for the ARR outcome; data were derived from number of events in each arm and the total exposure time. The CDP for 12 weeks and CDP for 24 weeks end points were analyzed using a log hazard scale model in which the hazard ratio (HR) or the log hazard ratio (log HR), along with the standard error of the log HR of the experimental treatment, were required from each study. The proportion of patients who were relapse-free and the serious adverse events and discontinuation outcomes were modelled using a binomial model from the number of events and the number at risk in each treatment group.

Sensitivity analyses were available for the choice of model (fixed-effects and an alternative prior for between-study variance). In addition, the authors conducted a network meta-regression to explore the effect of trial duration.

The authors provided subgroup analysis of patients with highly active RRMS despite prior treatment, and for patients with rapidly evolving severe RRMS. However, the authors included intention-to-treat population data from Avonex (interferon beta-1a), Betaferon (interferon beta-1b), Copaxone (glatiramer acetate), and Rebif (interferon beta-1a) to connect the networks for subgroups under the assumption that these drugs would have the same treatment effects on these subgroups.

Results

The authors identified 46 eligible studies that fit their inclusion and exclusion criteria. Of these, only 33 studies reported data sufficient to be included in a network meta-analysis (NMA). However, a detailed list of reasons why each excluded study was omitted from the analysis was not provided. The majority of the included RCTs were double-blind; four studies used a single-blind design, and two were open-label. A summary of the baseline and demographic characteristics of the patients enrolled in each study is presented in Table 35. The clinical expert consulted by CADTH suggested that baseline and demographic characteristics appeared to be comparable across the individual studies.

There was variation in the definition of outcomes among the trials. The authors reported that the ARR was largely undefined in most of the included trials. However, relapse was defined in all but one of the included trials; the definition of relapse was commonly based on the presence of new or recurrent neurological symptoms. However, some of the included studies used changes in EDSS score as an indication of relapse. The clinical

expert consulted by CADTH suggested that these definitions could be considered comparable across the included studies.

CDP was another outcome with varied definitions across the individual studies. Three commonly used definitions were all based on the EDSS score:

- a sustained increase over 12 weeks of one or more points on the EDSS from a baseline score of 1, or an increase of 1.5 from a baseline score of zero
- an increase of one point for at least six months
- a sustained increase over six months of one point if the baseline score was between 0 and 5.0, or a 0.5 point if the baseline score was 5.5.

The clinical expert suggested these definitions could be considered comparable across the included studies.

Similarly, three variable definitions for no evidence of disease activity (NEDA) were used in the randomized controlled trials that reported this outcome: 11 of these trials used the absence of both clinical disease (through EDSS score or absence of relapse) and disease activity (determined by MRI) to define NEDA; eight trials used only the absence of clinical disease; and four used only the absence of disease activity determined by MRI. The clinical expert suggested these definitions could be considered comparable across the included studies.

The results of the network meta-analysis demonstrated that [redacted]

[redacted]

Table 35: Summary of Baseline Characteristics

Trial Name	Treatment	N	Male n (%)	Age Mean (SD)	Treatment-Naive	Disease Duration Mean (SD)	EDSS Score Mean (SD)	MSFC Score Mean (SD)	Previous Relapses	
									Past Year Mean (SD)	Past 2 Years Mean (SD)
Intervention										
Kappos et al. 2011	Placebo	54	18 (33)	38 (8.8)	No	Median: 4.8 (range 0.6 to 26.2)	3.2 (1.4)	NR	NR	NR
	IM IFNB-1a 30 mcg, q.w.	54	22 (41)	38.1 (9.3)		Median: 5.3 (range 0.8 to 35.2)	3.1 (1.5)	NR	NR	NR
	OCR 600 mg	55	20 (36)	35.6 (8.5)		Median: 6.5 (range 0.5 to 20.5)	3.5 (1.5)	NR	NR	NR
	OCR 2,000 mg	55	17 (31)	38.5 (8.7)		Median: 7.7 (range 0.25 to 28)	3.4 (1.3)	NR	NR	NR
OPERA-I	SC IFNB-1a 44 mcg, t.i.w.	411	139 (33.8)	36.9 (9.3)	No	6.25 (5.98)	2.75 (1.29)	0.03 (0.64)	1.33 (0.64)	1.74 (0.91)
	OCR 600 mg	410	140 (34.1)	37.1 (9.3)		6.74 (6.37)	2.86 (1.24)	–0.01 (0.76)	1.31 (0.65)	1.79 (0.87)
OPERA-II	SC IFNB-1a 44 mcg, t.i.w.	417	138 (33)	37.4 (9)	No	6.68 (6.13)	2.84 (1.38)	–0.02 (0.67)	1.34 (0.73)	1.78 (0.92)
	OCR 600 mg	417	146 (35)	37.2 (9.1)		6.72 (6.1)	2.78 (1.3)	0.01 (0.64)	1.32 (0.69)	1.78 (0.95)
Comparators										
ADVANCE	Placebo	500	142 (28)	36.3 (9.7)	No	6.3 (6.3)	2.44 (1.18)	NR	1.6 (0.67)	NR
	PEG-IFNB-1A 125 mcg, q.2.w.	512	151 (29)	36.9 (9.8)		6.9 (6.6)	2.47 (1.26)	NR	1.6 (0.67)	NR
	PEG-IFNB-1A 125 mcg, q.4.w.	500	148 (30)	36.4 (9.9)		6.5 (6.1)	2.48 (1.24)	NR	1.5 (0.62)	NR
AFFIRM	Placebo	315	104 (33)	36.7 (7.8)	No	Median: 6 (range 0 to 33)	2.3 (1.2)	NR	1.5 (0.77)	NR
	NAT 300 mg, q.4.w.	627	178 (28)	35.6 (8.5)		Median: 5 (range 0 to 34)	2.3 (1.2)	NR	1.53 (0.91)	NR
BEYOND	SC IFNB-1b 250 mcg, q.o.d.	897	270 (30)	35.8 (NR)	Yes	5.3 (NR)	2.35 (NR)	NR	1.6 (NR)	NR
	SC IFNB-1b 500 mcg, q.o.d.	899	270 (30)	35.9 (NR)		5.4 (NR)	2.33 (NR)	NR	1.6 (NR)	NR
	GA 20 mg, q.d.	448	142 (32)	35.2 (NR)		5.1 (NR)	2.28 (NR)	NR	1.6 (NR)	NR
Bornstein et al. 1987	Placebo	23	10 (43)	31.1 (NR)	Unclear	6.4 (NR)	3.1 (NR)	NR	NR	NR
	GA 20 mg, q.d.	25	11 (44)	30 (NR)		4.9 (NR)	2.9 (NR)	NR	NR	NR
BRAVO	Placebo	450	129 (28.7)	Median: 37.5	No	Median: 4.7	Median: 2.5	NR	Median: 1	NR

Trial Name	Treatment	N	Male n (%)	Age Mean (SD)	Treatment-Naive	Disease Duration Mean (SD)	EDSS Score Mean (SD)	MSFC Score Mean (SD)	Previous Relapses	
									Past Year Mean (SD)	Past 2 Years Mean (SD)
				(IQR 30.3 to 45.4)		(IQR 2 to 9.7)	(IQR 1.5 to 3.5)		(IQR 1 to 2)	
	IM IFNB-1a 30 mcg, q.w.	447	140 (31.3)	Median: 38.5 (IQR 30.3 to 45.9)		Median: 5.3 (IQR 2.4 to 10.3)	Median: 2.5 (IQR 1.5 to 3.5)	NR	Median: 1 (IQR 1,2)	NR
Calabrese 2012	Placebo (reference RRMS population untreated)	50	14 (28)	39.6 (11.8)	No	6 (4.8)	1.3 (0.9)	NR	NR	NR
	IM IFNB-1a 30 mcg, q.w.	47	15 (32)	34.8 (9.6)	Yes	5.3 (5.1)	1.9 (0.8)	NR	NR	NR
	SC IFNB-1a 44 mcg, t.i.w.	46	14 (30.4)	35.9 (9.1)		5.7 (4.9)	1.9 (1)	NR	NR	NR
	GA 20 mg, q.d.	48	13 (27.1)	38.9 (10.2)		5.5 (6.1)	2.1 (1.1)	NR	NR	NR
CAMMS22	SC IFNB-1a 44 mcg, t.i.w.	111	40.0 (36)	32.8 (8.8)	Yes	Median: 1.4 (range 0.2 to 6.3)	1.9 (0.83)	NR	NR	NR
	ALEM 12 mg	113	39.6 (35.7)	31.9 (8)		Median: 1.3 (range 0.1 to 3.5)	1.9 (0.74)	NR	NR	NR
	ALEM 24 mg	110	39.4 (35.5)	32.2 (8.8)		Median: 1.2 (range 0.3 to 3.2)	2 (0.73)	NR	NR	NR
CARE-MS I	SC IFNB-1a 44 mcg, t.i.w.	187	65 (35)	33.2 (8.5)	Yes, except CS	2(1.3)	2 (0.8)	NR	1.8 (0.8)	NR
	ALEM 12 mg, q.d.	376	133 (35)	33 (8)		2.1 (1.4)	2 (0.8)	NR	1.8 (0.8)	NR
CARE-MS II	SC IFNB-1a 44 mcg, t.i.w.	202	71 (35)	35.8 (8.77)	No	4.7 (2.86)	2.7 (1.21)	NR	1.5 (0.75)	NR
	ALEM 12 mg, q.d.	426	145 (34)	34.8 (8.36)		4.5 (2.68)	2.7 (1.26)	NR	1.7 (0.86)	NR
	ALEM 24 mg, q.d.	170	50 (29)	35.1 (8.4)		4.3 (2.77)	2.7 (1.17)	NR	1.6 (0.86)	NR
CLARITY	Placebo	437	149 (34.1)	38.7 (9.9)	No	8.9 (7.4)	2.9 (1.3)	NR	NR	NR
	CLAD 3.5 mg/kg	433	135 (31.2)	37.9 (10.3)		7.9 (7.2)	2.8 (1.2)	NR	NR	NR
	CLAD 5.25 mg/kg	456	144 (31.6)	39.1 (9.9)		9.3 (7.6)	3 (1.4)	NR	NR	NR
CombiRx	IM IFNB-1a 30 mcg, q.w.	250	77 (30.8)	37.6(10.2)	No	1.4 (4)	2 (1.2)	NR	1.7 (0.9)	NR
	GA 20 mg, q.d.	259	74 (28.6)	39 (9.5)		1 (2.9)	1.9 (1.2)	NR	1.6 (0.7)	NR
CONFIRM	Placebo	363	112 (31)	36.9 (9.2)	No	NR	2.6 (1.2)	NR	1.4 (0.8)	NR
	GA 20 mg, q.d.	350	103 (29)	36.7 (9.1)		NR	2.6 (1.2)	NR	1.4 (0.6)	NR
	DMF 240 mg, b.i.d.	359	114 (32)	37.8 (9.4)		NR	2.6 (1.2)	NR	1.3 (0.6)	NR
Copolymer 1 MS trial	Placebo	126	30 (23.8)	34.3 (6.5)	Unclear	6.6 (5.1)	2.4 (1.3)	NR	NR	2.9 (1.1)
	GA 20 mg, q.d.	125	37 (29.6)	34.6 (6)		7.3 (4.9)	2.8 (1.2)	NR	NR	2.9 (1.3)

Trial Name	Treatment	N	Male n (%)	Age Mean (SD)	Treatment-Naive	Disease Duration Mean (SD)	EDSS Score Mean (SD)	MSFC Score Mean (SD)	Previous Relapses	
									Past Year Mean (SD)	Past 2 Years Mean (SD)
DECIDE	IM IFNB-1a 30 mcg, q.w.	922	295 (32)	36.2 (9.3)	No	6.9 (6.3)	2.5 (1.3)	NR	1.6 (0.8)	NR
	DAC 150 mg, q.4.w.	919	294 (32)	36.4 (9.4)		7 (6.3)	2.5 (1.2)	NR	1.5 (0.7)	NR
DEFINE	Placebo	408	102 (25)	38.5 (9.1)	No	NR	2.48 (1.24)	NR	1.3 (0.7)	NR
	DMF 240 mg, b.i.d.	410	114 (28)	38.1 (9.1)		NR	2.4 (1.29)	NR	1.3 (0.7)	NR
DMSG	SC IFNB-1a 22 mcg, q.w.	143	48 (33.6)	Median: 37 (Range 18 to 55)	No	7.8 (NR)	2.98 (NR)	NR	NR	3.2 (NR)
	SC IFNB-1b 250 mcg, q.o.d.	158	59 (37.3)	Median: 38 (Range 19 to 55)		7.6 (NR)	2.82 (NR)	NR	NR	3.04 (NR)
Etemadifar et al. 2006	IM IFNB-1a 30 mcg, q.w.	30	6 (27.3)	28.1 (1.2)	No	2.9 (2.3)	1.9 (1.1)	NR	2 (0.8)	NR
	SC IFNB-1a 44 mcg, t.i.w.	30	7 (31.8)	27.4 (1.2)		3 (2.2)	2.1 (1)	NR	2.4(1)	NR
	SC IFNB-1b 250 mcg, q.o.d.	30	9 (40.9)	29.9 (1.4)		3.7 (2.3)	1.9 (0.7)	NR	2.2 (0.7)	NR
European/ Canadian Glatiramer Acetate trial	Placebo	120	33 (27.2)	34 (7.5)	No	8.3 (5.5)	2.4 (1.2)	NR	NR	2.5 (1.4)
	GA 20 mg, q.d.	119	27 (23)	34.1 (7.4)		7.9 (5.5)	2.3 (1.1)	NR	NR	2.8 (1.8)
EVIDENCE	IM IFNB-1a 30 mcg, q.w.	338	86 (25.4)	37.4 (NR)	No, only IFNB-naive	6.7 (NR)	2.3 (NR)	NR	NR	2.6 (NR)
	SC IFNB-1a 44 mcg, t.i.w.	339	85 (25.1)	38.3 (NR)		6.5 (NR)	2.3 (NR)	NR	NR	2.6 (NR)
FREEDOMS	Placebo	418	120 (28.7)	37.2 (8.6)	No	8.1 (6.4)	2.5 (1.3)	NR	1.4 (0.7)	2.2 (1.2)
	FINGO 0.5 mg, q.d.	425	129 (30.4)	36.6 (8.8)		8 (6.6)	2.3 (1.3)	NR	1.5 (0.8)	2.1 (1.1)
FREEDOMS II	Placebo	355	67 (19)	40.1 (8.42)	Yes, 27%	10.6(7.9)	2.4 (1.3)	NR	1.5 (0.9)	2.2 (1.5)
	FINGO 0.5 mg, q.d.	358	83 (23)	40.6 (8.39)	Yes, 26%	10.4 (8)	2.4 (1.3)	NR	1.4 (0.9)	2.2 (1.4)
GALA	Placebo	461	148 (32.1)	38.1 (9.2)	No	7.6 (6.4)	2.7 (1.2)	NR	1.3 (0.6)	1.9 (0.9)
	GA 40 mg, t.i.w.	943	302 (32)	37.4 (9.4)		7.7 (6.7)	2.8 (1.2)	NR	1.3 (0.6)	1.9 (0.9)
GATE	Placebo	84	27 (32.1)	32.6 (8.7)	No	5.7 (6)	2.7 (1.2)	NR	NR	1.9 (0.9)
	Generic GA 20 mg, q.d.	353	120 (34.0)	32.6 (8.6)		5.5 (5.3)	2.6 (1.2)	NR	NR	1.9 (0.9)
	Brand GA 20 mg, q.d.	357	119(33.3)	33.8 (9)		6.4 (6)	2.7 (1.2)	NR	NR	1.8 (0.9)
IFNB MS	Placebo	123	35 (28.5)	36 (NR)	No	NR	2.8 (NR)	NR	NR	3.6 (NR)
	SC IFNB-1b 250 mcg, q.o.d.	124	38 (30.6)	35.2 (NR)		NR	3 (NR)	NR	NR	3.4 (NR)
IMPROVE	Placebo	60	18 (30)	35.2 (10.5)	No	NR	NR	NR	NR	NR
	SC IFNB-1a 44 mcg, t.i.w.	120	32 (26.7)	34 (7.8)		NR	NR	NR	NR	NR
INCOMIN	SC IFNB-1b 250 mcg, q.o.d.	96	30 (31)	38.8(7.1)	Yes,	5.9 (4.2)	1.97 (0.7)	NR	NR	1.52 (0.67)

Trial Name	Treatment	N	Male n (%)	Age Mean (SD)	Treatment-Naive	Disease Duration Mean (SD)	EDSS Score Mean (SD)	MSFC Score Mean (SD)	Previous Relapses	
									Past Year Mean (SD)	Past 2 Years Mean (SD)
	IM IFNB-1a 30 mcg, q.w.	92	35 (38)	34.9 (7.9)	except CS	6.7 (5.4)	1.96 (0.7)	NR	NR	1.38 (0.52)
Knobler et al. 1993	Placebo (human serum albumin)	7	2 (28.5)	34.5 (NR)	NR	7 (NR)	3.1 (NR)	NR	NR	2.3 (NR)
	SC IFNB-1b 250 mcg, q.o.d.	6	4 (66.7)	35.4 (NR)		4.2 (NR)	2.7 (NR)	NR	NR	4 (NR)
	SC IFNB-1b 500 mcg, q.o.d.	6	4 (66.7)	35.7 (NR)		7.3 (NR)	2.9 (NR)	NR	NR	2 (NR)
MSCRG	Placebo	143	40 (28)	36.9 (NR)	No	6.4 (NR)	2.3 (NR)	NR	1.2 (NR)	NR
	IM IFNB-1a 30 mcg, q.w.	158	40 (25)	36.7 (NR)		6.6 (NR)	2.4 (NR)	NR	1.2 (NR)	NR
NCT01440101	Placebo	47	15 (31.9)	NR	No	NR	NR	NR	NR	NR
	NAT 300 mg, q.4.w.	47	13 (27.7)	NR		NR	NR	NR	NR	NR
Polman et al. 2003	Placebo	42	7(16.7)	35.4 (8.4)	No	Median: 5.5 (IQR 3 to 11)	NR	NR	NR	NR
	SC IFNB-1a 22 mcg, q.o.d.	44	14 (31.8)	36.8 (8.9)		Median: 5 (IQR 2.5 to 9)	NR	NR	NR	NR
PRISMS	Placebo	187	47 (25)	Median: 34.6 (IQR 28.8 to 40.4)	No	Median: 4.3 (IQR 2.4 to 8.4)	2.4 (1.2)	NR	NR	3(1.3)
	SC IFNB-1a 22 mcg, t.i.w.	189	62 (33)	Median: 34.8 (IQR 29.3 to 39.8)		Median: 5.4 (IQR 3 to 11.2)	2.5 (1.2)	NR	NR	3(1.1)
	SC IFNB-1a 44 mcg, t.i.w.	184	63 (34)	Median: 35.6 (IQR 28.4 to 41)		Median: 6.4 (IQR 2.9. 10.3)	2.5 (1.3)	NR	NR	3(1.1)
REFORMS	SC IFNB-1a 44 mcg, t.i.w.	65	19 (29.2)	40.26 (9.8)	No	4.51 (6.7)	NR	NR	1.36 (0.52)	NR
	SC IFNB-1b 250 mcg, q.o.d.	64	20 (31.2)	40.78 (9.56)		5.74 (6.66)	NR	NR	1.3 (0.46)	NR
REGARD	SC IFNB-1a 44 mcg, t.i.w.	386	119(31)	36.7 (9.8)	No	NR	2.35(1.28)	NR	NR	NR
	GA 20 mg, q.d.	378	106 (28)	36.8 (9.5)		NR	2.33(1.31)	NR	NR	NR
Saida et al. 2012	Placebo	57	18 (31.6)	35 (8.9)	No	8.2 (7.3)	2.1 (1.7)	NR	1.7(1.6)	2.8 (3)
	FINGO 0.5 mg, q.d.	57	17 (29.8)	35 (9)		8.2 (6.8)	2.3 (1.9)	NR	1.4(1)	2.2 (1.4)
Saida et al. 2016	Placebo	113	29 (26)	36 (8)	NR	NR	1.9 (1.3)	NR	NR	NR
	DMF 240 mg, b.i.d.	111	33 (30)	37 (8)		NR	2.2 (1.3)	NR	NR	NR
SELECT	Placebo	204	76 (37)	36.6 (9)	No	NR	2.7 (1.2)	NR	1.3 (0.6)	NR
	DAC 150 mg, q.4.w.	208	68 (33)	35.3 (8.9)		NR	2.8 (1.2)	NR	1.4 (0.7)	NR
	DAC 300 mg, q.4.w.	209	75 (36)	35.2 (8.7)		NR	2.7 (1.2)	NR	1.3 (0.7)	NR
Stepien et al.	SC IFNB-1b 250 mcg, q.o.d.	18	5 (27.8)	33.5 (3.6)	Yes	23 (22)	2.09 (0.97)	NR	1.47 (0.86)	NR

Trial Name	Treatment	N	Male n (%)	Age Mean (SD)	Treatment-Naive	Disease Duration Mean (SD)	EDSS Score Mean (SD)	MSFC Score Mean (SD)	Previous Relapses	
									Past Year Mean (SD)	Past 2 Years Mean (SD)
2013	IM IFNB-1a 30 mcg, q.w.	20	7(35)	32.6 (5.8)		19.1 (19.4)	2.27 (0.97)	NR	1.15 (0.6)	NR
TEMSO	Placebo	363	88 (24.2)	38.4 (9)	No	8.6 (7.1)	2.68(1.34)	NR	1.4 (0.7)	2.1
	TERI 7 mg, q.d.	366	111 (30.3)	37.4 (9)		8.8 (6.8)	2.68(1.34)	NR	1.4 (0.7)	2.3 (1.2)
	TERI 14 mg, q.d.	358	104 (29.1)	37.8 (8.2)		8.7 (6.7)	2.67(1.24)	NR	1.3 (0.7)	2.2 (1)
TENERE	SC IFNB-1a 44 mcg, t.i.w.	104	33 (32.7)	37(10.6)	No	7.7 (7.6)	2(1.2)	NR	1.2(1)	1.7 (1.1)
	TERI 7 mg. q.d.	109	39 (35.8)	35.2 (9.2)		7 (6.9)	2(1.2)	NR	1.3 (0.8)	1.7 (0.9)
	TERI 14 mg, q.d.	111	33 (29.7)	36.8 (10.3)		6.6 (7.6)	2.3 (1.4)	NR	1.4 (0.8)	1.7 (0.9)
Teriflunomide MS Trial	Placebo	61	20 (32.7)	39.2 (8.7)	No	8.6 (7.9)	Median: 2.5 (range 0 to 6)	NR	Median: 1 (range 0 to 3)	NR
	TERI 7 mg, q.d.	61	15 (24.6)	40.1 (9.3)		10.3 (8.1)	Median: 2.5 (range 0 to 6)	NR	Median: 1 (range 0 to 4)	NR
	TERI 14 mg, q.d.	57	12 (21.1)	40.1 (9.1)		8.5 (7.1)	Median: 2 (range 0 to 6.5)	NR	Median: 1 (range 0 to 3)	NR
TOWER	Placebo	389	116(30)	38.1 (9.1)	No	7.64 (6.7)	2.69(1.36)	NR	1.4 (0.8)	2.1 (1.1)
	TERI 7 mg. q.d.	408	108 (26)	37.4 (9.4)		8.18 (6.75)	2.71 (1.39)	NR	1.4 (0.7)	2.1 (1.1)
	TERI 14 mg, q.d.	372	114 (31)	38.2 (9.4)		8.18 (6.73)	2.71 (1.35)	NR	1.4 (0.7)	2.1 (1.2)
TRANSFORMS	IM IFNB-1a 30 mcg, q.w.	435	140 (32.2)	36 (8.3)	No	7.4 (6.3)	2.19 (1.26)	NR	1.5 (0.8)	2.3 (1.2)
	FINGO 0.5 mg, q.d.	431	149 (34.6)	36.7 (8.8)		7.5 (6.2)	2.24 (1.33)	NR	1.5 (1.2)	2.3 (2.2)
Wroe et al. 2005	Placebo (slow)	18	9 (27.3)	38 (NR)	No	NR	3.09 (NR)	NR	NR	2.47 (NR)
	Placebo (rapid)	15	NR	NR		NR	NR	NR	NR	NR
	SC IFNB-1b (slow) 250 mcg, q.o.d.	34	17 (26.2)	35 (NR)		NR	2.92 (NR)	NR	NR	2.66 (NR)
	SC IFNB-1b (rapid) 250 mcg, q.o.d.	31	NR	NR		NR	NR	NR	NR	NR

ALEM = alemtuzumab; b.i.d. = twice daily; CS = corticosteroids; DAC = daclizumab; DMF = dimethyl fumarate; EDSS = Kurtzke Expanded Disability Status Scale; FINGO = fingolimod; GA = glatiramer acetate; IM = intramuscular; IFNB = interferon beta; MSFC = Multiple Sclerosis Functional Composite; NAT = natalizumab; NR = not reported; OCR = ocrelizumab; PEG = pegylated; q.2.w. = twice weekly; q.4.w. = once every four weeks; q.d. = once daily; q.o.d. = every other day; q.w. = once weekly; SC = subcutaneous; SD = standard deviation; TERI = teriflunomide; t.i.w. = three times weekly.

Source: Manufacturer's ITC.[45]

Table 36: Results for Annualized Relapse Rate and Confirmed Disability Progression for 12 Weeks and 24 Weeks

Treatment	Outcomes		
	ARR RR (95% CrI)	CDP 12 Weeks Log HR (95% CrI)	CDP 24 Weeks Log HR (95% CrI)
OCR 600 mg relative to:			
Placebo	[redacted]	[redacted]	[redacted]
IM IFNB-1a 30 mcg, q.w.	[redacted]	[redacted]	[redacted]
TERI 7 mg, q.d.	[redacted]	[redacted]	[redacted]
SC IFNB-1b 250 mcg, q.o.d.	[redacted]	[redacted]	[redacted]
GA 20 mg, q.d.	[redacted]	[redacted]	[redacted]
TERI 14 mg, q.d.	[redacted]	[redacted]	[redacted]
GA 40 mg, t.i.w.	[redacted]	[redacted]	[redacted]
PEG-IFNB-1A 125 mcg, q.2.w.	[redacted]	[redacted]	[redacted]
SC IFNB-1a 44 mcg, t.i.w.	[redacted]	[redacted]	[redacted]
DMF 240 mg, b.i.d.	[redacted]	[redacted]	[redacted]
FIN 0.5 mg, q.d.	[redacted]	[redacted]	[redacted]
DAC 150 mg, q.4.w.	[redacted]	[redacted]	[redacted]
CLAD 5.25 mg/kg	[redacted]	[redacted]	[redacted]
CLAD 3.5 mg/kg	[redacted]	[redacted]	[redacted]
NAT 300 mg, q.4.w.	[redacted]	[redacted]	[redacted]
ALEM 12 mg	[redacted]	[redacted]	[redacted]
SC IFNB-1a 22 mcg, t.i.w.	[redacted]	[redacted]	[redacted]
Measures of model fit:			
Posterior mean residual deviance (mean) RE – uniform 0,5 tau	[redacted]	[redacted]	[redacted]
Posterior mean residual deviance (mean) RE – half normal tau	[redacted]	[redacted]	[redacted]
Posterior mean residual deviance (mean) FE	[redacted]	[redacted]	[redacted]
DIC RE – uniform 0,5 tau	[redacted]	[redacted]	[redacted]
DIC RE – half normal tau	[redacted]	[redacted]	[redacted]
DIC FE	[redacted]	[redacted]	[redacted]

ALEM = alemtuzumab; b.i.d. = twice per day; CLAD = cladribine; CrI = credible interval; DAC = daclizumab; DMF = dimethyl fumarate; q.o.d. = every other day; FE = fixed-effects; FIN = fingolimod; GA = glatiramer acetate; IFNB = interferon beta; IM = intramuscular; NAT = natalizumab; OCR = ocrelizumab; IFN = interferon; PEG = pegylated; q.2.w. = twice per week; q.o.d. = once every other day; q.d. = once daily; q.w. = once weekly; RE = random-effects; SC = subcutaneous; TERI = teriflunomide; t.i.w. = three times per week.

Source: Manufacturer-submitted ITC.[45]

Table 37: Results of Proportion of Patients Who Were Relapse-Free, Serious Adverse Events, and All-Cause Discontinuation

Treatment	Outcomes		
	Relapse-Free OR (95% CrI)	SAE OR (95% CrI)	All-Cause Discontinuation OR (95% CrI)
OCR 600 mg relative to:			
Placebo	[redacted]	[redacted]	[redacted]
IM IFNB-1a 30 mcg, q.w.	[redacted]	[redacted]	[redacted]
TERI 7 mg, q.d.	[redacted]	[redacted]	[redacted]
SC IFNB-1b 250 mcg, q.o.d.	[redacted]	[redacted]	[redacted]
GA 20 mg, q.d.	[redacted]	[redacted]	[redacted]
TERI 14 mg, q.d.	[redacted]	[redacted]	[redacted]
GA 40 mg, t.i.w.	[redacted]	[redacted]	[redacted]
PEG-INFB-1A 125 mcg, q.2.w.	[redacted]	[redacted]	[redacted]
SC IFNB-1a 44 mcg, t.i.w.	[redacted]	[redacted]	[redacted]
DMF 240 mg, b.i.d.	[redacted]	[redacted]	[redacted]
FIN 0.5 mg, q.d.	[redacted]	[redacted]	[redacted]
DAC 150 mg, q.4.w.	[redacted]	[redacted]	[redacted]
CLAD 5.25 mg/kg	[redacted]	[redacted]	[redacted]
CLAD 3.5 mg/kg	[redacted]	[redacted]	[redacted]
NAT 300 mg, q.4.w.	[redacted]	[redacted]	[redacted]
ALEM 12 mg	[redacted]	[redacted]	[redacted]
SC IFNB-1a 22 mcg, t.i.w.	[redacted]	[redacted]	[redacted]
Measures of Model fit:			
Posterior mean residual deviance (mean) RE – uniform 0,5 tau	[redacted]	[redacted]	[redacted]
Posterior mean residual deviance (mean) RE – half normal tau	[redacted]	[redacted]	[redacted]
Posterior mean residual deviance (mean) FE	[redacted]	[redacted]	[redacted]
DIC RE – uniform 0,5 tau	[redacted]	[redacted]	[redacted]
DIC RE – half normal tau	[redacted]	[redacted]	[redacted]
DIC FE	[redacted]	[redacted]	[redacted]

ALEM = alemtuzumab; b.i.d. = twice per day; CLAD = cladribine; CrI = credible interval; DAC = daclizumab; DIC = deviance information criterion; DMF = dimethyl fumarate; q.o.d. = every other day; FE = fixed-effects; FIN = fingolimod; GA = glatiramer acetate; IFNB = interferon beta; IM = intramuscular; NAT = natalizumab; OCR = ocrelizumab; PEG = pegylated; q.2.w. = twice per week; q.4.w. = once every four weeks; q.d. = once daily; q.o.d. = once every other day; q.w. = once weekly; RE = random-effects; SC = subcutaneous; TERI = teriflunomide; t.i.w. = three times per week.
Source: Manufacturer-submitted ITC.[45]

Critical Appraisal

The protocol for the systematic review and the eligibility criteria were comprehensive, capturing the relevant comparators and clinically relevant end points. The literature search strategy was comprehensive, involving eight bibliographical databases. The authors adhered to the NICE DSU guidelines in conducting the Bayesian NMA and reported all relevant diagnostic tests. Also, the authors made an appropriate choice of statistical distribution for the outcomes with proper associated measurements.

An important consideration when including a large number of trials is whether these trials are sufficiently similar to warrant valid comparison. Baseline and demographic characteristics of the included studies were reported in detail, and the clinical expert

consulted by CADTH considered the studies to be similar. Also, meta-regression was performed to adjust for differences in the duration of different trials. Differences in the definition of outcomes could also pose issues with regard to the similarity of the results, these were also reported in detail, and the clinical expert considered to the end points to be similar.

However, three main critical appraisal points can be made regarding the manufacturer's ITC:

- Lack of reporting on the method of screening, data extraction, and detailed reasons for excluding 13 studies from the analysis: The authors did not clearly report how the were articles screened (e.g., how many independent reviewers and how many stages) and how the data from included studies were extracted (e.g., single or duplicate extraction). The methodology used in conducting the systematic review may influence the rate of human error in the process. Also, the authors failed to report why 13 studies were not included in the NMA. While the general understanding is the studies were excluded due to missing data, it is not clear what was missing in each of the excluded studies, nor was a list of which studies were included in which networks made available.
- Lack of statistical analysis for inconsistency: In an NMA, the evidence gained from direct comparisons should be similar to that gained from ITCs; this is the transitivity assumption. To test this assumption, the authors should have compared the direct versus indirect evidence that is available from closed loops in the network. Inconsistency testing was absent in the manufacturer-submitted ITC, reducing the certainty of the synthesized evidence.
- The authors of the study provided a sensitivity analysis using different priors and a fixed-effects model, adjusted for trial durations. However, other sensitivity analyses to explore the potential effect of other relevant clinical covariates would have provided a higher level of certainty for the results (e.g., adjustments for the previous number of relapses, baseline EDSS, age, diagnostic criteria, etc.). It is known that these baseline characteristics may affect the treatment outcome. Considering the absence of any statistical analysis of inconsistency, it would have been even more important to quantitatively show the potential effect of clinical heterogeneity of the included studies.

Published Indirect Treatment Comparison Conducted by ICER

Objectives and Rationale

The authors of the ICER ITC aimed to analyze the comparative clinical effectiveness of DMTs in the treatment of RRMS and PPMS. This analysis was conducted as part of a health technology assessment of treatments for MS.

Study Eligibility, Selection Process, and Data Extraction

The authors provided clear, pre-specified, eligibility criteria for the inclusion of potential studies (Table 33). A comprehensive literature search strategy was provided in the report, involving more than four key bibliographical databases. A single reviewer screened all retrieved articles according to the designated inclusion and exclusion criteria. One reviewer extracted data from the included studies, while a second reviewer confirmed the accuracy of the extracted data. Disagreements were resolved through consensus.

Comparators

The authors planned to primarily compare DMTs for RRMS and PPMS, limiting the dosages to those approved by the FDA. If no FDA approval had been given, then the RCT dosages

were used in the analyses. The comparators that the authors planned are listed in Table 33.

Outcomes

The outcomes investigated in the ITC included relapse rate, disability progression, quality of life, specific MS-related symptoms, and drug-related adverse events (Table 33).

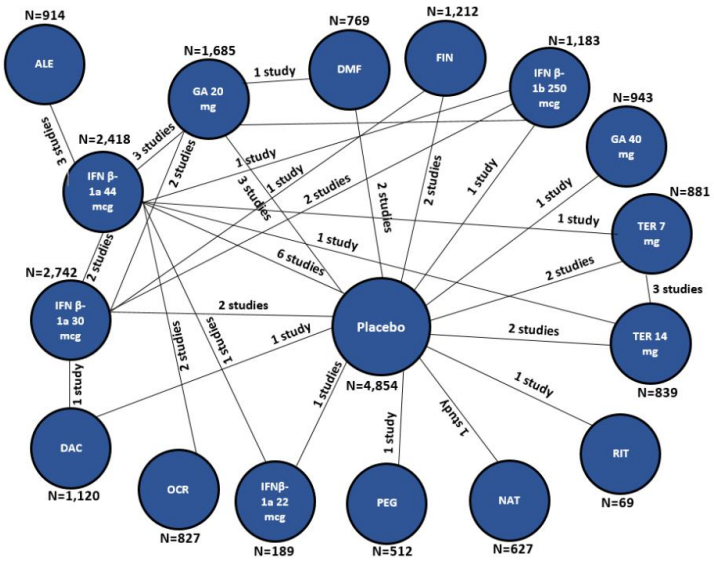
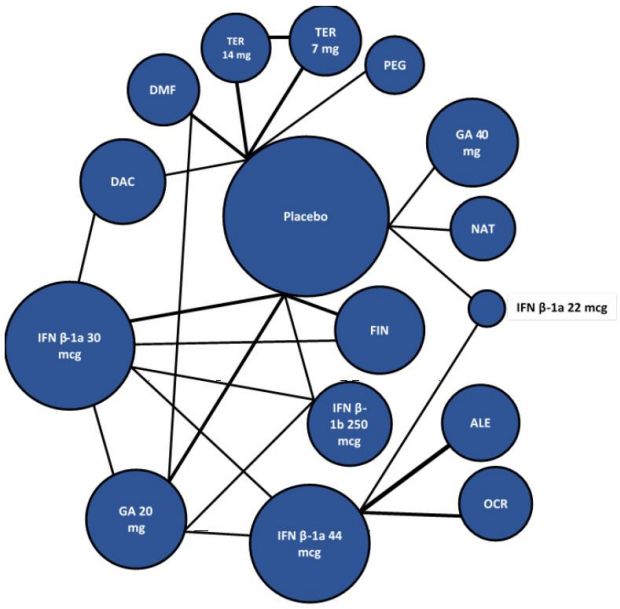
Quality Assessment of Included Studies

The authors reported using the criteria published by the US Preventive Services Task Force to assess the quality of clinical trials and cohort studies, using the categories “good,” “fair,” or “poor.” The results of the assessment were also reported in detail. The authors excluded poor-quality trials in sensitivity analyses.

Evidence Networks

Evidence network diagrams are presented in Table 38 for ARR and disability progression.

Table 38: Evidence Network Diagrams

Annualized Relapse Rate	
Disability progression	

ALE = alemtuzumab; DAC = daclizumab; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; IFN = interferon; NAT = natalizumab; OCR = ocrelizumab; PEG = pegylated interferon; RIT = rituximab; TER = teriflunomide.

Source: Reproduced with permission from the Institute for Clinical and Economic Review (ICER). Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value. March 2017. [46]

Indirect Treatment Comparison Methods

The authors of the ICER ITC used a Bayesian NMA approach. The authors used random-effects models for the primary results, vague "uninformative" priors, and meta-regression to control for potential confounding factors (i.e., disease duration, the mean number of baseline relapses in the year prior to study enrolment, and baseline EDSS score). In addition, the authors provided separate sensitivity analyses using a fixed-effects model,

different covariates, and trial quality. As well, they attempted several subgroup analyses and reported the results of direct meta-analyses where available.

The authors did not report the number of iterations or burn-ins, or the statistics used to assess convergence. The authors reported the use of DIC and residual posterior variance to assess the appropriateness of using the random-effects model versus the fixed-effects model.

The authors analyzed and reported the results of the ARR outcome using a Poisson model, and the data were derived from the number of events in each arm and the total exposure time. The authors of the ICER ITC combined the two outcomes of CDP for 12 weeks and CDP for 24 weeks in a single outcome in order to improve the robustness of the data, with the preference given to data for CDP for 24 weeks (i.e., if data for CDP at 24 weeks were missing or non-existent, data from CDP at 12 weeks were used to impute these data). Disability progression was analyzed as a binomial outcome using the number of progression events and the number of patients at risk.

Sensitivity and subgroup analyses were available for: fixed-effects model results, disease duration as a covariate, mean number of relapses in the prior year as covariate, baseline EDSS as convariate, treatment-naive population, treatment-experienced population, trials with fewer than 100 patients, trials using the Poser criteria, trials using the McDonald criteria, excluded poor-quality trials, excluded trials with short duration, excluded open-label trials, trials reporting 12-week disability progression, and trials reporting 24-week disability progression.

Results

The authors identified 35 eligible studies that fit the inclusion and exclusion criteria of the systematic review: 33 studies for RRMS patients and two studies for PPMS patients. Of these studies, 33 informed the ARR outcome, and 27 informed the disability progression outcome. No other outcomes were analyzed. While the report does not specifically list the methodological characteristics of the included studies, the authors reported that sensitivity analyses were conducted to assess the effect of including open-label trials. A summary of the baseline and demographic characteristics for each of the included studies is presented in Table 39. There was variation in the definition of outcomes between the included studies. The authors reported that these variations increased the uncertainty in the results, but provided no details regarding the definitions that were used in the individual trials.

Table 39: Summary of Baseline Characteristics

Trial	Treatment Groups	Age (Years)	Female (%)	White (%)	MS Duration	EDSS Baseline	Relapses Prior Year	MRI GdE Lesions
Hauser et al. 2008 HERMIS	RTX 1,000 mg IV on days 1 and 15 Placebo IV	41	78	NR	9.6	2.5	1.0	1.5
Hauser et al. 2017 OPERA-II	OCR 600 mg IV q.6.m. IFNB-1a 44 mcg SC t.i.w.	37	66	90	6.7	2.8	1.3	1.9
Hauser et al. 2017 OPERA-I	OCR 600 mg IV q.6.m. IFNB-1a 44 mcg SC t.i.w.	37	66	91	6.5	2.8	1.3	1.8
Gold et al. 2013 SELECT	DAC 150 mg SC q.4.w. Placebo SC q.4.w.	36	65	97	2.5	2.7	1.3	2.0
Kappos et al. 2015 DECIDE	DAC 150 mg SC q.4.w IFNB-1a 30 mcg IM q.w.	36	68	90	6.9	2.5	1.6	2.2
Coles et al. 2008 CAMMS223	ALEM 12 mg IV every year IFNB-1a 44 mcg SC t.i.w.	32	64	90	NR	2.0	2 years: 2.7	NR
Cohen et al. 2012 CARE-MS I	ALEM 12 mg IV every year IFNB-1a 44 mcg SC t.i.w.	33	65	95	2.1	2.0	1.8	2.3
Coles et al. 2012 CARE-MS II	ALEM 12 mg IV every year IFNB-1a 44 mcg SC t.i.w.	35	67	89	4.5	2.7	1.6	2.4
Polman et al. 2006 AFFIRM	NAT 300 mg IV q.4.w. Placebo IV q.4.w.	36	70	95	5	2.3	1.5	2.2
Fox et al. 2012 CONFIRM	Dimethyl fumarate 240 mg p.o. b.i.d. GA 20 mg SC q.d. placebo	37	70	84	4.7	2.6	1.4	NR
Gold et al. 2012 DEFINE	DMF240 mg p.o. b.i.d. Placebo p.o. b.i.d.	38	74	78	5.7	2.4	1.3	1.3
Confavreux et al. 2014 TOWER	TERI 7 mg p.o. q.d. TERI 14 mg p.o. q.d. Placebo p.o. q.d.	38	71	82	8.0	2.7	1.4	NR
Vermersch et al. 2014 TENERE	TERI 7 mg p.o. q.d. TERI 14 mg p.o. q.d. IFNB-1a 44 mcg SC t.i.w.	37	68	100	7.1	2.1	1.3	NR
O'Connor et al. 2011 TEMSO	TERI 7 mg p.o. q.d. TERI 14 mg p.o. q.d. Placebo p.o. q.d.	38	72	97	8.7	2.7	1.4	1.7

Trial	Treatment Groups	Age (Years)	Female (%)	White (%)	MS Duration	EDSS Baseline	Relapses Prior Year	MRI GdE Lesions
Cohen et al. 2010 TRANSFORMS	FIN 0.5 mg p.o. q.d. IFNB-1a 30 mcg IM q.w.	38	72	88	1.2	2.0	1.7	4.3
Kappos et al. 2010 FREEDOMS	FIN 0.5 mg p.o. q.d. Placebo p.o. q.d.	37	70	94	NR	2.9	2 years: 3.4	NR
Calabresi et al. 2014 FREEDOMS II	FIN 0.5 mg p.o. q.d. Placebo p.o. q.d.	40	79	NR	10.5	2.4	1.4	1.3
Calabresi et al. 2014 ADVANCE	Peg-IFNB-1a 125 mcg SC q.2.w. Placebo SC q.2.w.	37	71	NR	6.6	NR, 84% < 4	1.6	1.4
PRISMS 1998 PRISMS	IFNB-1a 22 mg SC t.i.w. IFNB-1a 44 mcg SC t.i.w. Placebo SC t.i.w.	35	69	NR	5.3	2.5	2 years: 3.0	NR
Panitch et al. 2002 EVIDENCE	IFNB-1a 44 mcg SC t.i.w. IFNB-1a 30 mcg IM q.w.	38	75	91	6.6	2.3	2 years: 2.6	NR
Mikol et al. 2008 REGARD	IFNB-1a 44 mcg SC t.i.w. GA 20 mg SC q.d.	37	71	94	6.2	2.3	NR	1.6
Bornstein et al. 1987	GA 20 mg SC q.d. Placebo SC q.d.	31	56	96	5.6	3.0	2 years: 3.8	NR
Johnson et al. 1995	GA 20 mg SC q.d. Placebo SC q.d.	34	73	94	6.9	2.6	2 years: 2.9	NR
Khan et al. 2013 GALA	GA 40 mg SC t.i.w. Placebo SC q.d.	37	68	98	7.7	2.8	1.3	1.6
IFINip MS Study Group 1993	IFNB-1b 250 SC mcg q.o.d. Placebo	35	70	94	NR	2.4	2 years: 2.6	4.3
Durelli et al. 2002 INCOMIN	IFNB-1b 250 SC mcg q.o.d. IFNB-1a 30 mcg IM q.w.	37	65	NR	6.3	2.0	1.5	NR
Etemadifar et al. 2006	IFNB-1b 250 SC mcg q.o.d. IFNB-1a 30 mcg IM q.w. IFNB-1a 44 mcg SC t.i.w.	29	76	NR	3.2	2.0	2.2	NR
Cadavid et al. 2009 BECOME	IFNB-1b 250 SC mcg q.o.d. GA 20 mg SC q.d.	36	69	52	1.1	2	1.9	NR
O'Connor et al. 2009 BEYOND	IFNB-1b 250 SC mcg q.o.d. GA 20 mg SC q.d.	36	69	91	5.3	2.3	1.3	2.1

Trial	Treatment Groups	Age (Years)	Female (%)	White (%)	MS Duration	EDSS Baseline	Relapses Prior Year	MRI GdE Lesions
Jacobs et al. 1996	IFNB-1a 30 mcg IM q.w. Placebo IM q.w.	37	73	92	6.5	2.4	1.2	NR
Calabrese et al. 2012	IFNB-1a 30 mcg IM q.w. IFNB-1a 44 mcg SC t.i.w. GA 20 mg SC q.d.	37	70	NR	5.6	2.0	1.2	NR
Lublin et al. 2013 CombiRx	IFNB-1a 30 mcg IM q.w. GA 20 mg SC q.d.	38	72	88	1.2	2.0	1.7	4.3
Vollmer et al. 2014 BRAVO	IFNB-1a 30 mcg IM q.w. Placebo IM q.w.	38	70	NR	5.0	2.5	1.0	65% with 0

ALEM = alemtuzumab; b.i.d. = twice daily; DAC = daclizumab; DMF = dimethyl fumarate; EDSS = Kurtzke Expanded Disability Status Scale; FIN = fingolimod; GA = glatiramer acetate; GdE = gadolinium-enhancing; IFNB = interferon beta; IM = intramuscular; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; NAT = natalizumab; NR = not reported; OCR = ocrelizumab; PEG = pegylated;; p.o. = orally; q.d. = once daily; q.o.d. = once every other day; q.w. = once weekly; q.6.m. = once every six months; q.2.w. = once every two weeks; q.4.w. = once every four weeks; RTX = rituximab; SC = subcutaneous; TERI = teriflunomide; t.i.w. = three times per week.

Source: Adapted with permission from the Institute for Clinical and Economic Review (ICER). Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value. March 2017.[46]

The results of the NMA demonstrated that ocrelizumab 600 mg was statistically significantly superior in terms of ARR (informed by 33 trials) when compared with placebo, interferon beta-1a 30 mcg, teriflunomide 7 mg, interferon beta-1a 22 mcg, glatiramer acetate 40 mg, teriflunomide 14 mg, interferon beta-1b 250 mcg, interferon beta-1a 44 mcg, peg-interferon beta-1a 125 mcg, glatiramer acetate 20 mg, and dimethyl fumarate 240 mg. No statistically significant difference was reported when comparing ocrelizumab 600 mg with daclizumab 150 mg, fingolimod 0.5 mg, natalizumab 300 mg, or alemtuzumab 12 mg (Table 40). The results of subgroup analyses, sensitivity analyses, and different modelling approaches were similar to those of the

analyses for ocrelizumab relative to placebo.These included the use of a fixed-effects model, adjustment for potential confounding factors (i.e., disease duration, relapses in the prior year, baseline EDSS state), and the exclusion of small and poor-quality trials, trials that did not use the McDonald criteria, trials with a duration of less than 18 months, and open-label trials.

With regard to the outcome of disability progression (informed through 27 studies), ocrelizumab 600 mg was shown to be statistically significantly superior to placebo, glatiramer acetate 40 mg daily, teriflunomide 7 mg, and interferon beta-1a 30 mcg. No statistically significant difference was observed in any other comparison (Table 41). When the authors broke down the disability outcome by trials that reported disability progression at 12 weeks and 24 weeks, the result of disability progression 12 weeks was largely similar to the base case, with the exception of four comparisons of ocrelizumab relative to interferon beta-1a 22 mcg, glatiramer acetate 20 mg, fingolimod 0.5 mg, and interferon beta-1b 250 mcg, for which differences were statistically significant. However, the subgroup of trials that reported disability progression at 24 weeks showed no statistically significant difference for any of the available comparisons, with associated large credible intervals. The results of subgroup analyses, sensitivity analyses, and different models were generally similar to the base-case analysis of ocrelizumab relative to placebo. These included fixed-effects results, disease duration, relapses in prior year, baseline EDSS state, and exclusion of small and poor-quality trials, trials with a duration of fewer than 18 months, and open-label trials. Only one sensitivity analysis of trials that used the McDonald criteria produced different results (0.47 [95% CrI, 0.28 to 0.76] in the base case and 0.75 [95% CrI, 0.39 to 1.47] in the sensitivity analysis).

No other outcomes were reported in the ICER ITC.

Table 40: Results for Annualized Relapse Rate

Treatment	ARR
	RR (95% CrI)
OCR 600 mg relative to:	
Placebo	**0.35 (0.27 to 0.44)**
IFNB-1a 30 mcg	**0.42 (0.32 to 0.53)**
TERI 7 mg	**0.45 (0.33 to 0.59)**
IFNB-1a 22 mcg	**0.50 (0.38 to 0.68)**
GA 40 mg	**0.52 (0.36 to 0.74)**
TERI 14 mg	**0.52 (0.39 to 0.69)**
IFNB-1b 250 mcg	**0.54 (0.41 to 0.71)**
IFNB-1a 44 mcg	**0.55 (0.45 to 0.67)**
PEG-INF B-1A 125 mcg	**0.56 (0.37 to 0.80)**

Treatment	ARR
	RR (95% CrI)
GA 20 mg	**0.55 (0.43 to 0.71)**
DMF 240 mg	**0.66 (0.48 to 0.90)**
DAC 150 mg	0.75 (0.54 to 1.01)
FIN 0.5 mg	0.76 (0.56 to 1.01)
NAT 300 mg relative to:	
OCR 600 mg	0.89 (0.65 to 1.29)
ALEM 12 mg relative to:	
OCR 600 mg	0.82 (0.61 to 1.05)

ALEM = alemtuzumab; ARR = annualized rate ratio; CrI = credible interval; DAC = daclizumab; DMF = dimethyl fumarate; EDSS = Kurtzke Expanded Disability Status Scale; FIN = fingolimod; GA = glatiramer acetate; IFNB = interferon beta; NAT = natalizumab; OCR = ocrelizumab; PEG = pegylated; RR = relative risk; TERI = teriflunomide.

Source: ICER report.[46]

Table 41: Results for Disability Progression

Treatment	Disability Progression Outcomes		
	Pooled 12 and 24 Weeks RR (95% CrI)	12 Weeks RR (95% CrI)	24 Weeks RR (95% CrI)
OCR 600 mg relative to:			
Placebo	**0.47 (0.28 to 0.76)**	**0.45 (0.26 to 0.66)**	0.50 (0.16 to 1.27)
GA 40 mg	**0.40 (0.20 to 0.81)**	**0.37 (0.19 to 0.73)**	NA
TERI 7 mg	**0.54 (0.30 to 0.95)**	**0.52 (0.28 to 0.84)**	NA
IFNB-1a 22 mcg	0.57 (0.32 to 1.01)	**0.56 (0.31 to 0.91)**	NA
IFNB-1a 30 mcg	**0.59 (0.35 to 0.97)**	**0.55 (0.33 to 0.84)**	0.64 (0.24 to 1.41)
GA 20 mg	0.63 (0.37 to 1.04)	**0.49 (0.28 to 0.85)**	0.67 (0.27 to 1.52)
IFNB-1a 44 mcg	**0.64 (0.44 to 0.92)**	**0.64 (0.46 to 0.86)**	0.64 (0.36 to 1.11)
TERI 14 mg	0.65 (0.36 to 1.17)	0.62 (0.33 to 1.00)	NA
FINGO 0.5 mg	0.68 (0.38 to 1.20)	**0.59 (0.33 to 0.96)**	0.70 (0.19 to 2.00)
IFNB-1b 250 mcg	0.71 (0.40 to 1.27)	**0.47 (0.25 to 0.89)**	0.99 (0.36 to 2.09)
PEG-INFB-1A 125 mcg	0.74 (0.37 to 1.51)	0.7 (0.35 to 1.28)	NA
DMF 240 mg	0.75 (0.41 to 1.31)	0.69 (0.37 to 1.11)	NA
NAT 300 mg	0.84 (0.43 to 1.59)	0.77 (0.41 to 1.37)	NA
DAC 150 mg	0.86 (0.47 to 1.60)	0.73 (0.42 to 1.21)	0.89 (0.26 to 2.40)
ALEM 12 mg relative to			
OCR 600 mg	0.91 (0.54 to 1.51)	0.72 (0.34 to 1.47)	0.89 (0.39 to 1.84)

ALEM = alemtuzumab; CrI = credible interval; DAC = daclizumab; DMF = dimethyl fumarate; FINGO = fingolimod; GA = glatiramer acetate; IFNB = interferon beta; NA = not applicable; NAT = natalizumab; OCR = ocrelizumab; PEG = pegylated; RR = relative risk; TERI = teriflunomide.

Source: ICER report.[46]

Critical Appraisal

The protocol for the systematic review and the eligibility criteria were comprehensive, capturing the relevant comparators and clinically relevant end points. The authors have provided a comprehensive list of sensitivity analyses and subgroup analyses to support the base-case analysis which accounted for many issues associated with statistical and clinical heterogeneity across the included studies.

Three main critical appraisal points can be made regarding the ICER ITC:

- Lack of reporting on the number of screeners/reviewers who were involved in the screening and data-extraction processes: This raises the possibility of human error, which could result in articles being missed or incorrect data being extracted, reducing the overall certainty of the results.
- Lack of reporting of key model diagnostics: The authors did not include the number of iterations and did not report whether the model achieved convergence. In addition, while the authors describe that the DIC was similar between the chosen random-effects model and the fixed-effects model, providing these numbers along with the posterior residual variance would have been helpful in assessing the extent of complexity and variance in the results.
- Pooling and handling of the end points for disability progression: The authors of the ICER ITC decided to pool the results for CDP for 12 weeks and CDP for 24 weeks in order to achieve a more robust analysis. While this would help to provide a more robust network to run an ITC, it also introduces additional measures of clinical and methodological heterogeneity and reduces the overall certainity in the results. The authors provided a sensitivity analysis of the results from CDP for 12 weeks and CDP for 24 weeks and contrasted that with the pooled results, which show that the results are highly influenced by the disability progression at 12 weeks. Also, the handling of the disability progression outcome as a binomial outcome in a dichotomous model reduced the overall validity of the result, and limits our ability to interpret these outcomes. CDP is usually handled as a survival model to allow the incorporation of unit time in the interpretation of the data. This, in addition to the pooling, further complicates the interpretation of the disability result.

The ICER ITC could have added greater value by extracting and analyzing more outcomes beyond the ARR and disability progression. In addition, two of the included studies were on the PPMS population.

Discussion

Both ITCs were conducted around the same time, with the ICER ITC search date being slightly older than the manufacturer-submitted ITC search date (September 2016 versus November 2016, respectively). The manufacturer's ITC protocol allowed for more comparators than the ICER ITC and included conducting a search on more bibliographical databases. Also, the ICER protocol allowed for the inclusion of studies on the PPMS population, while the manufacturer's ITC restricted the population to RRMS or, in cases of mixed population, to less than 50% secondary-progressive multiple sclerosis. While the systematic review for the manufacturer-submitted ITC included more studies than the one conducted by ICER, both ITCs included a similar number of studies in the NMA.

Both ITCs conducted Bayesian NMAs to provide an ITC. Both also provided their primary results using a random-effects prior with a vague "uninformative" prior. The manufacturer-submitted ITC conducted NMA analyses on six outcomes (ARR, CDP at 12 weeks, CDP at 24 weeks, proportion of patients who were relapse-free, serious adverse events, and all-cause discontinuations), as opposed to two outcomes conducted in the ICER ITC (ARR and pooled disability progression). Both ITCs handled the ARR outcome using a Poisson distribution model. The manufacturer's ITC handled the CDP outcomes using a survival model, while the ICER ITC handled the pooled disability progression as a binomial outcome in a dichotomous model.

[redacted]

[redacted] Table 42. [redacted]

Table 42: Annualized Relapse Rate Results From the Included Network Meta-Analyses

Treatment	ARR Outcome RR (95% CrI)	
	Manufacturer ITC	ICER ITC
OCR 600 mg relative to:		
Placebo	[redacted]	**0.35 (0.27 to 0.44)**
IM IFNB-1a 30 mcg, q.w.	[redacted]	**0.42 (0.32 to 0.53)**
TERI 7 mg, q.d.	[redacted]	**0.45 (0.33 to 0.59)**
SC IFNB-1b 250 mcg, q.o.d.	[redacted]	**0.54 (0.41 to 0.71)**
GA 20 mg, q.d.	[redacted]	**0.55 (0.43 to 0.71)**
TERI 14 mg, q.d.	[redacted]	**0.52 (0.39 to 0.69)**
GA 40 mg, t.i.w.	[redacted]	**0.52 (0.36 to 0.74)**
PEG-INFB-1A 125 mcg, q.2.w.	[redacted]	**0.56 (0.37 to 0.80)**
IFNB-1a SC 44 mcg, t.i.w.	[redacted]	**0.55 (0.45 to 0.67)**
DMF 240 mg, b.i.d.	[redacted]	**0.66 (0.48 to 0.90)**
FIN 0.5 mg, q.d.	[redacted]	0.76 (0.56 to 1.01)
DAC 150 mg, q.4.w.	[redacted]	0.75 (0.54 to 1.01)
CLAD 5.25 mg/kg	[redacted]	NR
CLAD 3.5 mg/kg	[redacted]	NR
NAT 300 mg, q.4.w.	[redacted]	NR
ALEM 12 mg	[redacted]	NR
IFNB-1a SC 22 mcg, t.i.w.	[redacted]	**0.50 (0.38 to 0.68)**
NAT 300 mg relative to:		
OCR 600 mg	[redacted]	0.89 (0.65 to 1.29)
ALEM 12 mg relative to:		
OCR 600 mg	[redacted]	0.82 (0.61 to 1.05)

ALEM = alemtuzumab; ARR = annualized relapse rate; b.i.d. = twice daily; CLAD = cladribine; CrI = credible interval; DAC = daclizumab; DMF = dimethyl fumarate; FIN = fingolimod; GA = glatiramer acetate; ICER = Institute for Clinical and Economic Review; ITC = indirect treatment comparison; IFNB = interferon beta; IM = intramuscular; NAT = natalizumab; NR = not reported; OCR = ocrelizumab; PEG = pegylated; q.d. = once daily; q.o.d. = once every other day; q.2.w. = once every two weeks; q.4.w. = once every four weeks; q.w. = once weekly; RR = relative risk; SC = subcutaneous; TERI = teriflunomide; t.i.w. = three times per week.

Source: Manufacturer-submitted ITC[45] and ICER report.[46]

[redacted]

[redacted]

Both ITCs included a considerable number of studies that have variable characteristics in the design, population, and definition of outcomes. This variability, while unavoidable, reduces the overall certainty of the results. However, the clinical expert consulted by CADTH suggested that, from a clinical standpoint, the patient characteristics and the definitions of outcomes were sufficiently similar to allow credible ITCs to be made.

Conclusion

Two ITCs were identified, reviewed, and critically appraised; one was submitted and commissioned by the manufacturer,[45] and one was published by ICER.[46] Both ITCs had approached the systematic review similarly, used Bayesian NMA to conduct the indirect analysis, and handled the outcome of ARR in the same manner. Differences between the two revolve around including the PPMS population in the ICER study and excluding non-FDA–approved doses, the handling of disability progression outcomes, and the number of outcomes reported in the manufacturer's ITC versus the ICER ITC.

[redacted]

Critical appraisal points involve the following: both ITCs lacked reporting on certain items that would better inform on the certainty of the indirect evidence in both ITCs; the manufacturer's ITC could have conducted more sensitivity and subgroup analysis to satisfy

the assumptions of transitivity and homogeneity; and the ICER ITC could have handled the outcome of disability progression in a manner that is more statistically appropriate and easier to interpret.

References

1. Summary of clinical efficacy: section 2.7.3. Ocrelizumab BLA 761053 [**CONFIDENTIAL** internal manufacturer's report]. San Francisco (CA): Genentech; [2016].
2. Summary of clinical safety: section 2.7.4. Ocrelizumab BLA 761053 [**CONFIDENTIAL** internal manufacturer's report]. San Francisco (CA): Genentech; [2016].
3. Multiple sclerosis in adults: management [Internet]. London: National Institute for Health and Care Excellence; 2014 Oct 8. [cited 2017 Mar 13]. (Clinical guideline; no. 186). Available from: https://www.nice.org.uk/guidance/cg186/resources/multiple-sclerosis-in-adults-management-35109816059077
4. Olek MJ. Clinical course and classification of multiple sclerosis. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2016 Oct [cited 2017 Feb 23]. Available from: www.uptodate.com Subscription required.
5. Helliwell CL, Coles AJ. Monoclonal antibodies in multiple sclerosis treatment: current and future steps. Ther Adv Neurol Disord [Internet]. 2009 Jul [cited 2017 Mar 13];2(4):195-203. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3002635
6. Tsang BK, Macdonell R. Multiple sclerosis - diagnosis, management and prognosis. Aust Fam Physician. 2011 Dec;40(12):948-55.
7. Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. Mayo Clin Proc. 2014 Feb;89(2):225-40.
8. The burden of neurological diseases, disorders and injuries in Canada [Internet]. Ottawa: Canadian Institute for Health Information; 2007. [cited 2017 Mar 13]. Available from: https://secure.cihi.ca/free_products/BND_e.pdf
9. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol [Internet]. 2011 Feb [cited 2017 Mar 13];69(2):292-302. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3084507
10. What is MS? [Internet]. Toronto: Multiple Sclerosis Society of Canada; 2017. [cited 2017 Mar 13]. Available from: https://mssociety.ca/about-ms/what-is-ms
11. Freedman MS, Selchen D, Arnold DL, Prat A, Banwell B, Yeung M, et al. Treatment optimization in MS: Canadian MS working group updated recommendations. Can J Neurol Sci. 2013 May;40(3):307-23.
12. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2017 [cited 2017 Mar 13]. Available from: https://www.e-therapeutics.ca Subscription required.
13. Aubagio© (teriflunomide tablets): 14 mg [product monograph] [Internet]. Mississauga (ON): Sanofi Genzyme, a division of sanofi-aventis Canada Inc.; 2017 Jan 25. [cited 2017 Oct 13]. Available from: https://pdf.hres.ca/dpd_pm/00038165.PDF
14. Tecfidera© (dimethyl fumarate delayed-release capsules): 12 mg and 240 mg [product monograph] [Internet]. Mississauga (ON): Biogen Canada Inc.; 2017 Feb 17. [cited 2017 Mar 13]. Available from: https://pdf.hres.ca/dpd_pm/00038163.PDF
15. Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis [Internet]. Ottawa: CADTH; 2013 Oct. [cited 2017 Mar 13]. (CADTH therapeutic review; vol. 1, no. 2b). Available from: https://www.cadth.ca/media/pdf/TR0004_RRMS_ScienceReport_e.pdf
16. Soelberg Sorensen P. Safety concerns and risk management of multiple sclerosis therapies. Acta Neurol Scand. 2016 Nov 27. Epub ahead of print.
17. Ocrevus (ocrelizumab): 300 mg/10 mL (30 mg/mL) [product monograph]. Mississauga (ON): Hoffman-La Roche Limited; 2017 Aug 14.
18. ZinbrytaT (daclizumab beta): 150 mg/mL solution for injection [product monograph]. Mississauga (ON): Biogen Canada Inc.; 2016 Dec 7.
19. PlegridyT(peginterferon beta-1a): liquid for injection 125 æg [product monograph] [Internet]. Mississauga (ON): Biogen Canada Inc.; 2016 Jun 16. [cited 2017 Mar 13]. Available from: https://pdf.hres.ca/dpd_pm/00035457.PDF

20. Lemtrada© (alemtuzumab): 12 mg/1.2 mL [product monograph] [Internet]. Mississauga (ON): Genzyme Canada, a division of sanofi-aventis Canada Inc.; 2016 Feb 26. [cited 2017 Mar 13]. Available from: https://pdf.hres.ca/dpd_pm/00033852.PDF

21. Gilenya© (fingolimod (as fingolimod hydrochloride)): oral capsules, 0.5 fingolimod [product monograph] [Internet]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2016 Dec 16. [cited 2017 Mar 13]. Available from: https://pdf.hres.ca/dpd_pm/00037481.PDF

22. Copaxone© (glatiramer acetate injection): 20 mg / 1 mL and 40 mg / 1 mL pre-filled syringes for subcutaneous injection [product monograph] [Internet]. Toronto: Teva Canada Limited; 2017 Feb 17. [cited 2017 Mar 13]. Available from: https://pdf.hres.ca/dpd_pm/00038162.PDF

23. Avonex© (interferon beta-1a): liquid for injection [product monograph] [Internet]. Mississauga (ON): Biogen Canada Inc.; 2016 Jun 27. [cited 2017 Mar 13]. Available from: https://pdf.hres.ca/dpd_pm/00035455.PDF

24. Rebif© (interferon beta-1a): 8.8 æg/0.2 mL, 22 æg/0.5 mL and 44 æg/0.5 mL solution for injection; multidose 22 æg x 3 (66 æg/1.5 mL); multidose 44 æg x 3 (132 æg/1.5 mL) solution for injection in pre-fille catridge. Rebif© RebiDoseT 8.8 æg/0.2 mL, 22 æg/0.5 mL and 44 æg/0.5 mL solution for injection [product monograph] [Internet]. Mississauga (ON): EMD Serono; 2011 May 9. [cited 2017 Mar 13]. Available from: https://pdf.hres.ca/dpd_pm/00013126.PDF

25. Extavia© (interferon beta-1b): lyophilized powder for subcutaneous injection 0.3 mg/vial [product monograph] [Internet]. Dorval (QC): Novartis Pharmaceuticals Canada Inc; 2016 May 24. [cited 2017 Mar 13]. Available from: https://pdf.hres.ca/dpd_pm/00036353.PDF

26. Betaseron© (interferon beta-1b): lyophilized powder for subcutaneous injection 0.3 mg/vial [product monograph] [Internet]. Mississauga (ON): Bayer Inc.; 2016 Aug 15. [cited 2017 Mar 13]. Available from: https://pdf.hres.ca/dpd_pm/00036140.PDF

27. Tysabri© (natalizumab): concentrate for solution for intravenous infusion 300 mg/15 mL [product monograph] [Internet]. Mississauga (ON): Biogen Canada Inc.; 2016 Aug 31. [cited 2017 Mar 13]. Available from: https://pdf.hres.ca/dpd_pm/00036917.PDF

28. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017 Jan 19;376(3):221-34.

29. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Ocrevus (ocrelizumab). Company: Genentech, Inc. Application no.: 761053. Approval date: 31/03/2017 [Internet]. Rockville (MD): FDA; 2017 Mar 28 [cited 2017 May 30]. (FDA drug approval package). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761053Orig1s000TOC.cfm

30. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Ocrevus (ocrelizumab). Company: Genentech, Inc. Application no.: 761053. Approval date: 28/03/2017 [Internet]. Rockville (MD): FDA; 2017 Mar 28 [cited 2017 May 30]. (FDA drug approval package). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761053Orig1s000TOC.cfm

31. Primary clinical study report: WA21092. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif ✹) in patients with relapsing multiple sclerosis [**CONFIDENTIAL** internal manufacturer's report]. Basel (CH): F. Hoffmann-La Roche Ltd; 2016 Mar. Report No.: 1062034

32. Primary clinical study report: WA21093. A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon beta-1a (Rebif ✹) in patients with relapsing multiple sclerosis [**CONFIDENTIAL** internal manufacturer's report]. Basel (CH): F. Hoffmann-La Roche Ltd; 2016 Mar. Report No.: 1062035

33. A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis. 2010 Nov 23 [cited 2017 Jun 14; updated 2016 Oct 10]. In: ClinicalTrials.gov. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/show/NCT01247324 NLM Identifier: NCT01247324.

34. A study of ocrelizumab in comparison with interferon beta-1a (Rebif) in participants with relapsing multiple sclerosis. 2011 Aug 8 [cited 2017 Jun 14; updated 2016 Oct 25]. In: ClinicalTrials.gov. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/show/NCT01412333 NLM Identifier: NCT01412333.

35. Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. Mult Scler. 1999 Aug;5(4):244-50.

36. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC Neurol [Internet]. 2014 Mar 25 [cited 2017 Aug 14];14:58. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3986942/pdf/1471-2377-14-58.pdf

37. Maruish M, Kosinski M, Bjorner JB, Gandek B, Turner-Bowker DM, Ware JE. User's manual for the SF-36v2 health survey. 3rd edition. Lincoln (RI): Quality Metric Incorporated; 2011.

38. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med [Internet]. 2001 Jul;33(5):350-7.

39. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. PharmacoEconomics. 1999 Feb;15(2):141-55.

40. Multiple endpoints in clinical trials: guidance for industry. Draft guidance [Internet]. Rockville (MD): Food and Drug Administration; 2017. [cited 2017 Aug 8]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536750.pdf

41. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis [Internet]. London: European Medicines Agency; 2015 Mar 26. [cited 2017 Apr 3]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500185161.pdf

42. CDR submission: Ocrevus (ocrelizumab), 300 mg/10 mL (30 mg/mL) concentrate for infusion. Company: Hoffman-La Roche Limited [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Hoffman-La Roche Limited; 2017 May 25.

43. A study of ocrelizumab in participants with relapsing remitting multiple sclerosis (RRMS) who have had a suboptimal response to an adequate course of disease-modifying treatment (DMT). 2015 Dec 18 [cited 2017 Jun 14; updated 2017 Jun 2]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/show/NCT02637856 NLM Identifier: NCT02637856.

44. A study of ocrelizumab in participants with relapsing remitting multiple sclerosis (RRMS) who have had a suboptimal response to an adequate course of disease-modifying treatment (DMT). 2016 Aug 5 [cited 2017 Jun 14; updated 2017 Jun 2]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/show/NCT02861014 NLM Identifier: NCT02861014.

45. Wilson K, McCool R, Glanville J, Edwards M, Fleetwood K. Systematic review and network meta-analysis of treatment for relapsing-remitting multiple sclerosis. York (GB): York Health Economics Consortium; 2017.

46. Disease-modifying therapies for relapsing-remitting and primary-progressive multiple sclerosis: effectiveness and value [Internet]. Boston (MA): Institute for clinical and economic review; 2017 Mar 6. [cited 2017 Aug 16]. Available from: https://icer-review.org/wp-content/uploads/2016/08/CTAF_MS_Final_Report_030617.pdf Prepared for California Technology Assessment Forum.

47. Hoffman-La Roche Limited comments regarding the draft Ocrevus CDR review [**CONFIDENTIAL** additional manufacturer's information]. Mississauga (ON): Hoffman-La Roche Limited; 2017 Aug 30.

48. Chapuis B, Helg C, Maurice P, Aapro M, Jeannet M, Irle C, et al. Super intensive treatment followed by bone marrow autograft in cases of hematologic neoplasms and solid tumors. Schweiz Med Wochenschr. 1988 Mar 12;118(10):341-6. French.

49. Ashton DS, Beddell CR, Cooper DJ, Lines AC. Determination of carbohydrate heterogeneity in the humanised antibody CAMPATH 1H by liquid chromatography and matrix-assisted laser desorption ionisation mass spectrometry. Anal Chim Acta. 1995;306(1):43-8.

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

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

52. Costelloe L, O'Rourke K, Kearney H, McGuigan C, Gribbin L, Duggan M, et al. The patient knows best: significant change in the physical component of the Multiple Sclerosis Impact Scale (MSIS-29 physical). J Neurol Neurosurg Psychiatry [Internet]. 2007 Aug [cited 2017 Feb 21];78(8):841-4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2117755/pdf/841.pdf

53. Bayes M, Rabasseda X, Prous JR. Gateways to clinical trials. Methods Find Exp Clin Pharmacol. 2007 Nov;29(9):625-55.

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

55. Hobart J, Freeman J, Lamping D, Fitzpatrick R, Thompson A. The SF-36 in multiple sclerosis: why basic assumptions must be tested. J Neurol Neurosurg Psychiatry. 2001 Sep;71(3):363-70. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1737568

56. Nortvedt MW, Riise T, Myhr KM, Nyland HI. Performance of the SF-36, SF-12, and RAND-36 summary scales in a multiple sclerosis population. Med Care. 2000 Oct;38(10):1022-8.

57. Rovira A, Auger C, Alonso J. Magnetic resonance monitoring of lesion evolution in multiple sclerosis. Ther Adv Neurol Disord [Internet]. 2013 Sep [cited 2017 Mar 14];6(5):298-310. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3755529

58. Klawiter EC. Current and new directions in MRI in multiple sclerosis. Continuum (Minneap Minn) [Internet]. 2013 Aug [cited 2017 Mar 14];19(4 Multiple Sclerosis):1058-73. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4234130

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

60. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012 Nov 24;380(9856):1829-39.

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

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

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

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