CADTH

Clinical Review Report

Ocrelizumab (Ocrevus)

(Hoffmann-La Roche Limited)

Indication: Management of adult patients with early primary progressive multiple sclerosis as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity.

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Abbreviations

9-HPT	9-Hole Peg Test
AE	adverse event
BMI	body mass index
CDR	CADTH Common Drug Review
CDP	confirmed disability progression
CI	confidence interval
CNS	central nervous system
DMT	disease-modifying therapy
ECT	extended controlled treatment
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
Gd	gadolinium
HRQoL	health-related quality of life
IgG	immunoglobulin G
ITT	intention-to-treat population
LSMD	least squares mean difference
MCID	minimal clinically important difference
MCS	mental component summary
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MS Society	Multiple Sclerosis Society of Canada
OLE	open-label extension
PAP	primary analysis period
PASAT	Paced Auditory Serial Addition Test
PCS	physical component summary
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
PRMS	progressive relapsing multiple sclerosis
QoL	quality of life
RCT	randomized controlled trial
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SPMS	Secondary Progressive Multiple Sclerosis
T25FW	Timed 25-Foot Walk

Drug	Ocrelizumab (Ocrevus)
Indication	Management of adult patients with early primary progressive multiple sclerosis (PPMS) as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity
Reimbursement request	As per indication
Dosage form(s)	300 mg vial
NOC date	February 14, 2018
Manufacturer	Hoffmann-La Roche Limited

Executive Summary

Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory disease of the central nervous system (CNS). MS causes disabling physical symptoms that stem from mobility, vision, and coordination problems as well as cognitive dysfunction, fatigue, and pain. The quality of life (QoL) of an individual living with MS is significantly impaired by mood disorders and limitations in employment and social functioning. MS is classified into four clinical subtypes: relapsing remitting MS (RRMS); primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS).

Approximately 85% to 90% of MS patients first present with the RRMS subtype. 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. It is estimated that 10% to 15% of MS patients have the PPMS subtype, which is characterized by consistent disease progression and is not typically associated with relapses. MS is associated with a major financial burden on patients, family, and the health care system. The Multiple Sclerosis Society of Canada (MS Society) estimates that there are currently 100,000 patients with MS in Canada.

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-cells. It has been approved by Health Canada for use in the following indications:

- Treatment of adult patients with RRMS with active disease defined by clinical and imaging features
- Management of adult patients with early PPMS as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity.

The recommended dose of ocrelizumab is 600 mg 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. It is available as single-use vials containing 300 mg of active substance.

The current CADTH Common Drug Review (CDR) submission for ocrelizumab is for use in the treatment of patients with PPMS. CADTH has previously reviewed ocrelizumab for use in the treatment of adult patients with RRMS.

Results and Interpretation

Included Studies

The CADTH systematic review included one phase III, multinational, multi-centre, parallel-group, double-blind, placebo-controlled, randomized controlled trial (RCT). Patients enrolled in the ORATORIO trial (N = 732) were randomized (2:1) to receive IV infusions of ocrelizumab or placebo every six months (as two infusions 14 days apart). The study evaluated clinical end points (e.g., confirmed disability progression [CDP]), magnetic resonance imaging (MRI) end points (e.g., changes in T1 and T2 lesions), walking ability (Timed 25-Foot Walk [T25FW]), and patient-reported end points (e.g., Short Form (36) Health Survey [SF-36]). During the
120-week treatment period, study participants were required to attend 17 scheduled assessment and/or infusion visits. Additionally, structured telephone interviews were conducted every four weeks starting at week eight to identify any new or worsening neurological symptoms that would require an unscheduled clinic visit.

Patients aged 18 years to 55 years with PPMS were eligible for enrolment in the ORATORIO trial if they had an Expanded Disability Status Scale (EDSS) score between 3.0 and 6.5 and a score of at least 2.0 on the functional systems scale for the pyramidal system due to lower extremity findings. The diagnosis of PPMS was made in accordance with the revised 2005 McDonald criteria. Patients also had to have a disease duration of less than 15 years (for those with an EDSS greater than 5.0) or less than 10 years (for those with an EDSS of 5.0 or less) at screening. Patients were excluded from the study if they had other MS types (i.e., RRMS, SPMS, or PRMS) or if they had any of the following: neurologic disorders other PPMS (including a history of progressive multifocal leukoencephalopathy [PML]); known active bacterial, viral, fungal, or mycobacterial infections; history of recurrent aspiration pneumonia requiring antibiotic therapy; or history of cancer.

Key limitations with the ORATORIO trial included the following: sensitivity of the results for 12-week CDP (primary end point), 24-week CDP (secondary end point), and T25FW to different methods and assumptions regarding the imputation of missing data; unplanned increase in sample size (i.e., from 630 to 732); the large and disproportionate rate of withdrawal across the study (i.e., 33.6% and 20.7% in the placebo and ocrelizumab groups, respectively); the potential for unblinding due to the adverse event (AE) profile of ocrelizumab (particularly those related to the administration of the study drug); and the need to impute a large amount of the data for some end points (e.g., SF-36 and changes in lesions). Generalizability of the results may be limited by the exclusion of patients older than 55 years of age and those with an EDSS score above 6.5; the uncertainty regarding the proportion of Canadian PPMS patients who would have evidence of active inflammation in the brain and/or spinal cord; and the extensive contact with health professionals during the study.

Efficacy

Treatment with ocrelizumab was associated with a statistically significant reduction of 24% in the hazard for CDP for at least 12 weeks (hazard ratio: 0.76; 95% confidence interval [CI], 0.59 to 0.98). The results in the intention-to-treat (ITT) population were sensitive to the

method of imputation that was used to account for patients who experienced an initial progression event but withdrew prior to having the event confirmed at least 12 weeks later. When these patients were considered as having CDP events, the results were statistically significant; but when these events were not imputed, the results were no longer statistically significant (hazard ratio: 0.82, 95% CI, 0.63 to 1.07). Subgroups of interest for this review included: age (dichotomized in ORATORIO as ≤ 45 years or > 45 years); disease severity as measured by EDSS at baseline (dichotomized in ORATORIO as ≤ 5.5 or > 5.5); and signs of active inflammation as measured by gadolinium (Gd)-enhancing lesion(s) at baseline (dichotomized in ORATORIO as "presence" or "absence"). The manufacturer conducted univariate subgroup analyses and a multivariate Cox regression analysis to investigate potential treatment-modifying effects. Ocrelizumab was statistically significantly superior to placebo in reducing 12-week CDP only in the subgroup of patients who were less than 45 years of age at baseline (hazard ratio: 0.64; 95% CI, 0.45 to 0.92). Reductions in 12-week CDP with ocrelizumab versus placebo were observed in other subgroups of interest. Interaction tests for the univariate subgroup analyses were not statistically significant. The multivariate analysis also demonstrated no statistically significant interaction effects. The results for time to CDP for at least 24 weeks were nearly identical to those reported for 12-week CDP. Ocrelizumab was associated with a statistically significant reduction of 25% in the hazard for CDP for at least 24 weeks compared with placebo (hazard ratio: 0.75; 95% CI, 0.59 to 0.98; $P = 0.0365$). As with the 12-week CDP, when analyzed without imputation, the results were no longer statistically significant (hazard ratio 0.82; 95% CI, 0.62 to 1.10). The rate of 12-week and 24-week CDP events in the ocrelizumab and placebo groups showed initial separation in the 12-week to 18-week range, then remained relatively stable between the two groups for approximately two years before showing additional separation beginning around week 120.

With respect to the MRI end points, treatment with ocrelizumab treatment was associated with reductions in the following compared with placebo: T2 lesion volume ($P < 0.0001$), rate of new and enlarging T2 hyperintense lesions (adjusted rate ratio: 0.081 [95% CI, 0.058 to 0.111]); rate of T1 Gd-enhancing lesions (adjusted rate ratio: 0.024 [95% CI, 0.011 to 0.051]), and brain volume loss (relative difference: 17.475% [95% CI, 3.206 to 29.251]).

T25FW times increased in both groups throughout the trial. There was a statistically significant difference between the ocrelizumab and placebo groups (relative reduction: 29.337% [95% CI, –1.618 to 51.456]; $P = 0.0404$). At week 120, the absolute difference between the placebo and ocrelizumab groups in mean change in T25FW time was 3.03 seconds (increase of 11.76 seconds in the placebo group and 8.79 seconds in the ocrelizumab group).

Change from baseline to week 120 in the SF36 physical component summary (PCS) was a pre-specified secondary end point; there was no statistically significant difference between the ocrelizumab and placebo groups (least squares mean difference [LSMD]: 0.377 [95% CI, –1.048 to 1.802]; $P = 0.6034$). Ocrelizumab-treated patients demonstrated an improvement in mean SF-36 mental component summary (MCS), whereas those treated with placebo experienced a reduction in mean SF-36 MCS (LSMD: 3.318 [95% CI, 1.414 to 5.221]; $P = 0.0007$).

Harms

Nearly all patients experienced at least one AE during the double-blind phase of the ORATORIO study (95.1% in the ocrelizumab group and 90.0% in the placebo group). Infections and infestations were the most frequently reported category of AE, with a similar

frequency in the ocrelizumab and placebo groups (69.8% and 67.8%, respectively). Relative to the placebo group, the ocrelizumab group reported a lower frequency of nasopharyngitis (22.6% versus 27.2%, respectively) and a greater frequency of upper respiratory tract infections (10.9% versus 5.9%, respectively).

Serious adverse events (SAEs) were reported for 22.2% of patients in the placebo group and 20.4% of those in the ocrelizumab group. The overall rate of SAEs was 11.67 per 100 patient-years in the placebo group and 10.24 per 100 patient-years in the ocrelizumab group. The proportion of patients who experienced an SAE that was categorized as an infection or infestation was similar in both the ocrelizumab and placebo groups (6.2% versus 5.9%). The proportion of patients with an SAE that was categorized as a neoplasm was greater in the placebo group compared with the ocrelizumab group (2.9% versus 1.6%).

AEs leading to withdrawal from the study treatments occurred for 4.1% of patients in the ocrelizumab group and 3.3% in the placebo group. Cancers were the most frequently reported category of AE leading to discontinuation from the ocrelizumab group (seven patients [1.4%] versus one patient [0.4%] in the placebo group). The proportion of patients who withdrew as a result of an infection was slightly lower in the ocrelizumab group compared with the placebo group (0.8% versus 1.3%). A greater proportion of ocrelizumab-treated patients experienced at least one AE that led to a modification or interruption of the study treatment compared with placebo (9.7% versus 5.0%).

Infusion-related reactions were more commonly reported in the ocrelizumab group compared with the placebo group (39.9% versus 25.5%). The most commonly reported symptoms associated with infusion-related AEs in the ocrelizumab group were pruritus, flushing, rash, pyrexia, headache, and throat irritation. Nearly all of the infusion-related AEs were mild or moderate in severity (98.8% in the ocrelizumab group and 98.3% in the placebo group were grade 1 or grade 2 events). The proportion of patients who withdrew as a result of an infusion-related reaction was 0.4% in both the placebo and ocrelizumab groups. The first 300 mg dosage of ocrelizumab was associated with the highest proportions of patients with an infusion-related event (27.4%). This was reduced to 11.5% with the next infusion (i.e., six months later), and subsequently reduced to ≤ 7.0% for the remaining infusions.

The overall proportion of patients with at least one potential opportunistic infection was slightly greater in the ocrelizumab group than in the placebo group (5.3% versus 3.8%); however, when adjusted for exposure, the overall rate of potential opportunistic infections was lower in the ocrelizumab group (2.33 per 100 patient-years) compared with the placebo group (3.03 per 100 patient-years). All of the events were mild to moderate in severity, with the exception of one SAE in the ocrelizumab group (neutropenic sepsis, which required hospitalization). The manufacturer reported that the majority of potential opportunistic infections were associated with the herpes virus and that oral herpes was more commonly reported in the ocrelizumab group compared with the placebo group (2.3% versus 0.4%). The manufacturer conducted a detailed medical review of these events and reported that none were considered to be opportunistic infections.

Malignancies were reported in a greater proportion of ocrelizumab-treated patients (11 patients [2.3%]; 13 events) compared with placebo-treated patients (two patients [0.8%]; two events). The rate of malignancy was 0.92 per 100 patient-years (95% CI, 0.49 to 1.57) in the ocrelizumab group and 0.30 per 100 patient-years (95% CI, 0.04 to 1.10) in the placebo group. The most commonly reported malignancies included breast cancer in

women (four ocrelizumab-treated patients and no placebo-treated patients) and basal cell carcinoma (three ocrelizumab-treated patients and one placebo-treated patient).

Potential Place in Therapy[1]

Prior to the approval of ocrelizumab, there were no approved disease-modifying therapies for PPMS; therefore, there is an unmet need for these patients. This is reflected in the patient group input provided for this submission, where patients articulated the desperation they feel living with a progressively disabling illness that has no available treatments. The clinical expert consulted by CADTH suggested that ocrelizumab may fulfill some of the unmet need for these patients.

Ocrelizumab will be most effective in the younger and less disabled PPMS patient population, and ideally, also in those who show some inflammatory activity. (The question remains as to whether those patients truly belong in the PPMS category or fall into the category of “active and with progression,” which would require both clinical and radiological confirmation.) The latter would increase the need to perform MRIs in an effort to identify patients with active inflammation and monitor the inflammation over time.

It is likely that many severely disabled (EDSS > 6.5) older patients and patients with a longer duration of PPMS will want to be treated with ocrelizumab in hopes of limiting or stopping progression of the disease. However, the ORATORIO trial does not provide sufficient evidence to support the efficacy of ocrelizumab in such patients.

Patients with a strong family history of cancer, or older patients, may not be good candidates for ocrelizumab given the possibility of an increased cancer risk. An informed discussion would be needed between the patient and prescriber.

Conclusions

One double-blind, phase III RCT (ORATORIO) demonstrated that ocrelizumab was superior to placebo for reducing the risk of disability progression at three and six months. While the results were sensitive to the choice of analytical approach, the observed effect was considered to be clinically relevant by regulatory authorities and the clinical expert consulted by CADTH. Further, notwithstanding the limitations of the subgroup analyses in the ORATORIO trial, the effect of ocrelizumab versus placebo might be greater in patients who are younger (i.e., less than 45 years of age) and in those with active inflammation, based on the presence of Gd-enhancing lesions at baseline (as reflected in the indication approved by Health Canada, which is limited to patients with early disease who have evidence of active inflammation). Treatment with ocrelizumab was associated with a statistically significant reduction in the deterioration of T25FW times compared with placebo. The absolute difference between the ocrelizumab and placebo groups was small (mean difference of approximately three seconds); however, the clinical expert consulted by CADTH suggested that the results could be meaningful for a subset of PPMS patients. There is uncertainty as to the effects of ocrelizumab on health-related quality of life (HRQoL) and other patient-reported outcomes.

The proportion of patients with AEs that were categorized as serious or led to discontinuation from the study treatments was generally similar between the ocrelizumab and placebo groups. Infusion-related reactions were the most commonly reported AE in the ORATORIO study and occurred at a greater frequency in the ocrelizumab group. Similar to

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

the RRMS studies on ocrelizumab, nearly all of the infusion-related AEs in PPMS patients 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. Malignancies were reported in a greater proportion of ocrelizumab-treated patients compared with placebo-treated patients. Overall, the clinical expert consulted by CADTH indicated that the AE profile for ocrelizumab is consistent with other available MS treatments and that PPMS patients would generally be willing to accept the risks of treatment to obtain the potential benefits of slowing disability progression. The longer-term safety of ocrelizumab is being further evaluated in an open-label extension phase of the ORATORIO trial and an additional planned post-marketing safety study.

Table 1: Summary of Efficacy Results

End Point	Parameters	Placebo (N = 244)	Ocrelizumab (N = 488)
Time to CDP for ≥ 12 weeks	n	244	487
	Patients with events	0.340	0.302
	HR (95% CI)	0.76 (0.59 to 0.98)	
	P value	0.0321	
Time to CDP for ≥ 24 weeks	n	244	487
	Patients with events	0.327	0.283
	HR (95% CI)	0.75 (0.58 to 0.98)	
	P value	0.0365	
Change in Timed 25-Foot Walk	n	174	397
	Adjusted geometric mean (% change)	55.097	38.933
	Per cent relative reduction (95% CI)	29.337 (–1.618 to 51.456)	
	P value	0.0404	
T2 lesion volume	n	183	400
	Adjusted geometric mean (% change)	7.426	–3.366
	Per cent relative reduction (95% CI)	NR	
	P value	0.0001	
Per cent change in brain volume from week 24 to 120	n	150	325
	Adjusted mean (% change)	–1.093	–0.902
	Per cent relative reduction (95% CI)	17.475 (3.206 to 29.251)	
	P value	0.0206	
Change from baseline in SF-36 PCS	n	128	292
	LSM (SE)	–1.108	–0.731
	LSMD (95% CI)	0.377 (–1.048 to 1.802)	
	P value	0.6034	
Change from baseline in SF-36 MCS	n	128	292
	LSM (SE)	–1.673 (0.874)	1.645 (0.629)
	LSMD (95% CI)	3.318 (1.414 to 5.221)	
	P value	0.0007[a]	
Change from baseline in MSFC	n	170	383
	LSM (SE)	–0.211 (0.058)	–0.125 (0.041)
	LSMD (95% CI)	0.086 (–0.051 to 0.222)	
	P value	0.2169[a]	
Change from baseline in MFIS	n	NR	NR
	LSM (SE)	2.994 (1.189)	–0.462 (0.857)

End Point	Parameters	Placebo (N = 244)	Ocrelizumab (N = 488)
	LSMD (95% CI)	–3.456 (–6.048 to –0.863)	
	P value	0.0091[a]	

CDP = confirmed disability progression; CI = confidence interval; HR = hazard ratio; LSM = least squares mean; LSMD = least squares mean difference; MFIS = Modified Fatigue Impact Scale; MSFC = Multiple Sclerosis Functional Composite; NR = not reported; 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.

Source: Clinical Study Report for ORATORIO.[1]

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

Table 2: Summary of Adverse Events

Adverse events, n (%)	Placebo (N = 239)	Ocrelizumab (N = 486)
At least one adverse event	215 (90.0)	462 (95.1)
Deaths	1 (0.4)	4 (0.8)
Serious adverse event	53 (22.2)	99 (20.4)
Withdrawal due to adverse event	8 (3.3)	20 (4.1)
Adverse event leading to dose modification/interruption	12 (5.0)	47 (9.7)
Malignancies	2 (0.8)	11 (2.3)
Infections	167 (69.9)	347 (71.4)
Serious infections	21 (8.8)	37 (7.6)

n = number of patients with event; N = number of patients in the analysis.

Source: Common Technical Document 2.7.3.[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 suggested that auto-reactive T-cells cross the blood-brain barrier, attack the myelin sheath and axons (leading to a cascade of inflammation), and subsequently affect the brain or spinal cord through a process called demyelination.[3,5]

MS causes bothersome or disabling physical symptoms involving mobility, vision, and coordination problems as well as cognitive dysfunction, fatigue, and pain. Patients' quality of life (QoL) 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.[6] MS is associated with a major financial burden on patients, families, and the health care system.[7] The Multiple Sclerosis Society of Canada (MS Society) estimates that there are currently 100,000 patients with MS in Canada, which is one of the highest prevalence rates in the world.[8]

MS is classified into four clinical subtypes: relapsing remitting MS (RRMS); primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS). The RRMS subtype comprises 85% to 90% of MS patients at first presentation, and is characterized by clearly defined relapses with full recovery or with sequelae and residual deficit upon recovery, with lack of progression of disability during the periods between relapses.[7] It is estimated that 10% to 15% of MS patients have the PPMS subtype of the disease, which is characterized by consistent disease progression and is not associated with relapses.[9,10]

According to the McDonald criteria (2010), PPMS can be diagnosed based on one year of disease progression and at least two of the following: evidence for dissemination in space in the brain; evidence for dissemination in space in the spinal cord; and/or positive cerebrospinal fluid (i.e., isoelectric focusing evidence of oligoclonal bands and/or elevated immunoglobulin G [IgG] index).[4] Table 3 provides a summary of the McDonald criteria for PPMS, including the most recent criteria (2010) and the criteria used in the pivotal trial for ocrelizumab (2005).

Table 3: McDonald Criteria for Progressive Primary Multiple Sclerosis (2005 and 2010)

McDonald 2005 Criteria for PPMS	McDonald 2010 Criteria for PPMS

• One year of disease progression (retrospectively or prospectively determined)
• At least two of the following:
  ○ Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive visual-evoked potential)
  ○ Positive spinal cord MRI (two focal T2 lesions)
  ○ Positive CSF (isoelectric focusing evidence of oligoclonal IgG bands, increased IgG index, or both)
	• One year of disease progression (retrospectively or prospectively determined)
	• At least two of the following:
	  ○ Evidence for dissemination in space in the brain by ≥ 1 T2 lesion(s) in at least one area characteristic for MS (periventricular, juxtacortical, or infratentorial)
	  ○ Evidence for dissemination in space in the spinal cord by ≥ 2 T2 lesions in the cord
	  ○ Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

CSF = cerebrospinal fluid; IgG = immunoglobulin G; MRI = magnetic resonance imaging; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis.

The progressive forms of MS can be further classified according to the level of disease activity (i.e., evidence of new or enlarging lesions) and disease progression (i.e., disability): active and with progression; active but without progression; not active but with progression; not active and without progression (e.g., stable disease).[11] However, the clinical expert consulted by CADTH suggested that such classifications are not routinely performed in Canadian clinical practice.

Standards of Therapy

Ocrelizumab is the first drug that has been approved for use in the treatment of PPMS in Canada. Treatment options prior to the approval of ocrelizumab focused on managing symptoms and maintaining QoL. Therapy typically involves both pharmacological and non-pharmacologic approaches to maintain proper bladder and bowel function, reduce muscle spasticity, and maintain the ability of the patient to move (including walking and using their hands).[12] Ocrelizumab is the first drug that has received Health Canada approval as a disease-modifying therapy for PPMS. The clinical expert consulted by CADTH suggested that ocrelizumab would likely be used in addition to symptomatic treatments in Canadian clinical practice.

Drug

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-cells.[13] It has been approved by Health Canada for use in the following indications:

- Treatment of adult patients with RRMS with active disease defined by clinical and imaging features
- Management of adult patients with early PPMS as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity. (Notice of Compliance with conditions.)

The recommended dose of ocrelizumab is 600 mg by 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.[13] To reduce the frequency and severity of infusion-related reactions, the product monograph recommends that patients could be treated with the following:[13]

- 100 mg IV methylprednisolone (or an equivalent steroid) approximately 30 minutes prior to each infusion, and
- An antihistaminic drug (e.g., diphenhydramine) approximately 30 to 60 minutes before each infusion

An antipyretic (e.g., acetaminophen) may also be considered.

The current CADTH Common Drug Review (CDR) submission for ocrelizumab is for use in the treatment of patients with PPMS. CADTH has previously reviewed ocrelizumab for use in the treatment of adult patients with RRMS.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of ocrelizumab for the treatment of adult patients with PPMS as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity.

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	Adults with primary progressive multiple sclerosis Subgroups: age, disease severity, active inflammation
Intervention	Ocrelizumab IV (600 mg every six months)
Comparators	Placebo
Outcomes	**Efficacy outcomes:** • Disability progression using a validated scale* • Walking ability • Health-related quality of life using a validated scale* • Symptoms (e.g., fatigue)* • Brain lesions (e.g., gadolinium-enhancing lesions; new or enlarging T2 lesions) • Brain atrophy or brain volume • Productivity (ability to attend work or school)[a] • Medication acceptance **Harms outcomes:** • Adverse events, serious adverse events, withdrawals due to adverse events, mortality • Adverse events of special interest: infusion-related adverse events, serious infections, opportunistic infections, malignancies
Study Design	Published and unpublished phase III randomized controlled trials

[a] These outcomes were identified as being of particular importance 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 & daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was ocrelizumab (Ocrevus). No methodological filters were applied to limit retrieval by study type. 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 November 23, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on March 21, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH *Grey Matters* checklist (https://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; Clinical trials; and Databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the drug manufacturer was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5.

Results

Findings from the Literature

A total of 214 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 5. There were no excluded studies.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

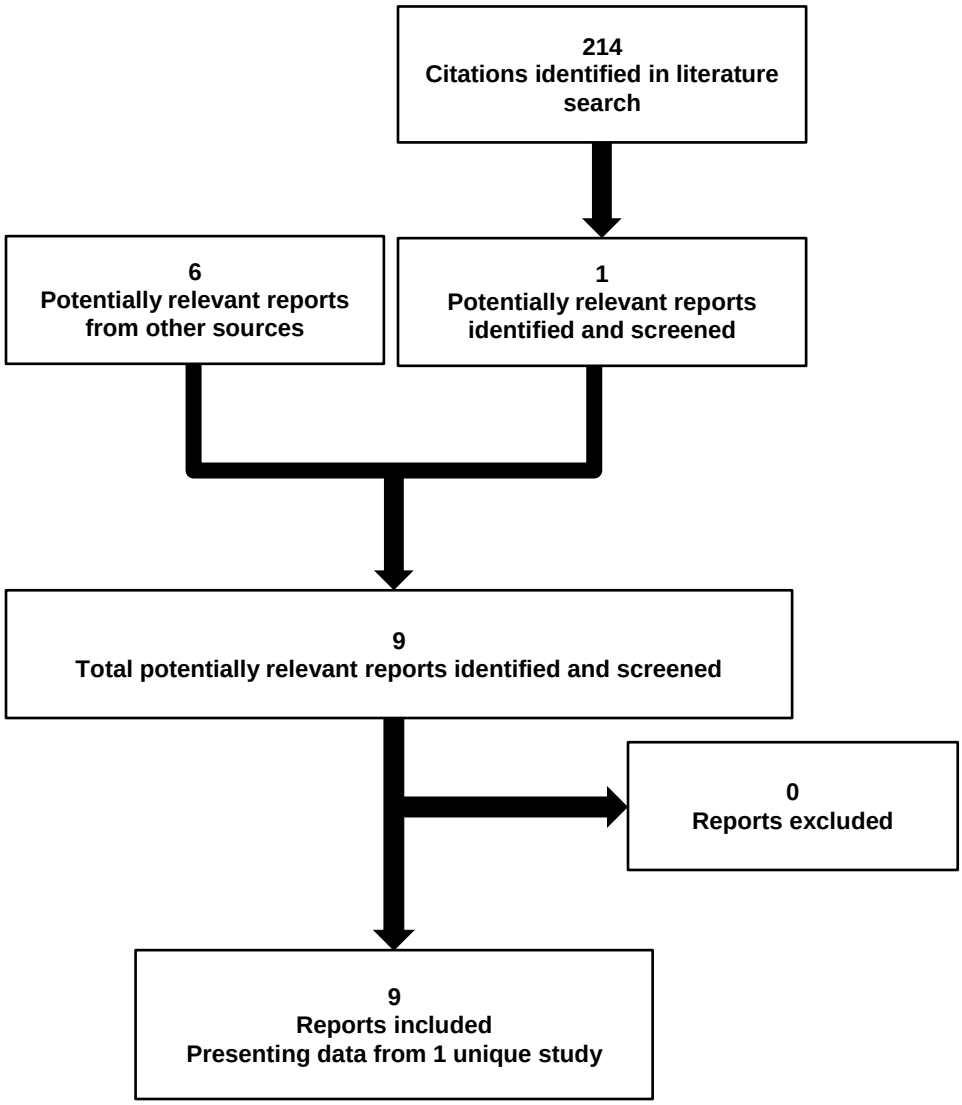


Table 5: Details of Included Study

		ORATORIO (WA25046)
Designs & Populations	**Study Design**	Phase III, multi-centre, parallel-group, double-blind, placebo-controlled RCT
	Locations	182 sites in 29 countries (Australia, Austria, Belgium, Bulgaria, Brazil, Canada, Switzerland, Czech Republic, Germany, Spain, Finland, France, UK, Greece, Hungary, Israel, Italy, Lithuania, Mexico, Netherlands, Norway, New Zealand, Peru, Poland, Portugal, Romania, Russia, Ukraine, USA).
	Randomized (N)	732 (ocrelizumab [n = 488] and placebo [n = 244])
	Inclusion Criteria	• Diagnosis of PPMS in accordance with the revised 2005 McDonald criteria • Ages 18 to 55 years • EDSS at screening from 3.0 to 6.5 points • Score of ≥ 2.0 on the functional systems scale for the pyramidal system that was due to lower extremity findings • Disease duration from onset of MS symptoms: (a) < 15 years if EDSS at screening > 5.0; (b) < 10 years if EDSS at screening ≤ 5.0
	Exclusion Criteria	• History of RRMS, SPMS, or PRMS • Inability to complete an MRI • Contraindications for or intolerance to oral or IV corticosteroids • Known presence of other neurologic disorders (including history of PML) • Known active bacterial, viral, fungal, or mycobacterial infection; history of recurrent aspiration pneumonia requiring antibiotic therapy; history of cancer • Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study • Previous treatment with B-cell targeted therapies, alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, bone marrow transplantation, lymphocyte trafficking blockers (e.g., natalizumab), beta-interferons, glatiramer acetate, IV immunoglobulin, plasmapheresis, or other immunomodulatory therapies within 12 weeks of randomization • Systemic corticosteroid therapy within 4 weeks prior to screening • CD4 count < 300/μl; serum creatinine > 1.4 mg/dL for women or > 1.6 mg/dL for men; AST or ALT ≥ 2.0 ULN; platelet count < 100,000/μl; hemoglobin < 8.5 g/dL; ANC < 1.5 X 10^3/μl; serum IgG 18% < LLN; serum IgM 8% < LLN
Drugs	**Intervention**	• Ocrelizumab 600 mg IV every six months (administered as two 300 mg doses 14 days apart)
	Comparator(s)	• Placebo IV infusion
Duration	**Phase**	
	Run-in	Up to 8 weeks
	Double-blind	120 weeks (after 253 CDP events)
	Follow-up	At least 48 weeks
	OLE	≥ 4 years
Outcomes	**Primary End Point**	The time to onset of CDP for at least 12 weeks
	Other End Points	**Secondary End points**
		• Time to onset of CDP for at least 24 weeks • Change in timed T25FW from baseline to week 120 • Change in total volume of T2 hyperintense lesions • Change in total brain volume (week 24 to week 120) • Change in SF-36 PCS from baseline to week 120

		ORATORIO (WA25046)
		Exploratory End points
		• Proportion of patients with 12-week CDP at week 120 • Change in EDSS score • Change in MSFC score from baseline to week 48, week 96, and week 120 • Time to confirmed composite disability progression • Time to sustained 20% increase in T25FW and 9-HPT • Proportion of patients with a 20% increase in T25FW • Proportion of patients with a 20% increase in 9-HPT time • Change in PASAT from baseline to week 120 • Number of Gd-enhancing T1 lesions • Number of new or enlarging T2 hyperintense lesions • Change in cortical grey matter volume from baseline to week 120 • Change in white matter volume from baseline to week 120 • Change from baseline in total non-enhancing T1 lesion volume • Change in fatigue, as measured by the MFIS • Change in SF-36 MCS from baseline to week 120
NOTES	**Publications**	• Montalban et al., 2016[14] • Clinical study report[1] • Common Technical Document[2,15] • FDA Reviewer and Summary Reports[16-18] • EMA Public Assessment Report[9] • Clinicaltrials.gov[19]

9-HPT = 9-Hole Peg Test; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate transaminase; CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; EMA = European Medicines Agency; Gd = gadolinium; IgG = immunoglobulin G; IgM = immunoglobulin M; LLN = lower limit of normal; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MSFC = multiple sclerosis functional component; PASAT = Paced Auditory Serial Addition Test; PML = progressive multifocal leukoencephalopathy; PPMS = primary progressive multiple sclerosis; PRMS = progressive relapsing multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SF-36 MCS = Short Form (36) Health Survey mental component summary; SF-36 PCS = Short Form (36) Health Survey physical component summary; SPMS = Secondary Progressive Multiple Sclerosis; T25FW = Timed 25-Foot Walk; ULN = upper limit of normal.

Source: Clinical Study Report for ORATORIO.[1]

Included Studies

Description of Studies

The ORATORIO study was a phase III, multinational, multi-centre, parallel-group, double-blind, placebo-controlled randomized controlled trial (RCT). Enrolled patients were randomized (2:1) to receive infusions of ocrelizumab or placebo every six months (as two infusions 14 days apart). Randomization was stratified by geographic region (US or non-US) and age (≤ 45 years or > 45 years). During the 120-week treatment period, study participants were required to attend 17 scheduled assessment and/or infusion 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.

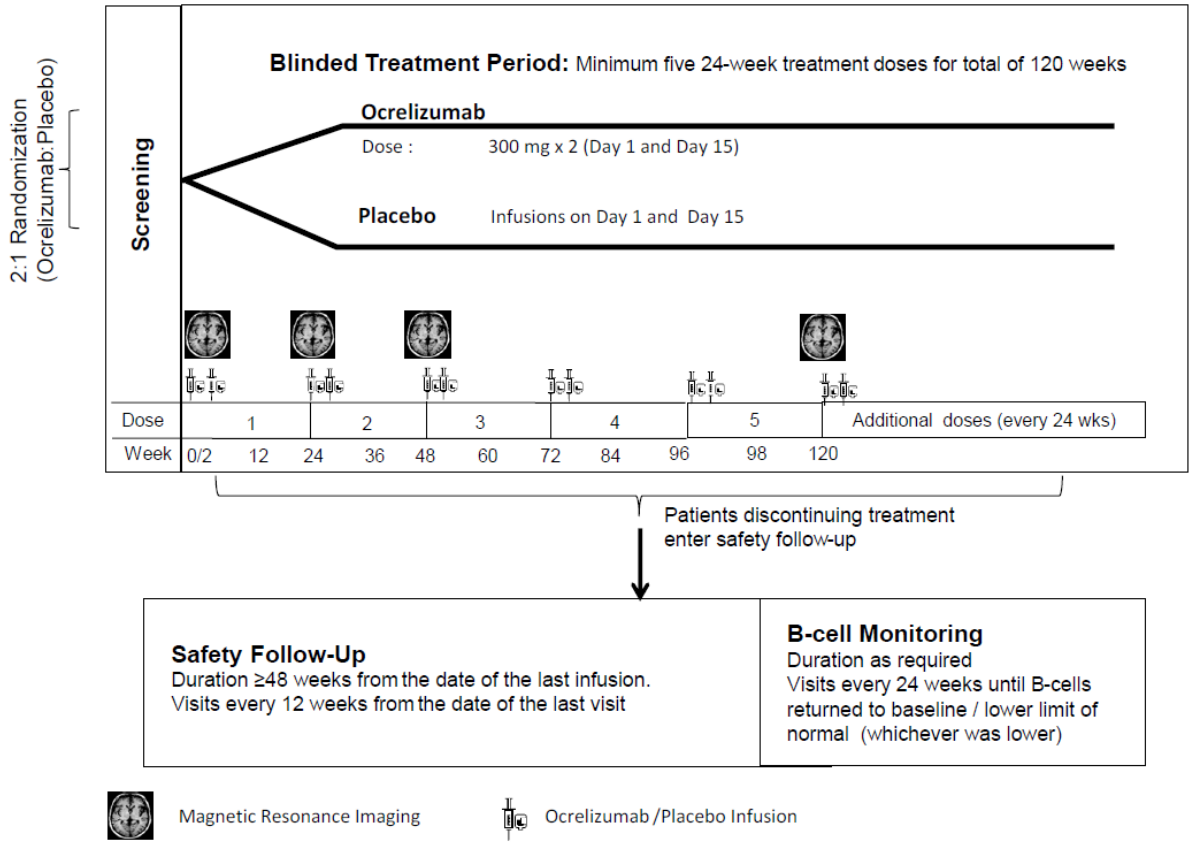
Each study site had the following two blinded investigators:

- A treating investigator responsible for patient care, who had access to patients' safety and blinded efficacy data
- An examining investigator, who performed the neurological examination, documented the Functional Systems scores, assessed patients using the Expanded Disability Status Scale (EDSS) and the Karnofsky Performance Status Scale.

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

The trial was conducted at 182 sites in 29 countries, including (sites): Australia (2), Austria (5), Belgium (2), Bulgaria (2), Brazil (4), Canada (7), Switzerland (2), Czech Republic (3), Germany (18), Spain (14), Finland (3), France (17), UK (5), Greece (3), Hungary (5), Israel (6), Italy (4), Lithuania (3), Mexico (4), Netherlands (2), Norway (1), New Zealand (2), Peru (3), Poland (7), Portugal (5), Romania (4), Russian Federation (1), Ukraine (11), and US (37). There were seven Canadian sites involving 22 patients (12 [4.9%] in the placebo group and 20 [4.1%] in the ocrelizumab group).

Figure 2: Schematic Showing the Design of the ORATORIO Trial



Source: Clinical Study Report for ORATORIO.[1]

Populations

Inclusion and Exclusion Criteria

Patients aged 18 years to 55 years with PPMS were eligible for enrolment in the ORATORIO trial if they had an EDSS score between 3.0 and 6.5 and a score of at least 2.0 on the functional systems scale for the pyramidal system that was due to lower extremity findings. The diagnosis of PPMS was made in accordance with the revised 2005 McDonald criteria. Patients also had to have a disease duration of less than 15 years for those with an

EDSS greater than 5.0 or less than 10 years for those with an EDSS of 5.0 or less at screening.[1]

Patients were excluded from the study if they had a history of RRMS, SPMS, or PRMS. Patients were also excluded if they had any of the following: neurologic disorders other than PPMS (including a history of progressive multifocal leukoencephalopathy [PML]); known active bacterial, viral, fungal, or mycobacterial infections; history of recurrent aspiration pneumonia requiring antibiotic therapy; or a history of cancer. As shown in Table 5, there were a number of exclusion criteria associated with laboratory values (e.g., CD4 count, serum creatinine, aspartate transaminase, alanine aminotransferase, platelet count, hemoglobin, absolute neutrophil count, serum immunoglobulin G [IgG] and immunoglobulin M [IgM]).[1]

Patients with prior exposure to a number of medications that could potentially be used for the treatment of MS were excluded from the study. These included any B-cell targeted therapies (e.g., rituximab), alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, natalizumab, total body irradiation, or bone marrow transplantation. Treatment with beta-interferons, glatiramer acetate, immunoglobulin, plasmapheresis, or other immunomodulatory therapies were not permitted with 12 weeks of randomization. Systemic corticosteroid therapy was not permitted within four weeks prior of screening.[1]

Baseline Characteristics

A summary of key baseline and demographic characteristics is provided in Table 6. The mean age was similar in the placebo and ocrelizumab groups (44.4 and 44.7 years, respectively). Almost half of the participants in each group were older than 45 years of age at baseline (51.6% and 52.9% in the placebo and ocrelizumab groups, respectively). The percentage of females was 50.8% in the placebo group and 48.6% in the ocrelizumab group. More than 90% of patients in each group were white and a majority were recruited from centres located in Europe (64.3% and 64.5% in the placebo and ocrelizumab groups, respectively). The mean duration since the onset of MS symptoms was 6.1 years in the placebo group and 6.7 years in the ocrelizumab group. The mean time since PPMS diagnosis was 2.8 and 2.9 years in the placebo and ocrelizumab groups, respectively. The mean EDSS at baseline was 4.7 in both groups.

Table 6: Summary of Baseline and Demographic Characteristics

Characteristics		Placebo (N = 244)	Ocrelizumab (N = 488)
Age (Years)	Mean (SD)	44.4 (8.3)	44.7 (7.9)
	≤ 45	118 (48.4%)	230 (47.1%)
	> 45	126 (51.6%)	258 (52.9%)
Sex	Male	120 (49.2%)	251 (51.4%)
	Female	124 (50.8%)	237 (48.6%)
Race	American Indian[a]	0	5 (1.0%)
	African American	5 (2.0%)	9 (1.8%)
	White	235 (96.3%)	454 (93.0%)
	Other	4 (1.6%)	18 (3.7%)
	Unknown	0	2 (0.4%)
Ethnicity	Hispanic or Latino	14 (5.7%)	32 (6.6%)

Characteristics		Placebo (N = 244)	Ocrelizumab (N = 488)
	Not Hispanic or Latino	206 (84.4%)	385 (79.2%)
	Not reported	16 (6.6%)	51 (10.5%)
	Unknown	8 (3.3%)	18 (3.7%)
Weight (kg)	Mean (SD)	72.81 (15.13)	72.46 (17.11)
	Median (range)	72.00 (45.0 to 136.0)	71.00 (40.2 to 135.9)
BMI (kg/m^2)	Mean (SD)	25.03 (4.77)	24.84 (4.92)
	Median (range)	23.85 (16.4 to 44.4)	24.03 (15.2 to 46.4)
Region	Non-US	210 (86.1%)	421 (86.3%)
	US	34 (13.9%)	67 (13.7%)
Sub-Region	EU/Switzerland/Norway	157 (64.3%)	315 (64.5%)
	Latin America	6 (2.5%)	16 (3.3%)
	Non-EU + Israel + Africa	32 (13.1%)	61 (12.5%)
	US/Canada/Australia/NZ	49 (20.1%)	96 (19.7%)
Duration Since MS Onset (Years)	Mean (SD)	6.14 (3.59)	6.66 (4.01)
	Median (range)	5.51 (0.9 to 23.8)	5.95 (1.1 to 32.9)
	≤ 3 years	53 (22.4%)	79 (16.7%)
	> 3 to ≤ 5 years	52 (21.9%)	111 (23.4%)
	> 5 to ≤ 10 years	96 (40.5%)	202 (42.6%)
	> 10 years	36 (15.2%)	82 (17.3%)
Duration Since PPMS Diagnosis (Years)	Mean (SD)	2.75 (3.32)	2.85 (3.16)
	Median (IQR)	1.34 (0.48 to 3.89)	1.58 (0.53 to 4.11)
EDSS	Mean (SD)	4.73 (1.17)	4.74 (1.18)
Prior Treatment With MS DMT	Yes	30 (12.3%)	55 (11.3%)
	No	214 (87.7%)	433 (88.7%)
Received Steroids as MS Therapy	Yes	45 (18.4%)	89 (18.2%)
	No	199 (81.6%)	399 (81.8%)
Gd-Enhancing T1 Lesions	Mean (SD)	0.60 (1.55)	1.21 (5.14)
	Median (range)	0.00 (0.0 to 10.0)	0.00 (0.0 to 77.0)
	0	183 (75.3%)	351 (72.5%)
	1	29 (11.9%)	62 (12.8%)
	2	15 (6.2%)	22 (4.5%)
	3	5 (2.1%)	17 (3.5%)
	≥ 4	11 (4.5%)	32 (6.6%)
Volume T2 Lesions (cm^3)	Mean (SD)	10.91 (12.95)	12.67 (15.11)
	Median (range)	6.17 (0.0 to 81.1)	7.31 (0.0 to 90.3)
Number of T2 Lesions	Mean (SD)	48.15 (39.31)	48.71 (38.16)
	Median (range)	43.00 (0.0 to 208.0)	42.00 (0.0 to 249.0)
	0 to 5	29 (11.9%)	50 (10.3%)
	6 to 9	6 (2.5%)	11 (2.3%)
	> 9	208 (85.6%)	425 (87.4%)
Normalized Brain Volume (cm^3)	Mean (SD)	1469.86 (88.73)	1462.91 (83.95)
	Median (range)	1464.51 (1216.3 to 1701.7)	1462.23 (1214.3 to 1711.1)

BMI = body mass index; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; EU = European Union; Gd = gadolinium;

IQR = interquartile range; MS = multiple sclerosis; N = number of patients in the analysis; NZ = New Zealand; PPMS = primary progressive multiple sclerosis; SD = standard deviation.

[a] Includes Alaska native.

Source: Clinical Study Report for ORATORIO.[1]

Prior Therapy with Multiple Sclerosis Treatments

The majority of patients had not received treatment with a disease-modifying therapy (DMT) for MS within two years of randomization (87.7% and 88.7% in the placebo and ocrelizumab groups, respectively). Of those who had prior exposure to a DMT, the majority received interferon beta-1a or interferon beta-1b (Table 7). Similarly, fewer than 20% of patients in each group had received treatment with steroids for their MS (18.4% and 18.2% with placebo and ocrelizumab, respectively). A detailed list of medications that had been received by the study participants is provided in Table 28. The proportion of patients with prior exposure to therapies that could potentially be used for the treatment of MS are summarized in Table 7. Overall, 11.3% of patients in the ocrelizumab group and 12.3% in placebo group reported exposure to at least one MS treatment prior to randomization. Interferon beta-1a and interferon beta-1b were the most common treatments, followed by glatiramer acetate. Although listed in the exclusion criteria of the study, one ocrelizumab-treated patient reported prior experience with natalizumab.[1]

Table 7: Prior Exposure to Multiple Sclerosis Therapies

Treatments, n (%)	Placebo (N = 244)	Ocrelizumab (N = 488)
Any MS medication	30 (12.3)	55 (11.3)
Interferon beta-1a IM	8 (3.3)	7 (1.4)
Interferon beta-1a SC	10 (4.1)	17 (3.5)
Interferon beta-1b SC	9 (3.7)	17 (3.5)
Glatiramer acetate	10 (4.1)	23 (4.7)
Natalizumab	0	1 (0.2)
Azathioprine	1 (0.4)	2 (0.4)
Normal immunoglobulin	0	2 (0.4)

IM = intramuscular; MS = multiple sclerosis; n = number of patients with event; N = number of patients in the analysis; SC = subcutaneous.

Source: Clinical Study Report for ORATORIO.[1]

Interventions

Study Treatments

Patients randomized to ocrelizumab received IV infusions every six months (as two 300 mg infusions 14 days apart). Those randomized to the placebo group received infusions with the matching IV placebo. In the event of an infusion-related reaction, the infusion rate could be reduced or interrupted according to the following pre-specified protocols:[1]

- Grade 1 or 2: the infusion rate was to be 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, or flushing, fever, and throat pain cluster: infusion interrupted immediately and the patient to receive aggressive symptomatic treatment. The infusion was to be 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: infusion stopped immediately and patient to receive appropriate treatment; these patients were to be withdrawn from study treatment and initiate the safety follow-up period.

Pre-Medication for Infusion-Related Reactions

All patients were to receive prophylactic treatment with 100 mg of methylprednisolone IV approximately 30 minutes before the start of each ocrelizumab infusion. In the event that the use of methylprednisolone was contraindicated, the patient was to receive an equivalent dose of an alternative steroid. The trial protocol 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 minutes to 60 minutes prior to the start of the infusion.[1]

Outcomes

The complete list of primary, secondary, and exploratory efficacy end points that were evaluated in the ORATORIO trial are provided in Table 8. Details regarding the end points of interest for this review are summarized after the table.

Table 8: Efficacy End Points in ORATORIO

Category	End Point
Primary End Point	Time to onset of CDP for at least 12 weeks
Secondary End Points	Time to onset of CDP for at least 24 weeks
	Change in T25FW from baseline to week 120
	Change in total volume of T2 hyperintense lesions
	Change in total brain volume (week 24 to week 120)
	Change in SF-36 PCS from baseline to week 120
Exploratory End Points	Proportion of patients with 12-week CDP at week 120
	Change in EDSS score
	Change in MSFC score from baseline to week 48, week 96, and week 120
	Time to confirmed composite disability progression
	The time to sustained 20% increase in T25FW and 9-HPT
	Proportion of patients with a 20% increase in T25FW
	Proportion of patients with a 20% increase in 9-HPT
	Change in PASAT from baseline to week 120
	Number of Gd-enhancing T1 lesions
	Number of new or enlarging T2 hyperintense lesions
	Change in cortical grey matter volume from baseline to week 120
	Change in white matter volume from baseline to week 120
	Change from baseline in total non-enhancing T1 lesion volume
	Change in fatigue, as measured by the MFIS
	Change in SF-36 MCS from baseline to week 120

9-HPT = 9-Hole Peg Test; CDP = confirmed disability progression; EDSS = Expended Disability Status Scale; Gd = gadolinium; MFIS = Modified Fatigue Impact Scale; MSFC = Multiple Sclerosis Functional Composite; 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 Report for ORATORIO.[1]

Confirmed Disability Progression

Time to confirmed disability progression (CDP) for 12 weeks was the primary end point of the study. Time to CDP for at least 24 weeks was a secondary end point. Disability progression was defined as an increase in a patient's EDSS score of at least 1.0 from baseline when the baseline score was ≤ 5.5; or an increase of 0.5 from baseline when the

baseline score was > 5.5. Disability progression was considered to be confirmed when the increase from baseline in EDSS was documented at a regularly scheduled clinic visit at least 12 weeks or 24 weeks after the patient's neurological worsening was initially documented. The EDSS is an ordinal scale used to measure disability in MS. It relies on the following eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. Each functional system is graded separately on a scale ranging from 0 (normal) to either 5 or 6. The EDSS score is a composite ranging from 0 to 10 (in increments of 0.5) that incorporates functional system grades as well as the degree of functional disability and ambulation. Scores from 0 to 4.5 represent normal ambulation, while scores of 5 and above represent progressive loss of ambulatory ability. All EDSS assessments were performed by blinded examiners who were not otherwise involved in the care of the study patients.

Timed 25-Foot Walk

The Timed 25-Foot Walk (T25FW) is one of three components of the Multiple Sclerosis Functional Composite (MSFC). The T25FW assessment involves the patient walking a 25-foot course as quickly as possible (but safely).[20] The time required to complete the 25-foot course is recorded and the task is immediately administered again by having the patient walk back the same distance. The score for the T25FW is the average of the two completed trials. Patients may use assistive devices when completing the T25FW (e.g., canes, crutches, walkers).[20] A change of at least 20% in the T25FW is commonly cited as the minimal clinically important difference (MCID) for patients with MS.[21-24]

Magnetic Resonance Imaging End Points

Efficacy end points that were evaluated using magnetic resonance imaging (MRI) included the following: change in brain volume from week 24 to week 120 (secondary end point); change in volume of T2 lesions from week 24 to week 120 (secondary end point); total number of new or newly enlarged T2 hyperintense lesions by week 120 (exploratory end point); total number of new T1 gadolinium (Gd)-enhancing lesions by week 120 (exploratory end point). MRIs were scheduled for day 1, week 24, week 48, and week 120. For those who withdrew early, an MRI was also to be performed at the visit when the patient withdrew.[1] Change in brain volume was assessed after 24 weeks of treatment due the potential for reduced inflammation following the initiation of treatment. Such a reduction in inflammation could appear as reduced volume due to reduced inflammation as opposed to capturing atrophy.

Multiple Sclerosis Functional Composite

Change from baseline to 96 weeks in the MSFC score was a secondary end point. The MSFC includes three objective and quantitative continuous scales that assess leg function and ambulation (with T25FW), arm and hand function (with the 9-Hole Peg Test [9-HPT]), and cognitive function (with the 3-second 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 T25FW trials and 9-HPT, and a 0.5 standard deviation (SD) change on PASAT-3, are considered clinically meaningful.[25,26] An MCID for the overall MSFC score has not been reported.

Short Form (36) Health Survey Physical Component Summary

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 (HRQoL). The eight sub-domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. The SF-36 items can be analyzed in the following two categories: the physical component summary (PCS), which measures physical functioning, role physical, bodily pain, and general health; and the mental component summary (MCS), which measures vitality, social functioning, role emotional, and mental health. Change from baseline in the SF-36 PCS and SF-36 MCS were secondary and exploratory end points in the ORATORIO trial, respectively.

Statistical Analysis

All statistical hypotheses for the primary and secondary end points were tested at a 5% significance level using a two-sided test. The methods used for statistical analysis of the efficacy end points are summarized in Table 9. The proportion of patients with CDP for at least 12 weeks or 24 weeks was estimated using Kaplan–Meier methodology; the hazard ratios were estimated using a Cox regression model stratified by region (US versus non-US) and age (≤ 45 years versus > 45 years).The ocrelizumab and placebo groups were compared using a two-sided log-rank test for the CDP end points.[1] In the primary analyses of CDP for at least 12 weeks (primary end point) and 24 weeks (secondary end point), any patients with an initial progression event who withdrew prior to confirmation at a follow-up visit (and thus, had a missing follow-up value) were counted as events (i.e., the data were included in the analyses as imputed CDP events and were not censored). Those who had an initial progression event and remained on treatment, but did not have a confirmation visit prior to the clinical cut-off, were censored.[1]

Sensitivity analyses used different approaches for handling missing data — including an intention-to-treat (ITT) analysis conducted without imputation, a multiple imputation approach where 50% of patients who discontinued after an initial progression event (but prior to a confirmation visit) were imputed as having CDP events, and a post hoc analysis where patients with initial disability progression who discontinued treatment prior to a confirmation visit were imputed as having CDP events if the reasons for withdrawal were reported as either “lack of efficacy” or “withdrawal by subject.” Additional sensitivity analyses were conducted for the CDP end points, including the use of a per-protocol data set; an analysis using baseline Gd-enhancing lesions (presence or absence) and baseline EDSS score (≤ 5.5 versus > 5.5) as additional covariates; an analysis that excluded events that occurred during the first 12 weeks of the trial; an analysis using the original planned sample size of 630 patients; and an analysis that excluded patients who had events that met the criteria for an MS relapse.[1]

Table 9: Statistical Analysis of Efficacy End Points

End Point	Statistical Model		Adjustment Factors	Sensitivity Analyses
	Effect Size	*P* Value		
Time to onset of CDP for at least 12 weeks	Cox regression	Log-rank test	• Region (US vs. non-US) • Age (≤ 45 vs. > 45 years)	**Pre-specified analyses:** • ITT without imputation • Per-protocol • Multiple imputation (50% CDP) • Additional covariates* • Exclusion of early CDP events • Restricted to first 630 patients **Post hoc analyses:** • Exclusion of those with relapses • Imputation by efficacy-related withdrawal reason • Including progression after treatment discontinuation
Time to onset of CDP for at least 24 weeks	Cox regression	Log-rank test	• Region (US vs. non-US) • Age (≤ 45 vs. > 45 years)	**Pre-specified analyses:** • Exclusion of patients with relapses • Exclusion of early CDP events **Post hoc analyses:** • ITT without imputation • Per-protocol • Multiple imputation (50% CDP) • Additional covariates* • Restricted to first 630 patients • Imputation by efficacy-related withdrawal reason
T25FW	MMRM	Ranked ANCOVA with LOCF[b]	• Region (US vs. non-US) • Age (≤ 45 vs. > 45 years) • Baseline T25FW	No sensitivity analyses
Change in T2 lesion volume	MMRM	Ranked ANCOVA with LOCF[b]	• Region (US vs. non-US) • Age (≤ 45 vs. > 45 years) • Baseline T2 lesion volume	
Change in brain volume	MMRM	MMRM	• Region (US vs. non-US) • Age (≤ 4 5 vs. > 45 years) • Brain volume at week 24	
T1 Gd-enhancing lesions	NBR	NBR	• Region (US vs. non-US) • Age (≤ 45 vs. > 45 years) • Baseline T1 Gd-lesion (present or not) • Number of MRIs (off-set)	

End Point	Statistical Model		Adjustment Factors	Sensitivity Analyses
	Effect Size	*P* Value		
T2 hyperintense lesions	NBR	NBR	• Region (US vs. non-US) • Age (≤ 45 vs. > 45 years) • Baseline T2 hyperintense lesion count • Number of MRIs (off-set)	
SF-36 PCS	MMRM	MMRM	• Baseline SF-36 PCS • Region (US vs. non-US) • Age (≤ 4 5 vs. > 45 years)	

ANCOVA = analysis of covariance; CDP = confirmed disability progression; Gd= gadolinium; ITT = intention-to-treat; LOCF = last observation carried forward; MMRM = mixed-effect model repeat measurement; MRI = magnetic resonance imaging; NBR = negative binomial regression; SF-36 PCS = Short Form (36) Health Survey physical component summary; T25FW = Timed 25-Foot Walk; vs. = versus.

[a] The additional covariates included: baseline Gd-enhancing lesions (presence or absence) and baseline EDSS score (≤ 5.5 vs. > 5.5).

[b] The non–parametric-ranked ANCOVA was used for comparison because the data were not normally distributed. This approach does not generate a point estimate, so MMRM was used to obtain a point estimate for the treatment effect.

Source: Clinical Study Report for ORATORIO.[1]

Analysis Populations

Three analysis populations were used in the evaluation of efficacy and safety end points in the ORATORIO study: ITT, per-protocol, and safety populations. Details of each analysis population are provided in Table 10.

Table 10: Efficacy and Safety Analysis Populations

Population	Description
Intent-to-Treat	All randomized patients were included in the ITT population. All efficacy analyses were performed using the ITT population.
Per-Protocol	All patients in the ITT population without major protocol violations that were deemed to potentially affect the efficacy of the study treatment. The PP population was used as a sensitivity analysis for CDP for 12 weeks and 24 weeks.
Safety	The safety population included all patients who received any study drug. This population was used for all summaries of safety data.

CDP = confirmed disability progression; ITT = intention-to-treat; PP = per-protocol.

Source: Clinical Study Report for ORATORIO.[1]

Multiple Comparisons

A summary of the statistical testing hierarchy used in the ORATORIO trial to adjust for inflated type I error associated with multiple statistical comparisons is provided in Table 11. All secondary efficacy end points were only tested in a confirmatory manner if the secondary end point located immediately above it in the hierarchy was statistically significant at $P < 0.05$.[1]

Table 11: Statistical Testing Hierarchy

Category	End Point	*P* value
Primary	Time to onset of confirmed disability progression for 12 weeks	0.0321
Secondary	Time to onset of confirmed disability progression for 24 weeks	0.0365
	Change in Timed 25-Foot Walk from baseline to week 120	0.0404
	Per cent change in total T2 lesion volume from baseline to week 120	< 0.0001
	Per cent change in total brain volume from week 24 to week 120	0.0206
	Change in the SF-36 PCS from baseline to week 120	0.6034

SF-36 PCS = Short Form (36) Health Survey physical component summary.

[a] *P* values reported in the ORATORIO trial.

Source: Common Technical Document 2.7.3.[2]

Sample Size

The planned sample size for the ORATORIO trial was 630 patients.[1] This was estimated based on the following assumptions: progression rates of 30% and 43% in patients receiving ocrelizumab and placebo (respectively); a one-year accrual period with a 3.5-year maximum treatment period; and a dropout rate of 20% over two years. It was calculated that 630 patients would provide approximately 80% and 92% power with type I error rates of 0.01 and 0.05, respectively. The statistical analysis plan indicated that 253 CDP events were required to maintain statistical power to detect the planned treatment difference. The manufacturer reported that there was an unexpected increase in screening for the study after the closing of enrolment was announced, resulting in 732 patients being randomized as opposed to the planned 630 patients. A sensitivity analysis was performed using the results of the first 630 randomized patients.

Subgroup Analyses

The manufacturer conducted the following univariate subgroup analyses: age (≤ 45 years or > 45 years); sex (male or female); EDSS (≤ 5.5 or > 5.5); region (non-US or US); Gd-enhancing lesion(s) at baseline (presence or absence); prior exposure to MS DMT (yes or no); duration since MS symptom onset (≤ 3 years, > 3 to ≤ 5 years, > 5 to ≤ 10 years, or > 10 years); weight (< 75 kg or ≥ 75 kg); and body mass index (BMI) (< 25 or ≥ 25 kg/m^2).[1] In addition, the manufacturer conducted a multivariate sensitivity analysis using all of the subgroup variables noted previously as main and treatment interaction effects, with the exception of weight (due to close association with BMI). In the multivariate analysis, the continuous subgroup variables (i.e., age, EDSS, duration since MS symptom onset, and BMI) were included as linear covariates. Subgroup interaction *P* values below 0.1 were considered statistically significant; those below 0.2 were considered “a trend;” and those between 0.2 and 0.3 were considered “a weak trend.”

Patient Disposition

Patient disposition for the double-blind phase of the ORATORIO study is summarized in Table 12. Patients were screened and enrolled in 29 countries at 182 investigational sites. A total of 943 patients were screened for the ORATORIO study; 732 were randomized. The manufacturer reported that the 211 screening failures were the result of patients failing to meet the eligibility criteria of the study or withdrawing consent (reasons for screening failure were not reported in aggregate, but individual reasons were included in the Clinical Study Report). Of the 732 patients who were randomized, 725 (99%) received at least one dose

of the study treatment. Withdrawals were more common in the placebo group (34%) compared with the ocrelizumab group (21%). The manufacturer reported that the difference in withdrawals was primarily due to increases in withdrawals due to “lack of efficacy” and “withdrawal by subject” in the placebo group compared with ocrelizumab group (11% versus 4% and 9% versus 5%, respectively). The FDA conducted a detailed review of the reasons for discontinuation (including those in the “other” or “withdrawal by subject” categories) to assess if lack of efficacy could have been a contributing factor. They reported that the proportions of patients who most likely withdrew due to a lack of efficacy was 7.2% and 17.2% in the ocrelizumab and placebo groups, respectively.[16] The proportions of patients who withdrew as a result of adverse events (AEs) was similar in the placebo (5%) and ocrelizumab (4%) groups.[1]

Table 12: Patient Disposition

Disposition, n (%)	Placebo (N = 244)	Ocrelizumab (N = 488)
Screened	943	
Randomized	244	488
Treated	243 (99.6)	482 (98.8)
Ongoing at time of data cut-off	162 (66)	387 (79)
Discontinued treatment	82 (33.6)	101 (20.7)
Adverse event	12 (4.9)	18 (3.7)
Death	1 (0.4)	3 (0.6)
Lack of efficacy	27 (11.1)	21 (4.3)
Lost to follow-up	1 (0.4)	4 (0.8)
Non-compliance	2 (0.8)	2 (0.4)
Non-compliance with study drug	2 (0.8)	2 (0.4)
Other	13 (5.3)	20 (4.1)
Physician decision	2 (0.8)	6 (1.2)
Pregnancy	1 (0.4)	1 (0.2)
Protocol violation	0	2 (0.4)
Withdrawal by subject	21 (8.6)	22 (4.5)
Intention-to-treat population	244 (100.0)	488 (100.0)
Per-protocol population	232 (95.1)	470 (96.3)
Safety population	239 (98.0)	486 (99.6)

n = number of patients with event; N = number of patients in the analysis.

Source: Clinical Study Report for ORATORIO.[1]

Exposure to Study Treatments

Study Treatments

Table 13 provides a summary of exposure to the study treatments. The mean and median number of doses was greater in the ocrelizumab group compared with the placebo group (6.6 versus 6.1 and 7.0 versus 6.0, respectively).[1] The majority of patients in both groups received at least 120 weeks of exposure, though the proportion was greater in the ocrelizumab group (81%) compared with the placebo group (70%).

Table 13: Summary of Exposure to Study Treatments

Summary of Exposure		Placebo (N = 244)	Ocrelizumab (N = 488)
Treatment Duration (Weeks) n (%)	0 to 23	12 (5.0)	25 (5.1)
	24 to 47	11 (4.6)	13 (2.7)
	48 to 71	15 (6.3)	13 (2.7)
	72 to 95	13 (5.4)	11 (2.3)
	96 to 119	16 (6.7)	20 (4.1)
	120 to 143	56 (23.4)	108 (22.2)
	144 to 167	43 (18.0)	113 (23.3)
	168 to 191	42 (17.6)	115 (23.7)
	192 to 215	29 (12.1)	60 (12.3)
	216+	2 (0.8)	8 (1.6)
Number of Doses n (%)	1	12 (5.0)	25 (5.1)
	2	11 (4.6)	13 (2.7)
	3	15 (6.3)	13 (2.7)
	4	13 (5.4)	11 (2.3)
	5	18 (7.5)	22 (4.5)
	6	54 (22.6)	109 (22.4)
	7	44 (18.4)	114 (23.5)
	8	44 (18.4)	107 (22.0)
	9	26 (10.9)	65 (13.4)
	10	2 (0.8)	7 (1.4)
	Mean (SD)	6.1 (2.2)	6.6 (2.1)
	Median	6.0	7.0

n = number of patients with event; N = number of patients in the analysis; SD = standard deviation.

Source: Clinical Study Report for ORATORIO.[1]

Concomitant Medications

Concomitant medications used in the ORATORIO trial are summarized in Table 14. At least one concomitant medication was used by 93.0% of patients in the ocrelizumab group and 89.5% in the placebo group. The proportion of patients who were receiving treatment with fampridine or dalfampridine was 21.8% in the placebo group and 18.9% in the ocrelizumab group. A greater proportion of placebo-treated patients received corticosteroids during the trial compared with ocrelizumab-treated patients (38.9% versus 32.7%). The use of antispasmodics/anticholinergics (20.1% with placebo and 21.0% with ocrelizumab) and anticonvulsants (19.2% with placebo and 20.4% with ocrelizumab) was balanced between the groups. Patients treated with ocrelizumab were more likely to use antihistamines (22.2% versus 9.6%).

Table 14: Summary of Exposure to Concomitant Medications

Concomitant Medications, n (%)	Placebo (N = 244)	Ocrelizumab (N = 488)
Any concomitant medication	214 (89.5)	452 (93.0)
NSAIDs	92 (38.5)	203 (41.8)
Analgesics	82 (34.3)	187 (38.5)
Corticosteroids	93 (38.9)	159 (32.7)
Muscle relaxants	74 (31.0)	168 (34.6)
Surgical and medical procedures	70 (29.3)	159 (32.7)
Vitamins and minerals	58 (24.3)	155 (31.9)
Penicillins	59 (24.7)	125 (25.7)
Investigations	46 (19.2)	120 (24.7)
Miscellaneous neurological drugs	59 (24.7)	103 (21.2)
Antispasmodics and anticholinergics	48 (20.1)	102 (21.0)
Anticonvulsants	46 (19.2)	99 (20.4)
Supplements	48 (20.1)	93 (19.1)
Quinolone antibiotics	45 (18.8)	88 (18.1)
Antihistamines	23 (9.6)	108 (22.2)
Selective serotonin reuptake inhibitors	41 (17.2)	90 (18.5)
Proton pump inhibitors	46 (19.2)	81 (16.7)
Benzodiazepines	39 (16.3)	86 (17.7)
Opioid analgesics	37 (15.5)	75 (15.4)
Miscellaneous antimicrobials	26 (10.9)	68 (14.0)
Cephalosporin antibiotics	27 (11.3)	59 (12.1)
Laxatives and stool softeners	29 (12.1)	56 (11.5)
Vaccines, toxoids and serologic drugs	16 (6.7)	56 (11.5)
Cough preparations	16 (6.7)	49 (10.1)
Botanicals	21 (8.8)	42 (8.6)
Anticoagulants	21 (8.8)	39 (8.0)
Cold and sinus remedies	16 (6.7)	44 (9.1)
Macrolide antibiotics	19 (7.9)	39 (8.0)
Antifungal drugs	15 (6.3)	39 (8.0)
Salicylates	15 (6.3)	39 (8.0)
Adrenergics/sympathomimetics	17 (7.1)	36 (7.4)
Antidepressants	20 (8.4)	32 (6.6)
Sulfonamides and trimethoprim	17 (7.1)	34 (7.0)
Dopaminergic drugs	18 (7.5)	30 (6.2)
Tricyclic antidepressants	15 (6.3)	32 (6.6)
Local anesthetics	11 (4.6)	35 (7.2)
Miscellaneous drugs	14 (5.9)	32 (6.6)
Alpha-adrenoreceptor antagonists	15 (6.3)	30 (6.2)
Sedatives and hypnotics	23 (9.6)	21 (4.3)

Concomitant Medications, n (%)	Placebo (N = 244)	Ocrelizumab (N = 488)
Nitrofurans	14 (5.9)	29 (6.0)
Mucolytics	14 (5.9)	28 (5.8)
Anorexiants and CNS stimulants	15 (6.3)	24 (4.9)
Statins	8 (3.3)	28 (5.8)
Peripheral and cerebral vascular drugs	10 (4.2)	25 (5.1)
Antiviral drugs	13 (5.4)	21 (4.3)

CNS = central nervous system; n = number of patients with event; N = number of patients in the analysis.

Source: Clinical Study Report for ORATORIO.[1]

Critical Appraisal

Internal Validity

Randomization in the ORATORIO trial 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 geographic region (US or non-US) and age (≤ 45 years or > 45 years). Key demographic characteristics were generally balanced between the ocrelizumab and placebo groups.[16] However, the mean number of Gd-enhancing lesions at baseline was greater in the ocrelizumab group compared with the placebo group (1.21 [5.14] versus 0.60 [1.55]). This imbalance could introduce bias if the efficacy of ocrelizumab is different in the presence of acute inflammation; the clinical expert consulted for this review agreed with this potential limitation, and the FDA medical review also noted this as a potential concern.[16] However, post hoc sensitivity analyses were conducted for the CDP end points that included the presence or absence of a Gd-enhancing lesion as an additional covariate, and the results were similar to the primary analyses. The study protocol for the ORATORIO trial stated that investigators should attempt to maintain treatments for MS symptoms throughout the study; however, changes in therapy were permitted if they were considered appropriate for the well-being of the patient.[1] The number of patients using fampridine or dalfampridine increased throughout the study in both the placebo group (5.0% to 21.8%) and ocrelizumab group (7.2% to 18.9%). Since fampridine is indicated for improving walking ability in MS patients, the use of this medication could influence the results of the T25FW (a secondary end point of the study). Analyses were not performed to examine any potential impact of fampridine use; therefore, the magnitude and direction of any potential bias due to fampridine use is unclear. Of note, this was not cited as a concern by the FDA or the European Medicines Agency (EMA).[9,16-18]

The study treatments in ORATORIO were administered in a double-blind manner. Differences in the AE profiles related to the administration of the study drugs could have allowed some patients and investigators to infer which patients had been administered the active treatment. For example, infusion-related reactions were more commonly reported in the ocrelizumab group compared with the placebo group (39.9% versus 25.5%) and the use of antihistamines was more common in patients treated with ocrelizumab (22.2% versus 9.6%).[1] EDSS was evaluated by a blinded examining investigator who was not involved in the medical management of patients and did not have access to the patients' data. MRI scans for efficacy end points were evaluated by a centralized reading centre that was blinded to allocated treatment.

The disposition of patients who were screened and enrolled in ORATORIO was appropriately reported in the Clinical Study Report.[1] The planned sample size for the ORATORIO trial was 630 patients; however, 732 patients were randomized due to an unexpected increase in screening after the closing of enrolment was announced by the manufacturer. This 16.2% increase in the sample size of the trial was not specified in a protocol amendment and had a measurable impact on the results of the study. A sensitivity analysis demonstrated that the primary end point of the trial would have not have met statistical significance without the enrolment of these additional patients.

The rate of withdrawal was disproportionate, with more patients discontinuing in the placebo group (33.6%) compared with the ocrelizumab group (20.7%). The proportion of patients who withdrew from the study exceeded the 20% cited in the sample-size calculation.[1,9] The FDA noted that the proportion of withdrawals in each group exceeded the absolute difference of 7.1% between the two groups with respect to the primary end point, leading to uncertainty regarding the accuracy of treatment effect.[18]

Significant protocol violations were rare in the ORATORIO trial and were balanced between the two treatment groups (i.e., the per-protocol population included 96% and 95% of patients in the ocrelizumab and placebo groups, respectively); therefore, protocol violations were unlikely to affect the interpretation of the study results. Reviewers for the FDA also noted this.[16] Although not counted as significant protocol violations by the manufacturer, 67% of patients in the study had their baseline EDSS measurements recorded after randomization (29% after receiving an infusion of the study treatment). A breakdown by treatment group was not reported; therefore, it is unclear whether the percentage of patients in the study who had their baseline EDSS measurement recorded after randomization was differential between groups and may have affected internal validity. The FDA reviewers noted that this is an unusually extensive failure of study investigators to follow a clinical trial protocol.[16]

Pre-specified sensitivity analyses that did not use imputed data for the primary end point failed to demonstrate statistical significance for 12-week and 24-week CDP. The use of imputed data in the primary efficacy analysis (which demonstrated statistical significance in favour of ocrelizumab) is not the method that is typically used to evaluate CDP in relapsing MS trials.[16] The primary method of analysis that is typically used for CDP end points in relapsing trials does not include imputed data, as was the case with pivotal ocrelizumab trials for the RRMS indication (OPERA-I and OPERA-II). The manufacturer reported that this approach was used because disability progression is different in PPMS than in RRMS. Specifically, they cited evidence of a higher rate of EDSS confirmation in progressive MS versus relapsing MS from a 2008 study[27] that reported 12-week CDP confirmation rates in progressive MS patients of approximately 80%. An FDA reviewer had concerns regarding the analysis of the CDP end point in the ORATORIO trial, noting that the use of imputed data in the primary analysis may have biased the results in favour of ocrelizumab with respect to demonstrating statistical significance for the primary end point. Further analysis demonstrated that 23% of patients who had an initial disability progression event did not have it confirmed at least 12 weeks afterwards in ORATORIO (which is similar to the 80% confirmation rate cited by the manufacturer). The FDA conducted additional analyses of the CDP end point, investigating the assumption that 23% of the 21 patients (i.e., five patients) who had imputed CDP events would not have satisfied the criteria for CDP. In particular, they randomly selected five of these 21 patients, modified their event status from the CDP to censoring at withdrawal, applied the same log-rank test as the manufacturer's primary analysis to obtain a *P* value for the treatment comparison, then repeated this procedure 500

times, each with a different set of five randomly selected patients. According to the FDA, the results "indicated that the statistical significance of the primary outcome was a valid representation" of the observed treatment in ORATORIO (Table 31 on page 12).[18]

Similar to the results for CDP, the results for the T25FW test were sensitive to the method of imputation that was used to handle missing values. Missing T25FW values were imputed using last observation carried forward; there were more patients in the placebo group with imputed values compared with the ocrelizumab group at week 120 (29% and 19%, respectively). However, the FDA noted that there were slightly more patients in the ocrelizumab group than in the placebo group who had only baseline measurements available (15 [3.1%] versus five [2.1%]). The FDA conducted an exploratory analysis excluding patients who lacked post-baseline T25FW values and reported that the analysis was no longer statistically significant (i.e., the *P* value increased from 0.0404 to 0.0528). Similarly, the FDA conducted an analysis using MMRM to handle missing T25FW values and reported a non-statistically significant *P* value of 0.0783. Baseline T25FW was greater in the ocrelizumab group (14.6 seconds) compared with the placebo group (12.8 seconds); however, the T25FW analyses were adjusted for the baseline values.

All efficacy end points were reported as being analyzed using the ITT population, which was to consist of all randomized patients. However, the evaluation of the MRI end points, SF-36, and T25FW were conducted with a subset of randomized patients. The rationale for reporting that these analyses were conducted in the ITT population is unclear. There was a considerable amount of missing data for these outcome measures (e.g., data for change in brain volume were missing for approximately 35% of randomized patients by week 120), and the impact of this missing data is uncertain. 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 the ORATORIO study. The EMA noted that the hierarchy used in the ORATORIO trial was appropriate.[9] A rationale regarding the order of outcomes in the hierarchy (e.g., clinical importance) was not specified.

External Validity

The clinical expert consulted by CADTH suggested that the patients enrolled in the pivotal trials were reasonably reflective of patients encountered in routine Canadian practice, though they may have been slightly younger on average than the overall Canadian PPMS patient population. This likely reflects the inclusion criteria, which limited enrolment to patients between the ages of 18 and 55 years of age. Patients were required to have an EDSS score of 3.0 to 6.5 to be eligible for the ORATORIO trial. This excludes a number of patients with more severe disability (i.e., EDSS between 7 and 8) or less severe disability (EDSS < 3.0) who could be eligible to receive ocrelizumab in clinical practice. The efficacy and safety of ocrelizumab in such patients is uncertain and will be evaluated in future phase IIIb studies.[9] Clinical experts who provided input into the EMA review of ocrelizumab also suggested that the ORATORIO study population had a greater proportion of younger patients who were more likely to have active disease and suggested that the generalizability of the results to the full spectrum of PPMS patients was questionable.[9]

The proportions of patients with at least one T1 Gd-enhancing lesion at baseline were 27.5% and 24.7% in the ocrelizumab and placebo groups, respectively. The proportions are similar to those reported in a prior phase II/III study of rituximab in PPMS (24.5%; OLYMPUS),[28] but higher than the proportion enrolled in PPMS studies for glatiramer acetate (14%; PROMISE) or fingolimod (13%; INFORMS).[9,29] The EMA also noted that data regarding the presence of T1 Gd-enhancing lesions in PPMS are sparse and largely limited

to characteristics reported in clinical trials.[9] The clinical expert consulted by CADTH noted that patients with PPMS are not routinely scanned for T1 Gd-enhancing lesions; therefore, it is challenging to evaluate whether or not this reflects the Canadian PPMS patient population. Furthermore, the clinical expert also indicated that inflammatory activity is not typically observed in PPMS patients and that the appearance of Gd-enhancing lesions could lead them to question the diagnosis (e.g., the patient may have a form of progressive relapsing MS where relapses are not occurring or being detected).

The diagnosis of PPMS for inclusion in the ORATORIO trial was based on the 2005 revised MacDonald criteria, as opposed to the more recent 2010 McDonald criteria (Table 3). The clinical expert consulted by CADTH noted that the 2010 criteria are currently used in Canadian clinical practice, but that the use of the 2005 criteria in the ORATORIO trial is acceptable and does not limit the generalizability of the findings. It should also be noted that the initial version of the protocol for the ORATORIO trial (August 25, 2010) pre-dated the publication of the MacDonald 2010 criteria.[1]

Placebo is considered an appropriate comparator and is aligned with guidance from the EMA, which states that a placebo-controlled trial is required due to the absence of any other of any treatments approved for PPMS.[1,9] The outcomes in the ORATORIO trial included clinical end points (e.g., disability progression), MRI end points (e.g., changes in T2 lesions and brain volume), 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 EMA on the design of trials for PPMS treatments.[9,30] However, the manufacturer used 12-week CDP as the primary end point as opposed to 24-week CDP, which the clinical expert indicated was a more clinically relevant end point. The clinical expert noted that the CDP end points studied in the pivotal trials are typically only used in clinical trials, as disability progression is evaluated over a much longer period in Canadian clinical practice.

The dose of ocrelizumab was administered in accordance with recommendations in the product monograph for the first dosage
(i.e., 300 mg on day 1 and 300 mg on day 15).[13] However, the subsequent dosages during the double-blind phase were also administered as two 300 mg infusions separated by 14 days, which is not reflective of the product monograph, which recommends a single 600 mg IV infusion once every six months. The clinical expert consulted by CADTH suggested that the dosage regimen used in the ORATORIO trial is unlikely to have affected the efficacy of the treatment relative to the dosage regimen that would be used in clinical practice; however, it could make the treatment more tolerable for some patients. Use of the split dosage regimen required patients to undergo twice as many infusion visits than would be required in routine clinical practice. It is unclear if this additional treatment burden could have influenced patient adherence with the study protocol. All-cause withdrawal for ocrelizumab-treated patients was greater in the ORATORIO trial (20.7%) compared with the pivotal ocrelizumab RRMS trials, which used single 600 mg IV infusions (10.7% to 13.7%); however, this could be attributable to the greater duration of the PPMS trial or to differences in the patient populations. The clinical expert consulted by CADTH noted that increasing the number of clinic visits can be particularly challenging for patients with ambulatory difficulties.

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 that were used in the study for PPMS (ORATORIO)[1] and RRMS (OPERA-I and OPERA-II).[31] The clinical expert

consulted by CADTH suggested similar protocols would be applied in Canadian clinical practice.

As is common in clinical trials, the study participants received extensive contact with health professionals, including 17 scheduled assessment and/or treatment visits and telephone interviews every four weeks.[1] This is not reflective of routine clinical practice in Canada, where follow-up with patients is considerably less frequent. The clinical expert consulted by CADTH indicated that patients with PPMS are typically seen once every six months after they first present with symptoms; after the diagnosis has been established, they are seen approximately once every 12 months, or as needed.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported here (Methods, Table 4).

Confirmed Disability Progression

Confirmed Disability Progression for at Least 12 Weeks

Figure 3 provides a summary of the results for CDP for at least 12 weeks. In the primary efficacy analysis, ocrelizumab treatment was associated with a statistically significant reduction in the hazard for CDP for at least 12 weeks (hazard ratio: 0.76; 95% confidence interval [CI], 0.59 to 0.98). As shown in Figure 5, the rate of CDP events in the ocrelizumab and placebo groups shows initial separation at the 12-week to 18-week range, then remains relatively stable between the two groups for approximately two years. The rate of CDP events shows additional separation between the two groups beginning at approximately week 120. However, the FDA noted that the number of patients remaining in the trial began to diminish rapidly diminish after the two-year time point.[16]

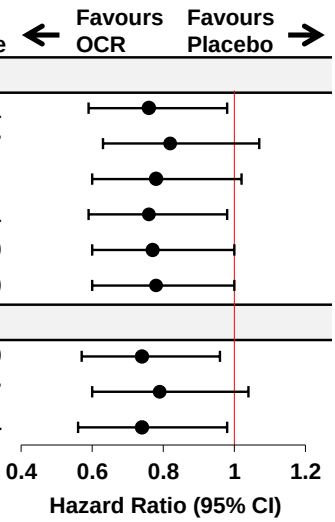
The results in the ITT population were sensitive to the method of imputation that was used to account for missing data. There were 21 patients (12 placebo and nine ocrelizumab) who experienced an initial progression event but withdrew prior to having the event confirmed at least 12 weeks later. When these patients were considered as having CDP events, the imputed results of the primary end point were statistically significant (hazard ratio: 0.76; 95% CI, 0.59 to 0.98); however, when these events were not imputed, the results were no longer statistically significant (hazard ratio: 0.82; 95% CI, 0.63 to 1.07). Similarly, an analysis using multiple imputation (i.e., 50% of these events were imputed as CDP) failed to demonstrate statistical significance (hazard ratio: 0.78; 95% CI, 0.60 to 1.02). An additional sensitivity analysis was conducted to adjust for the presence or absence of Gd-enhancing lesions at baseline and baseline EDSS score (≤ 5.5 versus > 5.5); the results were identical to the primary analysis (hazard ratio: 0.76; 95% CI, 0.59 to 0.98).

As the planned sample size for the study was 630 patients, the manufacturer conducted a sensitivity analysis using the results for the first 630 patients who were randomized; the results were not statistically significant (hazard ratio: 0.79; 95% CI, 0.60 to 1.04). This analysis also imputed events where initial disability progression was recorded, but not confirmed due to withdrawal by patient, as CDP events. A sensitivity analysis that excluded early progression events (i.e., those that occurred within 12 weeks of randomization) demonstrated results that were nearly identical to the primary analysis (hazard ratio: 0.78; 95% CI, 0.60 to 1.00). This analysis only excluded two events from the placebo group, which further highlights the sensitivity of the observed treatment effect, as the *P* value

shifted from 0.0321 with the primary analysis to a non-statistically significant 0.05 with the exclusion of these two events. Results for the following sensitivity analyses were statistically significant and favoured treatment with ocrelizumab: per-protocol data set (hazard ratio: 0.74, 95% CI, 0.57 to 0.96); exclusion of patients with relapses (hazard ratio: 0.74; 95% CI, 0.56 to 0.98); and an analysis where patients with an initial progression event but no confirmation were counted as having CDP if the reason for withdrawal was cited as "withdrawal by subject" or "lack of efficacy" (hazard ratio: 0.77; 95% CI, 0.60 to 1.00).

Figure 3: Time to Confirmed Disability Progression for at Least 12 Weeks

Study	Patients with CDP, n/N (%) Placebo	Patients with CDP, n/N (%) OCR	OCR vs. Placebo HR (95% CI)	P value
ITT Data Set				
Primary analysis	96/244 (39.3)	160/487 (32.9)	0.76 (0.59 to 0.98)	0.0321
No imputation	84/244 (34.4)	151/487 (31.0)	0.82 (0.63 to 1.07)	0.1477
Multiple imputation	NA	NA	0.78 (0.60 to 1.02)	NA
Adj. T1 GdE lesions and EDSS	96/244 (39.3)	160/487 (32.9)	0.76 (0.59 to 0.98)	0.0321
Imp. for efficacy-related W/D	92/244 (37.7)	156/487 (32.0)	0.77 (0.60 to 1.00)	0.0490
Exclusion of early events	94/244 (38.5)	160/487 (32.9)	0.78 (0.60 to 1.00)	0.0500
Alternative Data Sets				
Per-protocol	91/232 (39.2)	153/469 (32.6)	0.74 (0.57 to 0.96)	0.0239
First 630 patients	83/209 (39.7)	145/420 (34.5)	0.79 (0.60 to 1.04)	0.0867
Excluding pts with relapses	77/204 (37.7)	144/456 (31.6)	0.74 (0.56 to 0.98)	0.0324



Adj. = adjusted; CDP = confirmed disability progression; CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; ITT = intention-to-treat population; GdE = gadolinium-enhancing; OCR = ocrelizumab; n = number of patients with an event; N = number of patients in the analysis; NA = not applicable; pts = patients; vs. = versus; WD = withdrawal.

Source: Clinical Study Report for ORATORIO.[1]

The manufacturer conducted univariate subgroup analyses and a multivariate Cox regression analysis to investigate potential treatment-modifying effects. The results for the subgroup analyses of interest for this review are summarized in Table 29. Ocrelizumab was statistically significantly superior to placebo in reducing 12-week CDP only in the subgroup of patients who were less than 45 years of age at baseline (hazard ratio: 0.64; 95% CI, 0.45 to 0.92). The interaction tests for the univariate subgroups were not statistically significant (i.e., $P > 0.1$).[1,32] The multivariate analysis demonstrated no statistically significant interaction effects, but the manufacturer reported a potential for interaction for T1 Gd-enhancing lesions.

Confirmed Disability Progression for at Least 24 Weeks

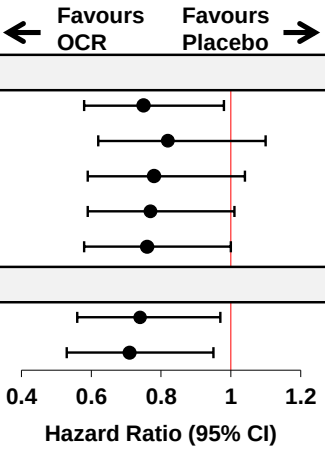
Figure 4 provides a summary of the results for CDP for at least 24 weeks, a secondary end point of the ORATORIO trial. Ocrelizumab treatment was associated with a statistically significant reduction in the hazard for CDP for at least 24 weeks compared with placebo (hazard ratio: 0.75; 95% CI, 0.59 to 0.98). Similar to the results for CDP for at least 12 weeks, the rate of CDP for at least 24 weeks in the ocrelizumab and placebo groups shows

initial separation at the 12-week to 18-week range, then remains relatively unchanging between the two groups for approximately two years (Figure 5). The rate of CDP events shows additional separation between the two groups beginning at approximately week 120.

Similar to CDP for at least 12 weeks, the results for the 24-week end point were sensitive to the method of imputation that was used to account for patients who experienced an initial progression event, but who discontinued prior to an EDSS evaluation to meet the criteria for CDP. When analyzed without imputation or with multiple imputation (i.e., 50% of these events were imputed as CDP), the results were no longer statistically significant (hazard ratio: 0.82 [95% CI, 0.62 to 1.10] and 0.78 [95% CI, 0.59 to 1.04], respectively). Likewise, an analysis that excluded progression events that occurred within 12 weeks of randomization failed to demonstrate statistical significance (hazard ratio: 0.77; 95% CI, 0.59 to 1.01; *P* = 0.0589). Results for the following sensitivity analyses were statistically significant and favoured treatment with ocrelizumab: per-protocol data set (hazard ratio: 0.74; 95% CI, 0.56 to 0.97); exclusion of patients with relapses (hazard ratio: 0.71; 95% CI, 0.53 to 0.95); and an analysis where patients with a disease progression event but no confirmation were counted as having CDP if the reason for withdrawal was cited as "withdrawal by subject" or "lack of efficacy" (hazard ratio: 0.76; 95% CI, 0.58 to 1.00). Subgroup analyses were similar to those reported for 12-week CDP (Table 29).

Figure 4: Time to Confirmed Disability Progression for at Least 24 Weeks

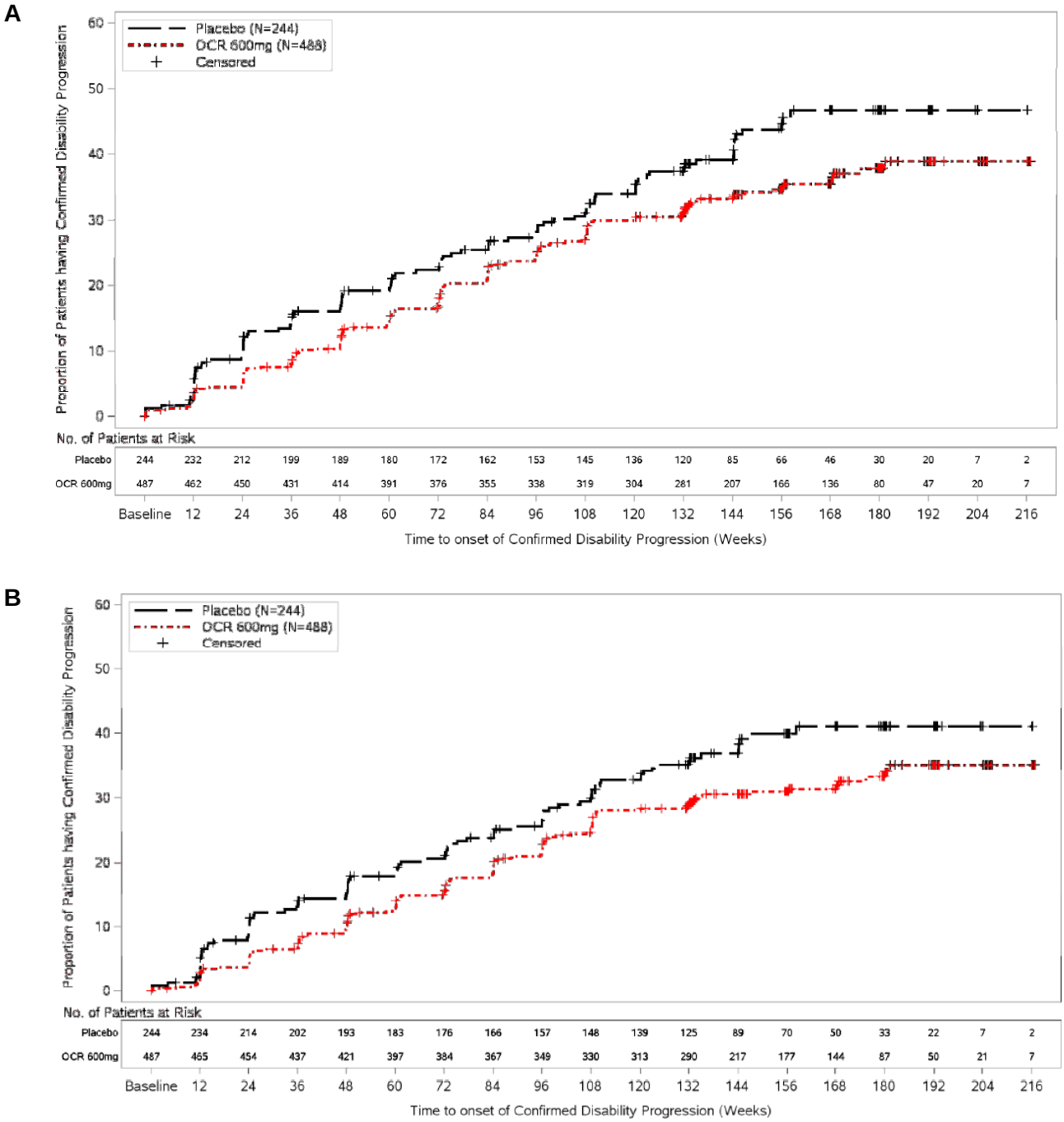
Study	Patients with CDP to n/N (%)		OCR vs. Placebo	P value
	Placebo	OCR	HR (95% CI)	
ITT Data Set				
Primary analysis	87/244 (35.7)	144/487 (29.6)	0.75 (0.58 to 0.98)	0.0365
No imputation	71/244 (29.1)	128/487 (26.3)	0.82 (0.62 to 1.10)	0.1884
Multiple imputation	NA	NA	0.78 (0.59 to 1.04)	NA
Exclusion of early events	85/244 (34.8)	144/487 (29.6)	0.77 (0.59 to 1.01)	0.0589
Imp. for efficacy-related W/D	82/244 (33.6)	137/487 (28.1)	0.76 (0.58 to 1.00)	0.0493
Alterative Data Sets				
Per-protocol	82/232 (35.3)	137/469 (29.2)	0.74 (0.56 to 0.97)	0.0290
Excluding pts with relapses	71/204 (34.8)	128/456 (28.1)	0.71 (0.53 to 0.95)	0.0188



CDP = confirmed disability progression; CI = confidence interval; HR = hazard ratio; Imp. = imputation; ITT = intention-to-treat population; OCR = ocrelizumab; n = number of patients with an event; N = number of patients in the analysis; NA = not applicable; pts = patients; vs. = versus; WD = withdrawal.

Source: Clinical Study Report for ORATORIO.[1]

Figure 5: Kaplan–Meier Curves for Time to Onset of CDP for at Least 12 Weeks (A) and 24 Weeks (B)



N = number of patients in the analysis; OCR = ocrelizumab.

Source: Clinical Study Report for ORATORIO.[1]

Walking Ability

Change from baseline in T25FW was a secondary outcome. The results are summarized in Table 15. T25FW times increased in both groups throughout the trial (Table 30). There was a statistically significant difference between the ocrelizumab and placebo groups (relative difference: 29.337%; 95% CI, –1.618% to 51.456%). At week 120, the absolute difference between the placebo and ocrelizumab groups in mean change in T25FW time was 3.03 seconds (increase of 11.76 seconds in the placebo group and 8.79 seconds in the ocrelizumab group). Figure 6 shows the percentage change in T25FW from baseline to week 120 for both the placebo and ocrelizumab groups.

The manufacturer conducted an exploratory analysis to investigate the time to a 20% increase from baseline in T25FW and reported that ocrelizumab was associated with a reduced risk for experiencing an increase of 20% compared with placebo during the study period (hazard ratio: 0.75; 95% CI, 0.61 to 0.92; *P* = 0.0053). The Kaplan–Meier curves are shown in Figure 6.

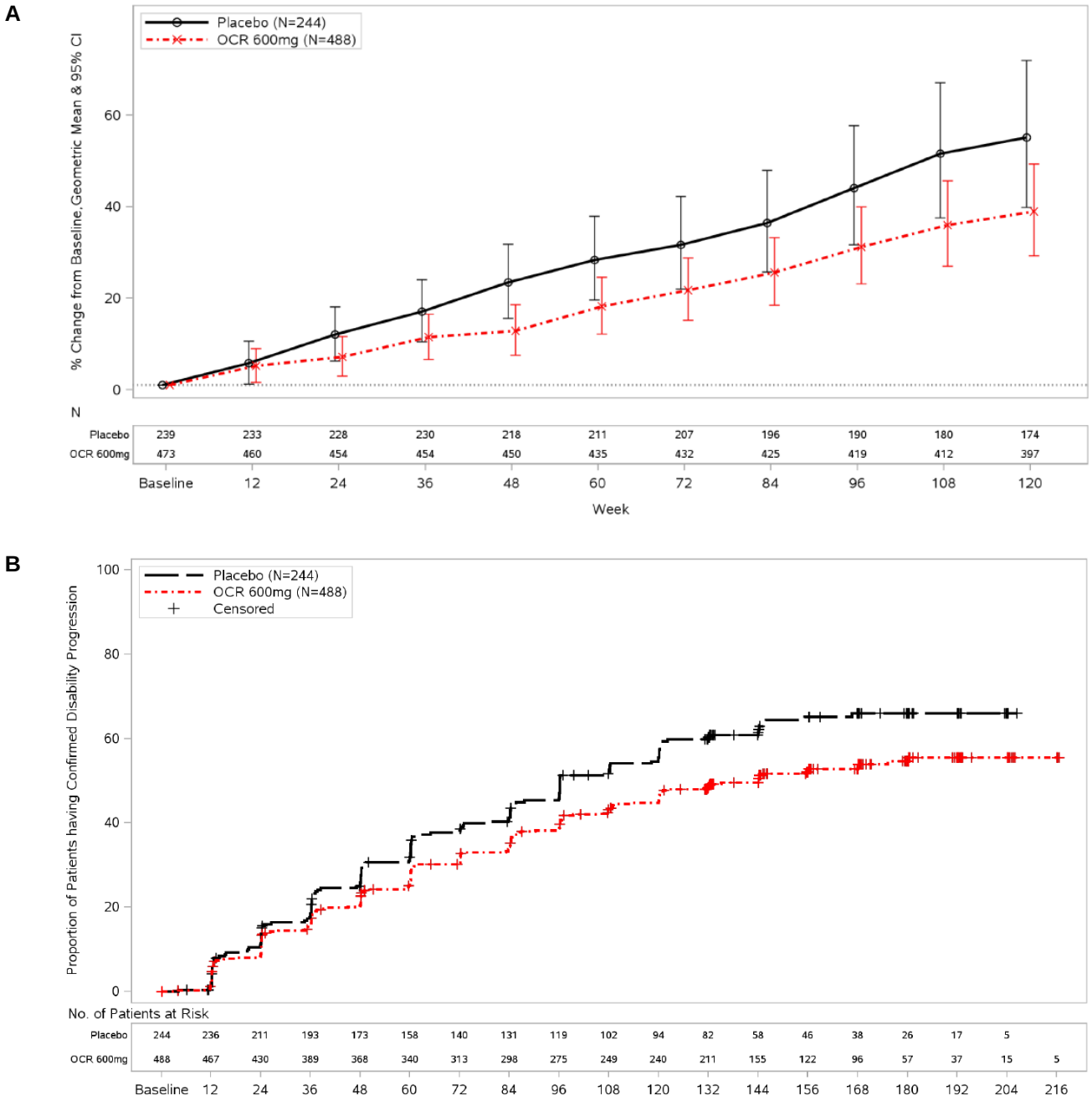
Table 15: Change From Baseline to Week 120 in Timed 25-Foot Walk

Time Point	Parameters	Placebo (N = 244)	Ocrelizumab (N = 488)
Baseline	N	239	473
	Mean (SE) (seconds)	12.781 (1.00)	14.573 (0.95)
Week 120	N	174	397
	AGM (95% CI) (seconds)	1.551 (1.399 to 1.720)	1.389 (1.292 to 1.494)
	Percentage change	55.10	39.93
	Ratio of AGM (95% CI)	0.896 (0.792 to 1.013)	
	Relative difference (%) (95% CI)	29.337 (–1.618 to 51.456)	
	P value	0.0404	

AGM = adjusted geometric mean; CI = confidence interval; SE = standard error.

Source: Clinical Study Report for ORATORIO.[1]

Figure 6: Percentage Change From Baseline in T25FW (A) and Time to 20% Increase in T25FW (B)



CI = confidence interval; N = number of patients in the analysis; OCR = ocrelizumab.

Source: Clinical Study Report for ORATORIO.[1]

T1 and T2 Lesions

Volume of T2 Lesions

Table 16 summarizes the change from baseline in the volume of T2 lesions. The percentage change from baseline in the volume of T2 lesions was a pre-specified secondary end point. Baseline data were reported for 95.9% (234/244) of patients in the placebo group and 95.1% (464/488) of those in the ocrelizumab group. The mean volume of T2 lesions at baseline was greater in the ocrelizumab group compared with the placebo group (12.761 cm^3 versus 11.039 cm^3). At week 120, results were available for 78.2% (183/244) of placebo-treated patients and 82.0% (400/464) of ocrelizumab-treated patients. Treatment with ocrelizumab treatment was associated with a statistically significant reduction in T2 lesion volume compared with placebo (decrease of 3.4% versus increase of 7.4%, respectively; $P < 0.0001$).

Table 16: Change From Baseline to Week 120 in Volume of T2 Lesions

Time point	Parameters	Placebo (N = 244)	Ocrelizumab (N = 488)
Baseline	N	234	464
	Mean (SE)	11.039 cm^3 (0.858)	12.761 cm^3 (0.709)
Week 120	n	183	400
	Change from baseline (ratio relative to baseline)		
	AGM (95% CI)	1.074 (1.050 to 1.099)	0.966 (0.950 to 0.983)
	Ratio of AGM (95% CI)	0.900 (0.876 to 0.924)	
	Percentage change (%)		
	AGM (95% CI)	7.426 (4.967 to 9.942)	–3.366 (–4.987 to –1.718)
	P value	< 0.0001	

AGM = adjusted geometric mean; CI = confidence interval; SE = standard error.

Source: Clinical Study Report for ORATORIO.[1]

New and Enlarging T2 Hyperintense Lesions

The number of new and enlarging T2 hyperintense lesions was an exploratory end point. As shown in Table 17, the rate of new and enlarging T2 hyperintense lesions was lower in the ocrelizumab group compared with the placebo group (adjusted rate ratio: 0.081; 95% CI, 0.058 to 0.111). At 120 weeks, placebo-treated patients had experienced 2027 new and enlarging T2 hyperintense lesions compared with 388 in the ocrelizumab group.

Table 17: Change From Baseline to Week 120 in T2 Lesions

Parameters	Placebo (N = 244)	Ocrelizumab (N = 488)
n	234	465
Total number of T2 lesions	2027	388
Total number of brain MRI scans	636	1315
Adjusted rate (95% CI)	3.880 (2.841 to 5.299)	0.313 (0.246 to 0.397)
Adjusted rate ratio (95% CI)	0.081 (0.058 to 0.111)	
P value	< 0.0001[a]	

CI = confidence interval; MRI = magnetic resonance imaging.

Source: Clinical Study Report for ORATORIO.[1]

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

T1 Gadolinium-Enhancing Lesions

The number of Gd-enhancing T1 lesions was an exploratory end point. Treatment with ocrelizumab was associated with a reduction in the number of T1 Gd-enhancing lesions compared with the placebo group. The adjusted rate ratio was 0.024 (95% CI, 0.011 to 0.051) favouring ocrelizumab compared with placebo (Table 18).

Table 18: Change From Baseline to Week 120 in T1 Lesions

Parameters	Placebo (N = 244)	Ocrelizumab (N = 488)
n	233	463
Total number of T1 lesions	350	106
Total number of brain MRI scans	632	1307
Adjusted rate (95% CI)	1.861 (1.087 to 3.186)	0.045 (0.028 to 0.072)
Adjusted rate ratio (95% CI)	0.024 (0.011 to 0.051)	
P value	< 0.0001[a]	

CI = confidence interval; MRI = magnetic resonance imaging; n = number of patients.

Source: Clinical Study Report for ORATORIO.[1]

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

Change in Brain Volume

Table 19 summarizes the results for change in brain volume from week 24 to week 120, a pre-specified secondary end point of the ORATORIO trial. There was a statistically significant difference favouring ocrelizumab compared with placebo with a relative reduction in brain volume loss of 17.475% (95% CI, 3.206 to 29.251). The absolute difference between the two groups was 0.192% (95% CI, 0.030 to 0.354).

Table 19: Change in Brain Volume From Week 24 to Week 120

Time point	Parameters	Placebo (N = 244)	Ocrelizumab (N = 488)
Week 24	n	203	407
	Mean (SE)	1467.186 (6.34)	1458.473 (4.17)
Week 120	n	150	325
	Percentage change (%)		
	AGM (95% CI)	–1.093 (–1.236 to –0.951)	–0.902 (–1.004 to –0.799)
	Difference in AGM (95% CI)	0.192 (0.030 to 0.354)	
	Relative reduction (95% CI)	17.475 (3.206 to 29.251)	
	P value	0.0206	

AGM = adjusted geometric mean; CI = confidence interval; SE = standard error.

Source: Clinical Study Report for ORATORIO.[1]

Multiple Sclerosis Functional Composite

Results for change from baseline in the MSFC are summarized in Table 20. There was no difference between the ocrelizumab and placebo groups for change from baseline in the MSFC (least squares mean difference [LSMD]: 0.086; 95% CI, –0.051 to 0.222).

Table 20: Change from Baseline to Week 120 in Multiple Sclerosis Functional Composite

Time point	Parameters	Placebo (N = 244)	Ocrelizumab (N = 488)
Baseline	n	237	465
	Mean (SE)	0.026 (0.044)	0.008 (0.033)
Week 120	n	170	383
	Change from baseline		
	LSM (SE)	–0.211 (0.058)	–0.125 (0.041)
	LSMD (95% CI)	0.086 (–0.051 to 0.222)	
	P value	0.2169[a]	

CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; n = number of patients in the analysis; SE = standard error.

Source: Clinical Study Report for ORATORIO.[1]

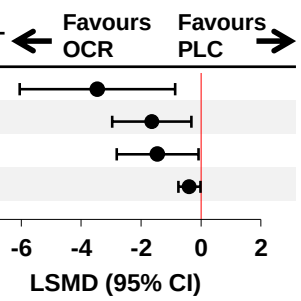
[a] This analysis was conducted outside of the statistical testing hierarchy and is non-confirmatory.

Modified Fatigue Impact Scale

Ocrelizumab was associated with a decrease in fatigue compared with placebo as assessed by the Modified Fatigue Impact Scale (MFIS) from baseline to week 120 (LSMD: –3.456; 95% CI, –6.048 to –0.863). As shown in Figure 7, treatment with ocrelizumab was also superior to placebo in the MFIS subscales (i.e., physical impact, cognitive impact, and psychosocial impact).[1]

Figure 7: Change From Baseline in Modified Fatigue Impact Scale

Study	Mean Change (SE)		OCR vs. Placebo	
	Placebo	OCR	LSMD (95% CI)	P value
Total Score	**2.994 (1.189)**	**-0.462 (0.857)**	**-3.456 (-6.048 to -0.863)**	**0.0091[a]**
Physical Impact	**0.798 (0.603)**	**-0.842 (0.434)**	**-1.640 (-2.959 to -0.322)**	**0.0149[a]**
Cognitive Impact	**1.880 (0.628)**	**0.432 (0.453)**	**-1.448 (-2.815 to -0.080)**	**0.0380[a]**
Psychosocial Impact	**0.378 (0.170)**	**-0.009 (0.122)**	**-0.386 (-0.757 to -0.016)**	**0.0411[a]**



CI = confidence interval; LSMD = least squares mean difference; OCR = ocrelizumab; PLC = placebo; SE = standard error.

Source: Clinical Study Report for ORATORIO.[1]

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

Short Form (36) Health Survey

Results for change from baseline in the SF-36 PCS and SF-36 MCS are summarized in Table 21. Change from baseline to week 120 in the SF-36 PCS was a pre-specified secondary end point and there was no statistically significant difference between the ocrelizumab and placebo groups (LSMD: 0.377; 95% CI, –1.048 to 1.802). Change from baseline to week 120 in the SF-36 MCS was an exploratory end point. Ocrelizumab-treated patients demonstrated an improvement in mean SF-36 MCS; those treated with placebo experienced a reduction in mean SF-36 MCS (LSMD: 3.318; 95% CI, 1.414 to 5.221).

Table 21: Change From Baseline to Week 120 in Short Form (36) Health Survey PCS and MCS

End Point	Time Point	Parameter	Placebo (N = 244)	Ocrelizumab (N = 488)
SF-36 PCS	Baseline	n	185	384
		Mean (SE)	35.553 (0.655)	36.102 (0.488)
	Week 120	n	128	292
		LS Mean (SE)	–1.108 (0.654)	–0.731 (0.470)
		LSMD (95% CI)	0.377 (–1.048 to 1.802)	
		P value	0.6034	
SF-36 MCS	Baseline	n	185	384
		Mean (SE)	42.249 (0.861)	43.059 (0.638)
	Week 120	n	128	292
		LS Mean (SE)	–1.673 (0.874)	1.645 (0.629)
		LSMD (95% CI)	3.318 (1.414 to 5.221)	
		P value	0.0007[a]	

CI = confidence interval; LS = least squares; LSMD = least squares mean difference; n = number of patients; 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.

Source: Clinical Study Report for ORATORIO.[1]

[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. A summary of key harms data is reported in Table 22. The overall proportion of patients who experienced at least one AE was 95.1% in the ocrelizumab group and 90.0% in the placebo group. Serious adverse events (SAEs) were reported for 22.2% of patients in the placebo group and 20.4% of those in the ocrelizumab group. Events leading to withdrawal from the study treatments occurred for 4.1% in ocrelizumab group and 3.3% in the placebo group.

Table 22: Summary of Adverse Events

Adverse Events, n (%)	Placebo (N = 239)	Ocrelizumab (N = 486)
At least one adverse event	215 (90.0)	462 (95.1)
Deaths	1 (0.4)	4 (0.8)
Serious adverse event	53 (22.2)	99 (20.4)
Withdrawal due to adverse event	8 (3.3)	20 (4.1)
Adverse event leading to dose modification/interruption	12 (5.0)	47 (9.7)
Malignancies	2 (0.8)	11 (2.3)
Infections	167 (69.9)	347 (71.4)
Serious Infections	21 (8.8)	37 (7.6)

n = number of patients with event; N = number of patients in the analysis.

Source: Common Technical Document 2.7.3.[2]

Adverse Events

AEs that occurred in at least 5% of patients in either of the treatment groups are summarized in Table 23. Infusion-related reactions were the most commonly reported AEs in the ocrelizumab group. Infections and infestations were the most frequently reported category of AEs, with a similar frequency in the ocrelizumab and placebo groups (69.8% and 67.8%, respectively). Relative to the placebo group, the ocrelizumab group reported a lower frequency of nasopharyngitis (22.6% versus 27.2%, respectively) and a greater frequency of upper respiratory tract infections (10.9% versus 5.9%, respectively). Depression and contusions were more commonly reported in the placebo group compared with the ocrelizumab group (12.6% versus 7.6% and 17.9% versus 2.9%).

Table 23: Adverse Events Occurring in at Least 5% of Patients

Adverse Events, n (%)	Placebo (N = 239)	Ocrelizumab (N = 486)
At least one adverse event	180 (75.3)	400 (82.3)
Infusion-related reaction	61 (25.5)	194 (39.9)
Nasopharyngitis	65 (27.2)	110 (22.6)
Urinary tract infection	54 (22.6)	96 (19.8)
Headache	33 (13.8)	65 (13.4)
Back pain	36 (15.1)	59 (12.1)
Influenza	21 (8.8)	56 (11.5)
Depression	30 (12.6)	37 (7.6)
Upper respiratory tract infection	14 (5.9)	53 (10.9)
Arthralgia	21 (8.8)	38 (7.8)
Pain in extremity	25 (10.5)	33 (6.8)
Fatigue	24 (10.0)	27 (5.6)
Bronchitis	12 (5.0)	30 (6.2)
Insomnia	12 (5.0)	27 (5.6)
Oedema peripheral	12 (5.0)	26 (5.3)
Cough	8 (3.3)	29 (6.0)
Dizziness	11 (4.6)	25 (5.1)
Constipation	12 (5.0)	23 (4.7)
Diarrhea	12 (5.0)	23 (4.7)
Nausea	16 (6.7)	19 (3.9)
Hypertension	9 (3.8)	25 (5.1)
Contusion	19 (7.9)	14 (2.9)
Gastroenteritis	12 (5.0)	20 (4.1)
Musculoskeletal pain	12 (5.0)	19 (3.9)

n = number of patients with event; N = number of patients in the analysis.

Source: Common Technical Document 2.7.3.[2]

Serious Adverse Events

SAEs that occurred during the double-blind portion of the ORATORIO trial are summarized in Table 24. The overall proportion of patients who experienced at least one event was similar in the ocrelizumab and placebo groups (22.2% versus 20.4%). The overall rate of SAEs was 11.67 per 100 person-years in the placebo group and 10.24 per 100 person-

years in the ocrelizumab group during the controlled treatment period. The proportion of patients who experienced a serious event that was categorized as an infection or infestation was similar in both the ocrelizumab and placebo groups (6.2% versus 5.9%). The proportion of patients with a serious event that was categorized as a neoplasm was greater in the placebo group compared with the ocrelizumab group (2.9% versus 1.6%).

Table 24: Serious Adverse Events Occurring in at Least 1% of Patients

Serious Adverse Events, n (%)	Placebo (N = 239)	Ocrelizumab (N = 486)
At least one SAE	53 (22.2)	99 (20.4)
Events by System Organ Class		
Infections and infestations	14 (5.9)	30 (6.2)
Injury, poisoning, and procedural complications	11 (4.6)	19 (3.9)
Nervous system disorders	9 (3.8)	18 (3.7)
Neoplasms (benign, malignant, and unspecified)	7 (2.9)	8 (1.6)
Gastrointestinal disorders	3 (1.3)	10 (2.1)
Musculoskeletal and connective tissue disorders	6 (2.5)	6 (1.2)
General disorders and administration site conditions	3 (1.3)	6 (1.2)
Renal and urinary disorders	3 (1.3)	5 (1.0)
Hepatobiliary disorders	2 (0.8)	4 (0.8)
Blood and lymphatic system disorders	1 (0.4)	4 (0.8)
Cardiac disorders	2 (0.8)	3 (0.6)
Respiratory, thoracic, and mediastinal disorders	2 (0.8)	3 (0.6)
Psychiatric disorders	0	4 (0.8)
Reproductive system and breast disorders	2 (0.8)	2 (0.4)
Vascular disorders	2 (0.8)	1 (0.2)
Metabolism and nutrition disorders	1 (0.4)	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.4)	1 (0.2)
Eye disorders	0	1 (0.2)
Immune system disorders	0	1 (0.2)
Events Occurring in at Least 1% of Patients		
Pneumonia	2 (0.8)	6 (1.2)
Multiple sclerosis relapse	2 (0.8)	5 (1.0)
Urinary tract infection	2 (0.8)	5 (1.0)
Infusion-related reaction	0	5 (1.0)
Urosepsis	3 (1.3)	2 (0.4)

n = number of patients with event; N = number of patients in the analysis; SAE = serious adverse events.

Source: Clinical Study Report for ORATORIO.[1]

Withdrawals Due to Adverse Events

AEs that led to withdrawal from the study treatment are summarized in Table 25. Overall, 20 patients (4.1%) withdrew from ocrelizumab treatment as a result of AEs, and eight patients (3.3%) withdrew from the placebo group. Cancers were the most frequently reported category of AE leading to discontinuation from the ocrelizumab group (seven patients [1.4%]) and it occurred at a greater frequency than in the placebo group (one patient [0.4%]). The proportion of patients who withdrew as a result of an infection was 0.8% in the ocrelizumab group compared with 1.3% in the placebo group. The proportion of

patients who withdrew as a result of an infusion-related reaction was the same in the placebo and ocrelizumab groups (0.4% in each). A greater proportion of ocrelizumab-treated patients experienced at least one AE that led to a modification or interruption of the study treatment compared with those who received placebo (9.7% [65 events] versus 5.0% [14 events]) (Table 32).

Table 25: Withdrawals Due to Adverse Events

WDAEs, n (%)	Placebo (N = 239)	Ocrelizumab (N = 486)
At least one WDAE	8 (3.3)	20 (4.1)
Neoplasms (benign, malignant, and unspecified)	1 (0.4)	7 (1.4)
Invasive ductal breast carcinoma	0	2 (0.4)
Adenocarcinoma of the cervix	1 (0.4)	0
Anaplastic large-cell lymphoma	0	1 (0.2)
Breast cancer	0	1 (0.2)
Endometrial cancer	0	1 (0.2)
Invasive breast carcinoma	0	1 (0.2)
Malignant fibrous histiocytoma	0	1 (0.2)
Infections and infestations	3 (1.3)	4 (0.8)
Arthritis (infective)	1 (0.4)	0
Hepatitis (viral)	1 (0.4)	0
Infectious colitis	0	1 (0.2)
Meningitis (aseptic)	1 (0.4)	0
Pneumonia	0	1 (0.2)
Urinary tract infection	0	1 (0.2)
Viral infection	0	1 (0.2)
Nervous system disorders	2 (0.8)	2 (0.4)
Multiple sclerosis relapse	2 (0.8)	1 (0.2)
Optic neuritis	0	1 (0.2)
Injury, poisoning, and procedural complications	1 (0.4)	2 (0.4)
Infusion-related reaction	1 (0.4)	2 (0.4)
Skin and subcutaneous tissue disorders	0	2 (0.4)
Alopecia	0	1 (0.2)
Skin lesion	0	1 (0.2)
Cardiac disorders	0	1 (0.2)
Aortic valve incompetence	0	1 (0.2)
Gastrointestinal disorders	0	1 (0.2)
Crohn's disease	0	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.4)	0
Rheumatoid arthritis	1 (0.4)	0
Psychiatric disorders	0	1 (0.2)
Depression	0	1 (0.2)

n = number of patients with event; N = number of patients in the analysis; WDAE = withdrawal due to adverse events.

Source: Clinical Study Report for ORATORIO.[1]

Mortality

There were five deaths during the double-blind phase of the ORATORIO study: four in the ocrelizumab group (pulmonary embolism, pancreatic metastatic carcinoma, desquamative pneumonia, and aspiration pneumonia) and one in the placebo group (traffic accident). The investigators reported that all of the deaths were considered to be unrelated to the study drug, but the sponsor reported deaths due to desquamative pneumonia and aspiration pneumonia as related to the study drug.[1]

Infusion-Related Reactions

Table 26 provides a summary of the frequency, severity, and timing of the infusion-related AEs reported in the ORATORIO trial. Infusion-related reactions were the most commonly reported AE in the ocrelizumab group (39.9%); these events occurred with a greater frequency than in the placebo group (25.5%). The most commonly reported symptoms associated with infusion-related AEs in the ocrelizumab group were pruritus, flushing, rash, pyrexia, headache, and throat irritation. Nearly all of the infusion-related AEs were mild or moderate in severity (98.8% in the ocrelizumab group and 98.3% in the placebo group were grade 1 or 2 events). Grade 3 infusion-related AEs were reported for six ocrelizumab-treated patients (1.2%) compared with four (1.7%) patients in the placebo group. There were no infusion-related AEs of grade 4 or grade 5 severity. The proportion of patients who withdrew as a result of an infusion-related reaction was 0.4% in both the placebo and ocrelizumab groups.

The proportion of patients who experienced infusion-related AEs tended to decrease throughout the trial. The first 300 mg dosage of ocrelizumab was associated with the highest proportions of patients with an infusion-related event (27.4%). This was reduced to 11.5% with the next dose (i.e., six months later), and subsequently reduced to ≤ 7.0% for the remaining infusions.

Table 26: Infusion-Related Adverse Events

Dose			Day 1		Day 15	
			Placebo (N = 244)	Ocrelizumab (N = 488)	Placebo (N = 244)	Ocrelizumab (N = 488)
Dose 1	n		239	486	235	477
	At least one IRR		29 (12.1%)	133 (27.4%)	14 (6.0%)	35 (7.3%)
	Total number of IRRs		29	133	14	35
	Grade	1 (mild)	22 (9.2%)	98 (20.2%)	11 (4.7%)	30 (6.3%)
		2 (moderate)	7 (2.9%)	31 (6.4%)	3 (1.3%)	4 (0.8%)
		3 (severe)	0	4 (0.8%)	0	1 (0.2%)
Dose 2	n		227	465	219	449
	At least one IRR		18 (7.9%)	54 (11.6%)	10 (4.6%)	23 (5.1%)
	Total number of IRRs		18	54	10	23
	Grade	1 (mild)	14 (6.2%)	39 (8.4%)	10 (4.6%)	22 (4.9%)
		2 (moderate)	3 (1.3%)	15 (3.2%)	0	1 (0.2%)
		3 (severe)	1 (0.4%)	0	0	0
Dose 3	n		216	452	210	437
	At least one IRR		13 (6.0%)	52 (11.5%)	10 (4.8%)	22 (5.0%)

Dose			Day 1		Day 15	
			Placebo (N = 244)	Ocrelizumab (N = 488)	Placebo (N = 244)	Ocrelizumab (N = 488)
	Total number of IRRs		13	52	10	22
	Grade	1 (mild)	9 (4.2%)	39 (8.6%)	7 (3.3%)	19 (4.3%)
		2 (moderate)	4 (1.9%)	13 (2.9%)	3 (1.4%)	3 (0.7%)
		3 (severe)	0	0	0	0
Dose 4	n		201	439	197	430
	At least one IRR		11 (5.5%)	29 (6.6%)	8 (4.1%)	13 (3.0%)
	Total number of IRRs		11	29	8	13
	Grade	1 (mild)	8 (4.0%)	26 (5.9%)	4 (2.0%)	12 (2.8%)
		2 (moderate)	3 (1.5%)	3 (0.7%)	2 (1.0%)	1 (0.2%)
		3 (severe)	0	0	2 (1.0%)	0
Dose 5	n		188	428	178	414
	At least one IRR		9 (4.8%)	30 (7.0%)	3 (1.7%)	19 (4.6%)
	Total number of IRRs		9	30	3	19
	Grade	1 (mild)	7 (3.7%)	23 (5.4%)	3 (1.7%)	13 (3.1%)
		2 (moderate)	2 (1.1%)	7 (1.6%)	0	6 (1.4%)
		3 (severe)	0	0	0	0
Dose 6	n		170	406	159	382
	At least one IRR		5 (2.9%)	27 (6.7%)	2 (1.3%)	15 (3.9%)
	Total number of IRRs		5	28	2	15
	Grade	1 (mild)	2 (1.2%)	21 (5.2%)	1 (0.6%)	13 (3.4%)
		2 (moderate)	3 (1.8%)	6 (1.5%)	0	2 (0.5%)
		3 (severe)	0	0	1 (0.6%)	0

IRR = infusion-related reaction; N = number of patients in the safety analysis.

Source: Clinical Study Report for ORATORIO.[1]

Serious Infections

Table 27 provides a summary of the categories of serious infections that were documented during the double-blind phase of the ORATORIO study. The proportion of patients who experienced at least one serious infection was 8.8% in the placebo group and 7.6% in the ocrelizumab group. Urinary tract infections and pneumonia were the most frequently reported serious infections in both the ocrelizumab and placebo groups (1.4% versus 1.7% and 1.2% versus 1.2%, respectively). When adjusted for exposure, the event rates for serious infections were 4.24 per 100 patient-years with placebo and 3.74 per 100 patient-years with ocrelizumab (rate ratio: 0.8818; 95% CI, 0.558 to 1.394).

Table 27: Serious Infections

Serious Infections, n (%)	Placebo (N = 244)	Ocrelizumab (N = 488)
At least one adverse event	21 (8.8)	37 (7.6)
Overall total number of events	28	53
Urinary tract infection	4 (1.7)	7 (1.4)
Pneumonia	3 (1.3)	6 (1.2)
Urosepsis	3 (1.3)	2 (0.4)
Cellulitis	1 (0.4)	3 (0.6)
Appendicitis	0	2 (0.4)
Bronchitis	0	2 (0.4)
Diverticulitis	0	2 (0.4)
Infectious colitis	1 (0.4)	1 (0.2)
Pyelonephritis	0	2 (0.4)
Abscess (limb)	0	1 (0.2)
Abscess (eyelid)	1 (0.4)	0
Appendicitis (perforated)	1 (0.4)	0
Arthritis (infective)	1 (0.4)	0
Bacterial pyelonephritis	0	1 (0.2)
Bronchopneumonia	0	1 (0.2)
Bursitis (infective)	0	1 (0.2)
Clostridium difficile infection	1 (0.4)	0
Cystitis	1 (0.4)	0
Erysipelas	0	1 (0.2)
Gastroenteritis	0	1 (0.2)
Gastroenteritis (viral)	0	1 (0.2)
Gastrointestinal infection	0	1 (0.2)
Hepatitis (viral)	1 (0.4)	0
Impetigo	0	1 (0.2)
Infected dermal cyst	0	1 (0.2)
Mastitis	0	1 (0.2)
Meningitis (aseptic)	1 (0.4)	0
Neutropenic sepsis	0	1 (0.2)
Pelvic inflammatory disease	1 (0.4)	0
Peritonitis	0	1 (0.2)
Post-procedural cellulitis	0	1 (0.2)
Pyelonephritis (acute)	0	1 (0.2)
Septic shock	1 (0.4)	0
Sinusitis	1 (0.4)	0
Skin infection	1 (0.4)	0
Viral infection	0	1 (0.2)
Viral pericarditis	0	1 (0.2)
Colitis (ischemic)	0	1 (0.2)
Enteritis	0	1 (0.2)
Bronchitis (chronic)	1 (0.4)	0
Pneumonia aspiration	0	1 (0.2)

N = total number of patients.
Source: Clinical Study Report for ORATORIO.[1]

Opportunistic Infections

Potential opportunistic infections were analyzed using a basket of terms, including upper respiratory tract infection, lower respiratory tract infection, herpes virus-associated infections, skin infections, urinary tract infections, sepsis, and sepsis/systemic inflammatory response. The manufacturer conducted a detailed medical review of all potential opportunistic infections (i.e., identification of the pathogen, location, and endemicity of the infection) and reported that none of the infections were considered opportunistic.

The overall proportion of patients with at least one potential opportunistic infection was slightly greater in the ocrelizumab group than in the placebo group (5.3% versus 3.8%). However, when adjusted for exposure, the overall rate of potential opportunistic infections was lower in the ocrelizumab group (2.33 per 100 patient-years) compared with the placebo group (3.03 per 100 patient-years). All of the events were mild to moderate in severity, with the exception of one serious event in the ocrelizumab group (neutropenic sepsis, which required hospitalization). The manufacturer reported that the majority of potential opportunistic infections were associated with the herpes virus and that oral herpes was more commonly reported in the ocrelizumab group compared with the placebo group (2.3% versus 0.4%).

Malignancies

Malignancies were reported in a greater proportion of ocrelizumab-treated patients (11 patients [2.3%]; 13 events) compared with the placebo group (two patients [0.8%]; two events). The rate of malignancy was 0.92 per 100 patient-years (95% CI, 0.49 to 1.57) in the ocrelizumab group and 0.30 per 100 patient-years (95% CI, 0.04 to 1.10) in the placebo group. The most commonly reported malignancies included breast cancer in women (four ocrelizumab-treated patients and no placebo-treated patients) and basal cell carcinoma (three ocrelizumab-treated patients and one placebo-treated patient). Events of basal cell carcinoma were not classified as SAEs; hence, the proportion of ocrelizumab-treated patients with malignancies (2.3%) is greater than the proportion of patients who experienced an SAE that was classified as a neoplasm (1.6%).

Discussion

Summary of Available Evidence

The CADTH systematic review included one multi-centre, parallel-group, double-blind, placebo-controlled RCT (ORATORIO; N = 732). Patients were randomized (2:1) to receive ocrelizumab 600 mg IV every six months (as two 300 mg infusions 14 days apart) or matching placebo. The study evaluated clinical end points (e.g., CDP), MRI end points (e.g., changes in T1 and T2 lesions), walking ability (e.g., T25FW), and patient-reported end points (e.g., SF-36 PCS and SF-36 MCS). The controlled phase of the ORATORIO trial was 120 weeks in duration, with study participants eligible to enroll in an open-label extension following completion; therefore, CADTH also summarized the available data from the manufacturer's extended trial which provides additional uncontrolled efficacy and safety data for an additional six months. Ocrelizumab is the first treatment approved in Canada for the treatment of PPMS; therefore, there were no direct or indirect comparisons against active treatments submitted or considered in this CADTH review.

Key limitations with the ORATORIO trial included the following: sensitivity of the results for 12-week CDP (primary end point), 24-week CDP (secondary end point), and T25FW to different methods and assumptions regarding the imputation of missing data; the unplanned increase in sample size (i.e., from 630 to 732); the large and disproportionate rate of withdrawal across the study (i.e., 33.6% and 20.7% in the placebo and ocrelizumab groups, respectively); the potential for unblinding due to the AE profile of ocrelizumab (particularly events related to the administration of the study drug); and the need to impute a large amount of the data for some end points (e.g., SF-36 and changes in lesions). Generalizability of the results may be limited by the exclusion of patients older than 55 years of age and those with an EDSS score above 6.5; the uncertainty regarding the proportion of Canadian PPMS patients who would have evidence of active inflammation in the brain and/or spinal cord; and the extensive contact with health professionals during the study.

Interpretation of Results

Efficacy

Disability progression is an important clinical outcome and of major importance to MS patients. In the ORATORIO trial, treatment with ocrelizumab was shown to be statistically superior to placebo for reducing the hazard for experiencing CDP for at least 12 weeks and 24 weeks compared with placebo (hazard ratio: 0.76 [95% CI, 0.59 to 0.98] and 0.75 [95% CI, 0.58 to 0.98], respectively).[1] Sensitivity analyses demonstrated that the statistical significance of the reduction in CDP was susceptible to the methods and assumptions used for imputing missing data.[1] Specifically, the manufacturer's pre-specified sensitivity analyses, which did not count patients with initial progression events who discontinued prior to having a confirmation visit as having CDP, failed to demonstrate statistical significance for 12-week and 24-week CDP. The manufacturer reported that the approach used for handling missing data in the ORATORIO trial was appropriate, because of the high rates of disability confirmation that have been reported for PPMS patients who experience an initial event (i.e., 80%).[27,33] The FDA investigated this assumption in detail and reported that the statistical significance of the primary outcome was a valid representation of the observed treatment effect in the ORATORIO trial.[18]

There is no accepted MCID for CDP in PPMS patients.[9] The clinical expert consulted by CADTH suggested that the 24% and 25% reductions in 12-week and 24-week CDP were clinically relevant. The EMA noted that the effect of ocrelizumab on 12-week and 24-week CDP was modest and that the absolute difference in the proportion of patients with 12-week CDP was approximately 4% (number needed to treat of 25) based on Kaplan–Meier estimates at 120 weeks. However, the EMA concluded that the effect was clinically relevant in the context of a progressive illness where there are no alternative treatment options.[9] Patient group input has indicated that there is an unmet need for therapeutic options for PPMS; at least one of the FDA reviewers, who had concerns regarding the efficacy data from the ORATORIO trial, cited unmet therapeutic need as an important factor for recommending that ocrelizumab be approved for use in PPMS patients.[16]

Notwithstanding the limitations of the subgroup analyses in the ORATORIO trial (e.g., non-powered analyses excluded from the statistical analysis hierarchy), the effect of ocrelizumab might be greater in patients who are younger (i.e., less than 45 years of age) and those with active inflammation, based on the presence of Gd-enhancing lesions at baseline.[1] Similar subgroup results were reported in a phase II/III study (OLYMPUS) investigating the use of rituximab in patients with PPMS where the results for 12-week CDP were not statistically significant for the overall trial population, but were significant in a subgroup of younger patients (i.e., < 51 years of age (hazard ratio: 0.52; $P = 0.010$) and those with Gd-enhancing lesions (hazard ratio: 0.41; $P = 0.007$).[9,28] It has been suggested that these findings could be an indication that immunomodulatory treatments are more effective in the early stages of PPMS.[28,34] The PPMS indication for ocrelizumab that was approved by Health Canada and the EMA specifies that the use of ocrelizumab be limited to patients with early PPMS (in terms of disease duration and level of disability), and with imaging features characteristic of inflammatory activity.[9,35] This is more restricted than the indications that were approved by regulatory authorities in the US, Australia, and Switzerland, all of whom issued indications that were not limited by disease duration or inflammatory activity.[18,32,36]

The clinical expert consulted by CADTH indicated that identifying PPMS patients with active inflammation could be challenging and costly in routine Canadian clinical practice. It was noted that there are not necessarily signs or symptoms that can be used to identify patients with active inflammation in clinical practice; therefore, MRIs would likely be required to evaluate the presence of Gd-enhancing lesions or new or enlarging T2 lesions in the brain and spinal cord. Furthermore, the development of inflammation in PPMS is unpredictable and there are currently no guidelines for determining how frequently a patient with PPMS should be monitored for active inflammation (e.g., only at the time of diagnosis or at regular intervals to capture changes in inflammatory activity). In addition, it was noted that evidence is emerging that Gd can accumulate in the CNS; the potential clinical impact of this accumulation is uncertain.[37] The clinical expert noted that the potential for the accumulation of Gd is beginning to influence clinical practice and may reduce the number of MRIs performed to identify Gd-enhancing lesions.

Similar to the results for disability progression, the results for the T25FW test were sensitive to the method of imputation that was used to handle missing values. Sensitivity analyses conducted by the FDA demonstrated that changes in the imputation method resulted in the results being non-significant. Both the FDA and EMA questioned the clinical relevance of the results for the T25FW, noting the small absolute differences between the ocrelizumab and placebo groups. The mean absolute difference was approximately three seconds, which is reduced to 0.43 seconds when analyzed using unadjusted median values (noted

by the EMA as a more reliable estimate due to the skewed distribution of the T25FW data).[9] A reviewer for the FDA stated that the absolute change in the T25FW observed in the ORATORIO trial was less than the 20% change that is typically cited as being clinically important for this end point.[1]

The clinical expert consulted by CADTH noted that the reduced deterioration in walking with ocrelizumab may be clinically relevant for a subset of PPMS patients — particularly younger patients, for whom delayed deterioration in walking could have an important impact on their ability maintain employment. The clinical expert also indicated that walking ability is seldom evaluated using the T25FW in Canadian clinical practice. It was noted that the ability of MS clinics to perform such evaluations is limited by practical considerations, such as the time and space required to complete the evaluation. In its input for this review, the MS Society highlighted the importance of mobility in preserving the independence and well-being of MS patients. The clinical expert consulted by CADTH also indicated that, based on clinical observation, a treatment that is able to delay deterioration in walking ability is meaningful to patients.

The SF-36 was used in ORATORIO to measure the clinical benefits of ocrelizumab on HRQoL. There was no statistically significant difference between ocrelizumab and placebo for the SF-36 PCS, a pre-specified secondary end point of the pivotal trial. However, there was an improvement in the SF-36 MCS (LSMD: 3.318 [95% CI, 1.414 to 5.221]), which slightly exceeds the published MCID of 3.0, though the 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 was 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." Therefore, there remains uncertainty regarding the comparative effects of ocrelizumab on HRQoL and other patient-reported outcomes. There was no difference between the ocrelizumab and placebo groups for change from baseline in the MSFC (LSMD: 0.086 [95% CI, –0.051 to 0.222]); however, this was an exploratory end point in the ORATORIO trial.

Ocrelizumab was shown to be superior to placebo for the following MRI end points: volume of T2 lesions, new and enlarging T2 hyperintense lesion count, Gd-enhancing lesion count, and brain volume. There was a considerable amount of missing data for these outcome measures. For example, data for change in brain volume were missing for approximately 35% of randomized patients (i.e., the ITT population) by week 120. These are conventional MRI outcomes that are widely used to monitor treatment effects in clinical trials of MS. Their roles as surrogates for clinical outcomes, such as relapses and disability progression in RRMS, have been investigated in previous research, but inconsistent conclusions were drawn. The clinical expert consulted by CADTH indicated that the clinical relevance of these results is uncertain, but it is likely that reducing the number of lesions in the CNS and minimizing brain atrophy would potentially be associated with improvements in clinical end points.

The protocol for the ORATORIO study excluded patients who were older than the age of 55 years and those with an EDSS score greater than 6.5; therefore, there is uncertainty regarding the safety and efficacy of ocrelizumab in these patients. The manufacturer is planning to conduct a five-year, multi-centre, phase IIIb, double-blind, placebo-controlled RCT to evaluate the efficacy and safety of ocrelizumab in PPMS patients with more advance disease (described by the manufacturer as "later in their disease course").[9] The study protocol would target PPMS patients between 55 and 65 years of age and those with

greater burden of disability (EDSS 6.5 to 8).[9] This trial has not been initiated at the time of this review. It is estimated that the study will be completed in 2024.[9]

The extended controlled treatment period of ORATORIO provided additional efficacy data for up to six months of treatment prior to patients receiving their first open-label dose of ocrelizumab in the open-label extension trial. There were no safety data presented. The efficacy data, though similar to the primary analysis, were limited by the open-label administration of study treatments and incomplete reporting of results.

Harms

The mechanism of action for ocrelizumab involves the depletion of B-cells, which can increase the risk of AEs that are associated with decreased function of the immune system. Patients treated with ocrelizumab, an immunomodulator, may be at an increased risk of developing infections. In the ORATORIO trial, serious infections were reported at a similar frequency in the ocrelizumab and placebo groups. Previous studies in RRMS patients demonstrated that ocrelizumab was associated with numerically fewer serious infections compared with the interferon beta-1a groups.

PML is a serious condition that can develop in patients with reduced immune function as a result of infection by the John Cunningham virus. There were no events of PML in the pivotal studies for ocrelizumab (ORATORIO, OPERA-I, and OPERA-II); however, the Canadian product monograph for ocrelizumab contains a warning about this potential risk.[13] The product monograph recommends that patients should be monitored for early signs and symptoms of PML, noting these can seem 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. A case of PML has been reported for a patient who was treated with ocrelizumab; however, this patient had also received prior treatment with natalizumab for three years.[9] The clinical expert consulted by CADTH noted that specialized monitoring for PML would not likely occur for patients treated with ocrelizumab the way that it does for those treated with natalizumab.

Ocrelizumab is associated with infusion-related reactions, which were the most commonly reported AEs in both the ORATORIO study and the pivotal trials for the RRMS population (OPERA-I and OPERA-II). 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 that were used in the pivotal study. Similarly, the recommendations for pre-medication and dosage adjustment (i.e., slowing, interrupting, or stopping the infusion) in the product for the management of reactions are also consistent with the protocols that were used in the ORATORIO study protocol. This suggests that the infusion-related AEs observed in the pivotal trials would be similar to those observed in clinical practice. The clinical expert consulted by CADTH suggested that the infusion-related AEs associated with ocrelizumab are similar to those observed with other DMTs that require IV administration.

The Canadian product monograph for ocrelizumab states that an increased risk of malignancy may exist with ocrelizumab. In the ORATORIO trial, malignancies were reported in a numerically greater proportion of ocrelizumab-treated patients relative to the placebo group (11/488 [2.3%]) versus 2/244 [0.8%]). The proportion of ocrelizumab-treated patients with malignancies in the OPERA-I and OPERA-II trials was 0.5% (4/825). It is uncertain why the rate of malignancies was greater in the ORATORIO trial compared with the OPERA trials; however, the later age of onset for PPMS could be a contributing factor (i.e., the PPMS study population was older than the RRMS study population [mean ages of approximately 45 and 37 years, respectively]). Nevertheless, pooled data across the PPMS and RRMS populations are reported in the product monograph, which highlights that breast cancer was reported more frequently in women who received treatment with ocrelizumab (6/781 [0.76%]) compared with placebo or interferon beta 1a (0/668 [0%]) and states that patients should follow standard breast cancer screening guidelines. The clinical expert suggested that MS patients with a history of cancer would be consulted regarding the potential risks of ocrelizumab prior to initiating therapy.

Overall, safety data reported for ocrelizumab in PPMS patients are similar to what was previously submitted and reviewed for use in RRMS patients (i.e., the OPERA-I and OPERA-II trials). The clinical expert consulted by CADTH indicated that the AE profile for ocrelizumab is consistent with other available MS treatments (i.e., those that are currently used in the management of RRMS). The expert noted that patients are generally willing to accept the risks associated with various MS treatments in exchange for the potential benefits of slowing disability progression (most notably the ability to avoid the need for a wheelchair).

The manufacturer is currently conducting a long-term extension phase of the ORATORIO trial (estimated completion in 2021)[19] and is also planning to conduct a 10-year long-term study to further evaluate the safety of ocrelizumab in MS patients.[9] These studies will provide insight into the longer-term safety of ocrelizumab in MS patients.

Potential Place in Therapy[2]

Prior to the approval of ocrelizumab, there were no approved DMTs for PPMS; therefore, there is an unmet need for these patients. This is reflected in the patient group input provided for this submission, in which patients articulated the desperation they feel living with a progressively disabling illness that has no available treatments. The clinical expert consulted by CADTH suggested that ocrelizumab may fulfill some of these patients' unmet needs.

Ocrelizumab will be most effective in the younger and less disabled PPMS patient population as well as, ideally, those who show some inflammatory activity. (The question remains as to whether those patients truly have PPMS or fall into the category of "active and with progression," which would require both clinical and/or radiological confirmation.) The latter would increase the need to perform MRIs in an effort to identify patients with active inflammation and monitor the inflammation over time.

It is likely that many severely disabled patients (EDSS > 6.5), older patients, and patients with a longer duration of PPMS will want to be treated with ocrelizumab in hopes of limiting or stopping progression of the disease. However, the ORATORIO trial does not provide sufficient evidence to support the efficacy of ocrelizumab in such patients.

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

Older patients and those with a strong family history of cancer may not be good candidates for ocrelizumab, given the possibility of increased cancer risk. An informed discussion would be needed between the patient and prescriber.

Conclusions

One double-blind, phase III RCT (ORATORIO) demonstrated that ocrelizumab was superior to placebo for reducing the risk of disability progression at three and six months. While the results were sensitive to the choice of analytical approach, the observed effect was considered to be clinically relevant by regulatory authorities and the clinical expert consulted by CADTH. Further, notwithstanding the limitations of the subgroup analyses in the ORATORIO trial, the effect of ocrelizumab versus placebo might be greater in patients who are younger (i.e., less than 45 years of age) and those with active inflammation, based on the presence of Gd-enhancing lesions at baseline — as reflected in the indication approved by Health Canada, which is limited to patients with early disease who have evidence of active inflammation. Treatment with ocrelizumab was associated with a statistically significant reduction in the deterioration of T25FW times compared with placebo. The absolute difference between the ocrelizumab and placebo groups was small (mean difference of approximately three seconds); however, the clinical expert consulted by CADTH suggested that the results could be meaningful for a subset of PPMS patients. There is uncertainty as to the effects of ocrelizumab on HRQoL and other patient-reported outcomes.

The proportion of patients with AEs that were categorized as serious or led to discontinuation from the study treatments was generally similar between the ocrelizumab and placebo groups. Infusion-related reactions were the most commonly reported AE in the ORATORIO study and occurred at a greater frequency in the ocrelizumab group. Similar to the RRMS studies on ocrelizumab, nearly all of the infusion-related AEs in PPMS patients were mild or moderate in severity; the proportion of ocrelizumab-treated patients who experienced infusion-related reactions tended to decrease over the course of the trial. Malignancies were reported in a greater proportion of ocrelizumab-treated patients compared with placebo-treated patients. Overall, the clinical expert consulted by CADTH indicated that the AE profile for ocrelizumab is consistent with other available MS treatments, and that PPMS patients would generally be willing to accept the risks of treatment in exchange for the potential benefits of slowing disability progression. The longer-term safety of ocrelizumab is being further evaluated in an open-label extension phase of the ORATORIO trial and an additional planned post-marketing safety study.

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 Supplying Input

The Multiple Sclerosis Society of Canada (MS Society) provides services to people with multiple sclerosis (MS) and their families and caregivers. It also funds research to find the cause and a cure for the disease. Its mission is to be a leader in finding a cure for MS and enabling people affected by MS to enhance their QoL. Since 1948, the MS Society has contributed more than $140 million to MS research. This investment has enabled the advancement of critical knowledge of MS and the development of a pipeline of exceptional MS researchers.

The MS Society did not receive external help in the completion of its patient input submission to CADTH, nor in the collection or analysis of the data provided in this submission. The MS Society has received funding from a number of pharmaceutical companies, including: Roche, Bayer, Biogen, EMD Serono, Novartis, Pfizer, Genzyme, Allergan and Teva Neuroscience.

2. Condition-Related Information

In 2017, the MS Society of Canada launched an online survey by posting it in French and English on its Facebook page and on the main page of its national website, www.mssociety.ca. The goal was to acquire qualitative data on QoL and personal experiences with progressive MS. The survey regarding the use of ocrelizumab to treat primary progressive MS (PPMS) was posted October 18, 2017 and closed on November 8, 2017. In total, 358 responses were received, 90% of which were from respondents who identified themselves as living with MS; the remaining 10% of responses were from caregivers. Respondents' ages ranged from 25 years to older than 65 years of age, with the 45 years to 64 years of age range representing the majority of respondents (n = 208). Based on the responses, participants appeared to be from Canada, although the survey did not explicitly request this information. Among respondents, 186 identified themselves as having been diagnosed with PPMS. Those who reported a diagnosis other than PPMS were not prompted to complete the full survey.

PPMS is a devastating disease affecting approximately 15% of MS patients. The remaining 85% experience relapsing remitting multiple sclerosis (RRMS). PPMS differs from RRMS in that it affects both sexes equally, is usually diagnosed after the age of 40 (almost never in childhood), and tends to result in more lesions on the spinal cord. This less-common form of MS is characterized by continuous worsening of disease. Patients with PPMS are more likely to require a wheelchair and experience significant neurological disability. Symptoms include fatigue, cognitive impairment, weakness, spasticity, tremor, poor coordination, bladder and bowel problems, sexual dysfunction, depression, pain, dizziness, visual issues, and issues with speech and swallowing.

PPMS patients report losing the ability to participate in normal pursuits, including physical activities, social engagement, and employment. Over the course of their disease, they increasingly lose physical strength, the ability to live independently, and the capacity to participate in the outside world. Patients described themselves as being "a slave to this disease" and as having lost their "independence," "dignity," and "identity." One patient said: "I have gone from being very independent, having mobility, and being able to get around to having no mobility and having to rely on family and caregivers 24/7."

3. Current Therapy-Related Information

At present, there are no available disease-modifying therapies (DMTs) in Canada for patients with PPMS. All available DMTs for MS target the relapsing remitting form of the disease, and none has shown therapeutic benefit in the primary progressive form. About 20% of survey respondents with PPMS did say they had received DMTs indicated for RRMS. The majority did not feel that the medication had been beneficial.

Current treatment options and therapies for PPMS aim to control symptoms rather than to modify the course of the disease. These treatments include fampridine (indicated for walking improvement) and in rare cases, immunotherapy drugs, such as mitoxantrone and cyclophosphamide. Medications for symptom management are combined with complementary and alternative therapies, as well as many non-medicinal therapies and techniques, such as physiotherapy, physical activity, and rehabilitation. In light of the deteriorative nature of their condition, patients expressed frustration at the absence of available DMTs for PPMS, and believe that "all therapies that show even a little promise need to be made available to patients."

4. Expectations About the Drug Being Reviewed

There are no DMTs currently available to Canadian PPMS patients. As such, there is a significant unmet need in Canada. Ocrelizumab is the first and only drug to show therapeutic benefit in the treatment of PPMS. However, only 21 respondents had been informed about ocrelizumab by their health care provider as a future treatment for their disease; 121 respondents had not been informed. Those who had knowledge of ocrelizumab thought it had been recommended because "it is the only treatment for primary progressive MS" and it would "help slow the disease progression." Of the 175 patients who responded to questions about drug side effects and adverse events, 103 were willing to trade the risks associated with the treatment for the perceived benefit of the drug. Those who were unwilling or uncertain cited concerns about side effects or lack of long-term safety data.

Three survey respondents reported experience with ocrelizumab through a clinical trial. Among them, one patient felt that ocrelizumab had improved their condition: "This drug has brought improvements to my quality of life. I see hope, finally." The other two had not yet perceived an improvement. One patient experienced side effects from ocrelizumab treatment that included nausea, fatigue, headaches, and pruritis. The other two patients did not report side effects. Treatment-related challenges and concerns identified by patients included the need to travel to an infusion clinic, the high treatment cost or lack of coverage by drug plans, side effects, and a lack of long-term safety data.

While knowledge of and experience with ocrelizumab are limited in the Canadian population surveyed, the impression from this patient input submission is that patients with PPMS have few, if any, effective treatments available. Generally, they are looking for any option that may have a disease-modifying effect on their condition. The following quote summarizes both the impact of PPMS on patients and their hope for an effective treatment:

> *"I have been living with the effects of PPMS since 2000. Both legs and one arm are totally useless, while the other arm is losing function. I do not have the strength to keep my body upright while sitting and my vision gets blurrier each year. I do not have the strength in my chest muscles to cough or blow my nose in order to expel anything. There has been no disease-modifying drug available to me during all this time. If this drug has the potential to slow down or even stop the progression of this ugly, insidious disease, then all who suffer from it must be given the opportunity to have it."*

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 23, 2017
Alerts:	Bi-weekly search updates until March 21, 2018
Study Types:	No search filters were applied
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
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kw	Keyword
.kf	Author supplied keyword
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; MEDLINE ALL
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Search Strategy	
#	**Searches**
1	(ocrevus* or ocrelizumab* or PR070769 or PR0-70769 or "PR 070769" 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 medall
3	*ocrelizumab/
4	(ocrevus* or ocrelizumab* or PR070769 or PR0-70769 or "PR 070769" 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
8	7 not conference abstract.pt.
9	remove duplicates from 8

OTHER DATABASES		
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	Search current to November 20, 2017
Keywords:	ocrevus or ocrelizumab or PR070769 or PR0-70769 or "PR 070769" or R1594 or R-1594 or PRO70769 or PRO-70769
Limits:	No date or language limits used

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

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

Appendix 3: Detailed Outcome Data

Table 28: Prior Exposure to Treatments for Multiple Sclerosis

Treatments, N (%)	Placebo (N = 244)	Ocrelizumab (N = 488)
At least one treatment	82 (34.3)	160 (32.9)
Corticosteroids	44 (18.4)	87 (17.9)
Cytokines	23 (9.6)	36 (7.4)
Interferon beta-1a	15 (6.3)	21 (4.3)
Interferon beta-1b	9 (3.8)	17 (3.5)
Immunomodulators	10 (4.2)	22 (4.5)
Glatiramer acetate	10 (4.2)	22 (4.5)
Muscle relaxants	7 (2.9)	11 (2.3)
Anticonvulsants	5 (2.1)	9 (1.9)
Miscellaneous neurological drugs	6 (2.5)	3 (0.6)
Dalfampridine	1 (0.4)	2 (0.4)
Fampridine	1 (0.2)	2 (0.8)
Botulinum toxin NOS	2 (0.8)	0
Botulinum toxin type A	1 (0.4)	0
Antispasmodics and anticholinergics	1 (0.4)	4 (0.8)
Benzodiazepines	1 (0.4)	4 (0.8)
Peripheral and cerebral vascular drugs	1 (0.4)	4 (0.8)
Surgical and medical procedures	1 (0.4)	4 (0.8)
Alpha-adrenoreceptor antagonists	2 (0.8)	2 (0.4)
Opioid analgesics	1 (0.4)	3 (0.6)
Dopaminergic drugs	0	3 (0.6)
Immunosuppressants	1 (0.4)	2 (0.4)
Analgesics	0	2 (0.4)
Investigations	1 (0.4)	1 (0.2)
NSAIDS	0	2 (0.4)
SSRIs	1 (0.4)	1 (0.2)
Vaccines, toxoids, and serologic drugs	0	2 (0.4)
Vitamins and minerals	0	2 (0.4)
Anorexiants and CNS stimulants	1 (0.4)	0
Anxiolytics	0	1 (0.2)
Botanicals	0	1 (0.2)
Serenoa repens (saw palmetto)	0	1 (0.2)
Cannabinoids	1 (0.4)	0
Miscellaneous drugs	0	1 (0.2)
Miscellaneous urologicals	0	1 (0.2)
Monoclonal antibodies	0	1 (0.2)
Natalizumab	0	1 (0.2)

Treatments, N (%)	Placebo (N = 244)	Ocrelizumab (N = 488)
Nitrofurans	0	1 (0.2)
Opioid antagonists	0	1 (0.2)
Parasympathomimetics and antimyasthenics	1 (0.4)	0
Proton pump inhibitors	1 (0.4)	0
Salicylates	1 (0.4)	0
Supplements	0	1 (0.2)
Tricyclic antidepressants	0	1 (0.2)

CNS = central nervous system; NOS = not otherwise specified; SSRI = selective serotonin reuptake inhibitor.

Source: Clinical Study Report.[1]

Table 29: Subgroup Analyses for Confirmed Disability Progression

Characteristics (at Baseline)	Subgroup	N (Events)		HR (95% CI)	*P* values	
		Placebo	Ocrelizumab		Log-Rank	Interaction Test[a]
12-Week CDP						
Age	≤ 45 years	118 (96)	230 (160)	0.64 (0.45 to 0.92)	0.0160	0.2278
	> 45 years	120 (47)	237 (89)	0.88 (0.62 to 1.26)	0.4924	
EDSS	≤ 5.5	163 (61)	348 (100)	0.73 (0.53 to 1.00)	0.0512	0.6577
	> 5.5	81 (35)	139 (60)	0.84 (0.55 to 1.28)	0.4187	
GdE lesion(s)	Yes	60 (27)	133 (43)	0.65 (0.40 to 1.06)	0.0803	0.2076
	No	183 (68)	350 (115)	0.84 (0.62 to 1.13)	0.2425	
24-Week CDP						
Age	≤ 45 years	118 (46)	230 (65)	0.61 (0.42 to 0.90)	0.0105	0.1558
	> 45 years	126 (41)	257 (79)	0.92 (0.63 to 1.34)	0.6468	
EDSS	≤ 5.5	163 (55)	348 (90)	0.73 (0.52 to 1.03)	0.0682	0.7183
	> 5.5	81 (32)	139 (54)	0.84 (0.54 to 1.31)	0.4313	
GdE lesion(s)	Yes	60 (23)	133 (39)	0.67 (0.40 to 1.14)	0.1391	0.3518
	No	183 (63)	350 (103)	0.81 (0.59 to 1.10)	0.1765	
	≥ 25	118 (46)	230 (65)	0.86 (0.57 to 1.31)	0.4862	

CDP = confirmed disability progression; CI = confidence interval; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; HR = hazard ratio.

[a] The manufacturer considered subgroup interaction *P* values below 0.1 to be statistically significant; below 0.2 to represent a "trend;" and those between 0.2 and 0.3 to represent a "weak trend."

Source: Clinical Study Report for ORATORIO.[1]

Table 30: Detailed Results for Timed 25-Foot Walk

Visit	Parameter	Placebo (N = 244)		Ocrelizumab (N = 488)	
		Value at Visit	Change from BL	Value at Visit	Change from BL
Baseline	n	244	NA	488	NA
	Mean (SD)	12.94 (15.51)		14.83 (21.17)	
	Median	7.38		7.75	
Week 48	n	218	218	450	450
	Mean (SD)	20.47 (38.47)	7.76 (30.56)	17.06 (26.04)	2.59 (22.60)
	Median	8.00	0.55	8.30	0.20
Week 96	n	190	190	419	419
	Mean (SD)	22.73 (39.39)	10.48 (34.71)	22.12 (36.52)	7.97 (33.55)
	Median	8.75	1.10	8.95	0.60
Week 120	n	174	174	397	397
	Mean (SD)	24.32 (43.32)	11.76 (36.45)	22.62 (37.74)	8.79 (34.52)
	Median	9.53	1.23	8.80	0.80

BL = baseline; NA = not applicable; SD = standard deviation.

Source: Clinical Study Report for ORATORIO.[1]

Table 31: FDA Sensitivity Analysis for 12-Week Confirmed Disability Progression

Descriptive Statistics of 500 *P* values	*P* value
Mean	0.050
Minimum	0.0177
Maximum	0.0931
90% range	0.0256 to 0.0707

Source: Reproduced from FDA Summary Report.[18]

Table 32: Adverse Events Leading to Dose Modification or Interruption

Adverse Events Leading to Dose Modification or Interruption, n (%)	Placebo (N = 244)	Ocrelizumab (N = 488)
At least one adverse event leading to dose modification/interruption	12 (5.0)	47 (9.7)
Overall total number of events	14	65
Infections and infestations	6 (2.5)	24 (4.9)
Urinary tract infection	2 (0.8)	7 (1.4)
Nasopharyngitis	0	5 (1.0)
Upper respiratory tract infection	1 (0.4)	3 (0.6)
Bronchitis	0	2 (0.4)
Influenza	0	2 (0.4)
Clostridium difficile colitis	0	1 (0.2)
Conjunctivitis	0	1 (0.2)
Cystitis	0	1 (0.2)
Erysipelas	0	1 (0.2)
Gastroenteritis	0	1 (0.2)
Herpes simplex	1 (0.4)	0
Herpes zoster	1 (0.4)	0

Adverse Events Leading to Dose Modification or Interruption, n (%)	Placebo (N = 244)	Ocrelizumab (N = 488)
Pharyngitis	1 (0.4)	0
Respiratory tract infection	0	1 (0.2)
Tracheitis	0	1 (0.2)
Investigations	0	8 (1.6)
Alanine aminotransferase increase	0	3 (0.6)
Amylase increase	0	1 (0.2)
Aspartate aminotransferase increase	0	1 (0.2)
Blood creatinine increase	0	1 (0.2)
Blood test abnormal	0	1 (0.2)
Blood urea increase	0	1 (0.2)
Gamma-glutamyltransferase abnormal	0	1 (0.2)
Lipase increase	0	1 (0.2)
Liver function test abnormal	0	1 (0.2)
Injury, poisoning, and procedural complications	1 (0.4)	6 (1.2)
Infusion-related reaction	1 (0.4)	5 (1.0)
Subdural hematoma	0	1 (0.2)
General disorders and administration site conditions	1 (0.4)	2 (0.4)
Injection-site extravasation	0	1 (0.2)
Malaise	1 (0.4)	0
Edema peripheral	0	1 (0.2)
Musculoskeletal and connective tissue disorders	0	3 (0.6)
Back pain	0	1 (0.2)
Muscular weakness	0	1 (0.2)
Musculoskeletal pain	0	1 (0.2)
Pain in extremity	0	1 (0.2)
Cardiac disorders	1 (0.4)	1 (0.2)
Bradycardia	0	1 (0.2)
Tachycardia	1 (0.4)	0
Endocrine disorders	1 (0.4)	1 (0.2)
Hyperprolactinemia	0	1 (0.2)
Hyperthyroidism	1 (0.4)	0
Hepatobiliary disorders	2 (0.8)	0
Drug-induced liver injury	1 (0.4)	0
Hepatic function abnormal	1 (0.4)	0
Neoplasms (benign, malignant, and unspecified)	0	2 (0.4)
Basal cell carcinoma	0	1 (0.2)
Uterine leiomyoma	0	1 (0.2)
Psychiatric disorders	0	2 (0.4)
Abnormal behaviour	0	1 (0.2)
Mood disorder due to a general medical condition	0	1 (0.2)
Blood and lymphatic system disorders	0	1 (0.2)
Microcytic anemia	0	1 (0.2)
Eye disorders	0	1 (0.2)
Eye pain	0	1 (0.2)
Gastrointestinal disorders	0	1 (0.2)
Pancreatitis (acute)	0	1 (0.2)

Adverse Events Leading to Dose Modification or Interruption, n (%)	Placebo (N = 244)	Ocrelizumab (N = 488)
Nervous system disorders	0	1 (0.2)
Sciatica	0	1 (0.2)
Renal and urinary disorders	0	1 (0.2)
Calculus urinary	0	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	1 (0.4)	0
Bronchitis (chronic)	1 (0.4)	0
Vascular disorders	0	1 (0.2)
Dry gangrene	0	1 (0.2)
Peripheral arterial occlusive disease	0	1 (0.2)

Source: Clinical Study Report for ORATORIO.[1]

Table 33: Infusion-Related Adverse Events

Dose			Day 1		Day 15	
			Placebo (N = 244)	Ocrelizumab (N = 488)	Placebo (N = 244)	Ocrelizumab (N = 488)
Dose 1	n		239	486	235	477
	At least one IRR		29 (12.1%)	133 (27.4%)	14 (6.0%)	35 (7.3%)
	Total number of IRRs		29	133	14	35
	Grade	1	22 (9.2%)	98 (20.2%)	11 (4.7%)	30 (6.3%)
		2	7 (2.9%)	31 (6.4%)	3 (1.3%)	4 (0.8%)
		3	0	4 (0.8%)	0	1 (0.2%)
		4	0	0	0	0
		5	0	0	0	0
Dose 2	n		227	465	219	449
	At least one IRR		18 (7.9%)	54 (11.6%)	10 (4.6%)	23 (5.1%)
	Total number of IRRs		18	54	10	23
	Grade	1	14 (6.2%)	39 (8.4%)	10 (4.6%)	22 (4.9%)
		2	3 (1.3%)	15 (3.2%)	0	1 (0.2%)
		3	1 (0.4%)	0	0	0
		4	0	0	0	0
		5	0	0	0	0
Dose 3	n		216	452	210	437
	At least one IRR		13 (6.0%)	52 (11.5%)	10 (4.8%)	22 (5.0%)
	Total number of IRRs		13	52	10	22
	Grade	1	9 (4.2%)	39 (8.6%)	7 (3.3%)	19 (4.3%)
		2	4 (1.9%)	13 (2.9%)	3 (1.4%)	3 (0.7%)
		3	0	0	0	0
		4	0	0	0	0
		5	0	0	0	0
Dose 4	n		201	439	197	430
	At least one IRR		11 (5.5%)	29 (6.6%)	8 (4.1%)	13 (3.0%)
	Total number of IRRs		11	29	8	13
	Grade	1	8 (4.0%)	26 (5.9%)	4 (2.0%)	12 (2.8%)
		2	3 (1.5%)	3 (0.7%)	2 (1.0%)	1 (0.2%)
		3	0	0	2 (1.0%)	0

Dose			Day 1		Day 15	
			Placebo (N = 244)	Ocrelizumab (N = 488)	Placebo (N = 244)	Ocrelizumab (N = 488)
		4	0	0	0	0
		5	0	0	0	0
Dose 5	n		188	428	178	414
	At least one IRR		9 (4.8%)	30 (7.0%)	3 (1.7%)	19 (4.6%)
	Total number of IRRs		9	30	3	19
	Grade	1	7 (3.7%)	23 (5.4%)	3 (1.7%)	13 (3.1%)
		2	2 (1.1%)	7 (1.6%)	0	6 (1.4%)
		3	0	0	0	0
		4	0	0	0	0
		5	0	0	0	0
Dose 6	n		170	406	159	382
	At least one IRR		5 (2.9%)	27 (6.7%)	2 (1.3%)	15 (3.9%)
	Total number of IRRs		5	28	2	15
	Grade	1	2 (1.2%)	21 (5.2%)	1 (0.6%)	13 (3.4%)
		2	3 (1.8%)	6 (1.5%)	0	2 (0.5%)
		3	0	0	1 (0.6%)	0
		4	0	0	0	0
		5	0	0	0	0

IRR = infusion-related reaction.

Source: Clinical Study Report for ORATORIO.[1]

Appendix 4: Validity of Outcome Measures

Aim

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

- Expanded Disability Status Scale (EDSS)
- Timed 25-Foot Walk (T25FW)
- Multiple Sclerosis Functional Composite (MSFC)
- Short Form (36) Health Survey (SF-36)
- Magnetic Resonance Imaging (MRI) outcomes

Findings

Expanded Disability Status Scale

The EDSS is an ordinal scale used to measure disability in multiple sclerosis (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 34).[38] Scores from 0 to 4.5 represent normal ambulation, while scores of 5 and above represent a progressive loss of ambulatory ability.

The distribution of EDSS scores among MS patients is typically biphasic, accumulating around 2 to 3 points and 6 to 7 points, indicating that patients do not stay equally long at each step of the scale. There are many criticisms of the EDSS, including the fact that it has moderate intra-rater reliability (EDSS kappa values between 0.32 to 0.76 and between 0.23 to 0.58 for the individual FSs were reported),[38] offers poor assessment of upper limb and cognitive function, and lacks linearity between score difference and clinical severity.[39-42] Other limitations include that it relies heavily on the evaluation of motor function and the ability to walk; as such, a patient who might not be able to walk but maintains full dexterity is classified toward the severe end of the scale.

In published literature,[43] 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 between 5.5 and 8.5.

Table 34: Scoring of the 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 at grade 2; other 0 or 1).
2.5	Minimal disability in two FSs (two FSs at grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS at grade 3, others 0 or 1), or mild disability in three or four FSs (three/four FSs at grade 2, others 0 or 1), but fully ambulatory.
3.5	Fully ambulatory, but with moderate disability in one FS (one grade 3) and one or two FSs at grade 2; or two FSs at grade 3; or five FSs at grade 2 (others 0 or 1).
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS at grade 4 (others 0 or 1), or combinations of lesser grades exceeding the limits of previous steps. Able to walk without aid or rest 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 at grade 4 (others 0 or 1) or combinations of lesser grades exceeding the limits of previous steps. Able to walk without aid or rest for 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 at grade 3+.)
6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 metres without resting. (Usual FS equivalents are combinations with more than two FSs at grade 3+.)
7.0	Unable to walk beyond about 5 metres even with aid; essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS at grade 4+; very rarely, pyramidal grade 5 alone.)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS at grade 4+.)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems.)
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions. (Usual FS equivalents are combinations, generally 4+ in several systems.)
9.0	Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+.)
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+.)
10.0	Death due to MS.

FS = functional system; MS = multiple sclerosis.

Timed 25-Foot Walk

Walking dysfunction is a fundamental feature of MS; thus, it has become one of the main outcomes in research and clinical practice to monitor the disease. The T25FW assessment is a measure of gait velocity.[44] The measure has a standardized protocol to reduce variability between raters and across administration sites. The standard protocol involves the patient safely walking a clearly marked 25-foot course as quickly as possible. The course is a straight line. Using a stop watch, this time is calculated from the initiation of walk

from a static start position to completion (when the patient's foot crosses the plane of the 25-foot mark). Patients are instructed to continue walking beyond the marked 25-foot line before slowing down to minimize effects of deceleration. The task is immediately administered again by having the patient walk back the same distance. The score for the T25FW is the average of the two completed trials, reported in seconds. Patients may use assistive devices when completing the T25FW (e.g., canes, crutches, walkers).[45]

The T25FW is not appropriate for patients who are unable to walk 25 feet,[44] and, in some studies, has shown statistically significant improvement in patient performance during repeat test sessions, likely due to practice effect.[46,47] However, this adaptation to the T25FW has not be shown in other studies, in which the T25FW demonstrated good test-retest reliability.[21,48] The T25FW is considered "the best characterized objective measure of walking disability" in MS,[49] based on ease of administration, applicability among a wide range disability levels, and strong evidence of its psychometric properties in the adult population.[44,45,49,50] The T25FW has served as the primary outcome measure in a phase III clinical trial for MS of any course type[51] and in exercise therapy for MS.[52]

The T25FW is one of three components of the MSFC, a multi-dimensional measurement tool used in assessing patients with MS. The MSFC includes a measure of ambulation (T25FW), arm function (9-Hole Peg Test [9-HPT]) and cognition (3-second Paced Auditory Serial Addition Test [PASAT-3]).[45]

Summaries of studies supporting the validity, reliability, responsiveness, and clinical meaningfulness of the T25FW in adult MS patients were presented in the 2012 recommendations of the Multiple Sclerosis Outcomes Measures Taskforce[44] and updated in a 2017 invited review by the Multiple Sclerosis Outcomes Assessments Consortium.[45]

A change of at least 20% in the T25FW is commonly cited as the MCID for mixed MS populations.[45] Multiple studies have corroborated the minimally important difference (MID) or MCID as being ≥ 15% to 20% using a variety of approaches, including clinical anchors, patient-reported anchors, real-life anchors, and distribution-based methods.[21-24,45,53-57] The ≥ 20% MCID for the T25FW was supported by members of an FDA advisory committee.[58] One cross-sectional study of 159 MS patients (with relapsing and progressive forms) in the US identified three T25FW score thresholds (< 6 seconds, ≥ 6 seconds to 7.99 seconds, and ≥ 8 seconds) associated with real-world changes in patient employment status, instrumental activities of daily living, and the use of walking assistive devices.[24] These benchmarks warrant further investigation.

Multiple Sclerosis Functional Composite

The MSFC is a measure of MS disability that was developed in 1994 by a task force convened by the US National Multiple Sclerosis Society.[59,60] The MSFC assesses different clinical dimensions: arm (9-HPT, the time needed to insert and remove nine pegs), leg (T25FW, the time needed to walk 25 feet), and cognition (PASAT-3, the total 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., a mean of 0 and an SD of 1). A z score represents the number of SDs by which a patient's test result is higher (Z > 0) or lower (Z < 0) than the average test result (Z = 0) of the reference population. The mean and SD from test results at the baseline visit for all patients in each study were used as the reference population values to create the Z-scores for each component of the composite. The z score is calculated by subtracting the mean of the reference population from the test result and then dividing this by the SD of the reference population. For 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. In order to ensure that all measures are in the same direction, a transformation is necessary. In creating the composite outcome measure, it was decided that a higher test result would indicate improvement from baseline.[60] Psychometric properties and MCID in MS patients are provided as follows:

- *Test-retest reliability*: In a study of a small cohort of patients (10 patients) where 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 at 0.98 and 0.96, respectively.[38,47]
- *Construct validity*: Scores were lower in more disabled patients (–0.4 in PPMS and –0.3 in SPMS versus +0.42 in RRMS).[59]
- *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 PASAT-3. The authors suggested that this might confirm the observation of poor assessment of cognitive function by EDSS. The strongest correlation was between EDSS and T25WT (r = 0.84) followed by 9-HPT (r = 0.51) (which was moderately correlated); this was again consistent with the observation of poor assessment of upper limb function by EDSS. A systematic review of MSFC found the correlation with EDSS to range from –0.41 to –0.83.[38]
- *MCID*: A 20% change in scores on the T25FW test and 9-HPT, and a 0.5 SD change on the PASAT-3, are considered clinically meaningful; however, a clinically meaningful value for overall MSFC score has not been determined.[59]
- The MSFC has not been accepted by regulators as a primary end point in clinical trials.[45]

Short Form (36) Health Survey

The SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life (HRQoL). The SF-36 consists of 36 items representing eight dimensions: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Item response options are presented on a three- to six-point, Likert-like scale. Each item is scored on a 0 to 100 range and item scores are averaged to create the eight domain scores. The SF-36 also provides two component summaries — the physical component summary (PCS) and mental component summary (MCS) — which are created by aggregating the eight domains according to a scoring algorithm. Therefore, the PCS, MCS, and eight dimensions are each measured on a scale of 0 to 100, that have been standardized to the US general population.[61] Thus, a score of 50 on any scale would be at the average or norm of the general US population, while a score 10 points lower (i.e., 40) would be one SD below the norm.[61] On any of the scales, an increase in score indicates improvement in health status. In general use of the SF-36 (version 2), the user manual proposed the following MIDs: a change of 2 points on the PCS and a change of 3 points on the MCS.

Two versions of the SF-36 exist: the original and the SF-36 version 2, which became available in 1996.[61] Version 2 contains minor changes to the original, including changes to: instructions (reduced ambiguity), questions and answers (better layout), item-level response choices (increased), and cultural/language comparability (increased). It also eliminates a response option from the items in the mental health and vitality dimensions.[61]

Psychometric properties of the SF-36 have been studied in MS populations.[44,62-65] While some elements of validity and reliability have been tested and proven for individual SF-36 dimensions, the instrument has demonstrated numerous limitations in this disease:[44]

- Two studies in a broad range of MS patients found floor and ceiling effects in four of the eight dimensions of the SF-36: floor effects > 20% in PF, RP, RE[63,64] and ceiling effects > 20% in RE and BP.[63,64]
- According to Cohen's criterion, the SF-36 demonstrated limited responsiveness (negligible to small effect sizes) in all dimensions in an MS rehabilitation therapy group compared with other measures that found moderate effect sizes.[64]
- The SF-36 was shown to overestimate mental health in the MS population when compared with an external criterion measure.[62]
- The PCS and MCS, could not be validated in the MS population.[63]
  - While principle component analysis supported the two-dimension model, these summary scores explained less variance than required:
    - < 60% of the total reliable variance of the SF-36 dimensions
    - < 75% of the reliable variable in five of the eight dimensions
  - All other tested methods of extraction in factor analysis and oblique factor rotation generated similar results.
  - In the MS population studied, correlations between dimensions and component summary scores differed in pattern and magnitude from those originally used to determine the weighting coefficients, which generate the SF-36 summary scores.

Thus, unvalidated summary scores of SF-36 in the MS patient population should be interpreted with caution. Poor responsiveness, including floor and ceiling effects in four of the eight dimensions, may limit the usefulness of the SF-36 in clinical trials. If the SF-36 is selected for use in prospective studies or clinical trials, it is advisable to supplement the instrument with other disease-specific scales or measures in order to fully capture HRQoL in MS patient groups.[62-65]

Magnetic Resonance Imaging Outcomes

MRI techniques play an important role in the diagnosis of MS. In addition, they are valuable in monitoring treatment response and predicting disease progression. However, the correlation between the burden of lesions observed on MRI scans and the clinical manifestations of the disease remains controversial.[43,66,67]

In CARE MS II, a clinical trial on alemtuzumab for RRMS, the following MRI outcomes were measured between treatment groups: new and enlarging T2 hyperintense lesion count, T2 hyperintense lesion volume, and gadolinium (Gd)-enhancing 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 relapsing remitting multiple sclerosis (RRMS), have been investigated in previous research. Findings from systematic reviews and large randomized controlled trials (RCTs) reporting the correlations between the treatment effect on relapses and disability progression and the treatment effect on MRI lesions are presented in Table 35. In these studies, RRMS patients received interferon, cladribine, fingolimod, laquinimod, placebo, or no drug treatment. The correlations between MRI outcomes and clinical outcomes (relapses and disability progression) varied across studies.

Table 35: Summary of Correlations between MRI Outcomes and Clinical Outcomes

Study	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Authors' Conclusions
Bovis 2017[68]	• 2 RCTs collectively enrolling 2,432 RRMS patients (ALLEGRO: laquinimod vs. placebo; BRAVO: laquinimod vs. placebo vs. interferon beta-1a) • Follow-up: 24-months	• Brain atrophy: Study-grade MRI-derived NBV • 3-month CDP assessed by EDSS	Data from two RCTs were used to categorize patients as having high, medium, or low NBV, and to correlate these categories with 3-month CDP after 2 years in trial. Relative to high-NBV patients, medium-NBV patients had HR = 1.22 (95% CI, 0.85 to 1.76, *P* = 0.27); and low-NBV patients had HR = 1.69 (95% CI, 1.11 to 2.57, *P* = 0.01).	NBVs, adjusted for all other prognostic variables, have prognostic impact on the risk of disability progression. NBV categories or cut-offs represent clinically relevant atrophy in RRMS patients.
Sormani 2013[69]	• 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 control arm • REL effect: ratio between the relapse rate in the experimental arm and 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 the regression equation. $R^2 = 0.71$, suggesting a good degree of prediction of the REL effect using the MRI effect.	The effect of a treatment on relapses can be accurately predicted by the effect of that therapy on MRI lesions.
Sormani 2010[70]	• 3 RCTs enrolling RRMS patients (cladribine vs. placebo; fingolimod vs. placebo; fingolimod vs. interferon) • Follow-up: 12-24 months	• MRI effect: ratio between the average number of new and enlarging T2 lesions/patient in the experimental arm and control arm • REL effect: ratio between the annualized relapse rate in the experimental arm and control arm • DIS effect: ratio between % of patients with disability progression (≥ 1 point on EDSS at month 3) in experimental and control arm • Regression equations from previous meta-analyses were used to predict the drug effect on relapse (REL effect) and disability progression (DIS effect) based on MRI effect.	92% of observed effects of oral drugs (cladribine and fingolimod) on clinical outcomes 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	Authors' Conclusions
Sormani 2010[71]	• The PRISMS study enrolling 560 RRMS patients: subcutaneous interferon vs. placebo • Follow-up: 24 months	• The PTE on relapses that was accounted for by the effect of treatment on the MRI marker	New T2 lesions and relapses were significantly correlated: compared with placebo, interferon significantly reduced the new T2 lesion number by 60% over 2 years, and the number of relapses went down 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 a similar mechanism of action.
Kappos 1999[72]	• Patients were in natural-course studies or were treated with placebo or observed in the pre-treatment phase of controlled clinical trials. • 77% of the patients had RRMS; 23% had secondary progressive MS. • Follow-up: 6 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; CDP = confirmed disability progression; CI = confidence interval; DIS = disability; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GdE = gadolinium-enhancing; HR = hazard ratio; MRI = magnetic resonance imaging; MS = multiple sclerosis; NBV = normalized brain volume; OR = odds ratio; PTE = proportion of treatment effect; RCT = randomized controlled trial; REL = relative; RR = relative risk; RRMS = relapsing remitting multiple sclerosis; vs. = versus.

Conclusion

A summary of the characteristics of five instruments was provided: three measuring disability (EDSS, T25FW, and MSFC) and one measuring HRQoL (SF-36). In addition, the correlations between MRI outcomes and clinical outcomes, such as relapses and progression in disability in RRMS patients, were examined.

With respect to the reliability and validity of the instruments:

- The EDSS has moderate reliability and a published clinically important difference of 1.0 point when the score was 0 and 5.5, and 0.5 when the score was between 5.5 and 8.5.
- The T25FW has strong validity and reliability across a wider range of disability than the EDSS. A published MCID of ≥ 20% change has been corroborated.

- The MSFC shows good construct validity, but is only moderately correlated to EDSS.
- The SF-36 overestimates the mental health of MS patients, suffers from floor and ceiling effects, and requires detailed dimension reporting, as component summary scores have demonstrated unexplained variability.
- 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 RRMS; however, the correlations between MRI outcomes and clinical outcomes were not consistent across studies and are affected by the quality of the MRI data.

No MCID was available for the SF-36 with regard to patients with MS. A 20% change in scores on the T25FW test and 9-HPT, and a 0.5 SD change on the PASAT-3, are considered clinically meaningful in MSFC; however, an MCID for overall MSFC score has not been determined.

Appendix 5: Summary of Extended Controlled Treatment Period

Aim

To summarize the characteristics and results of the extended controlled treatment period of the ORATORIO trial.

Findings

Study Design

The objective of the extended controlled treatment (ECT) period of ORATORIO was to collect additional data prior to patients receiving their first dose of open-label ocrelizumab. The ECT period ranges from three to six months prior to the commencement of the single-arm, switch-over, open-label extension (OLE) of the randomized controlled trial (RCT). Patients who completed the double-blind, randomized, controlled period of ORATORIO up to the clinical cut-off date for the primary analysis period (PAP), and who remained on treatment leading up to the OLE, were included in the ECT analysis. Table 36 summarizes the dates of the PAP, ECT, and OLE periods of the ORATORIO trial. The analyses for the ECT period include all data from the PAP as well as patient data from the ECT, including the last day before each patient's entry into the OLE period. Patient unblinding occurred over the last three months of the ECT. The first three months of the ECT include blinded patient data; the last three months represent controlled follow-up data. January 20, 2017 was the cut-off date for the ECT period analyses.

Table 36: Key Timelines for the ORATORIO Trial

Study Period	Study Dates
Primary analysis period of RCT	March 3, 2011 through July 24, 2015 (clinical cut-off date)[1]
Extended controlled treatment period	July 24, 2015 through January 20, 2016[73]
Sponsor unblinding	September 22, 2015
Treatment site unblinding	October 12, 2015
Patient unblinding and switching to OLE	Oct. 12, 2015 through January 20, 2016 (clinical cut-off date)[73]
OLE period	Oct. 12, 2016 through estimated study completion date (April 2021)[19]

OLE = open-label extension; RCT = randomized controlled trial.

Sources: Clinical Study Report for ORATORIO;[1] ClinicalTrials.gov (NCT01194570);[19] Efficacy Data Memo for ORATORIO.[73]

Patient Population and Disposition

The intention-to-treat (ITT) population was used for all analyses. As the ECT period analyses include the PAP data, the patient demographics and baseline disease characteristics for this population are presented in the main report (Table 6).No additional data were reported for patient disposition and exposure in the ECT period.[73]

Intervention

Patients who elected to remain in the ORATORIO study after the PAP entered the ECT period (three to six months) and continued their blinded, randomized treatment regimen

until they were unblinded and given the option of entering into the single-arm ocrelizumab OLE period. No treatment adjustments were made.[73]

Outcomes

The primary efficacy outcome measured in the ECT period was the time to onset of 12-week confirmed disability progression (CDP). Other efficacy end points analyzed in the ECT period are presented in Table 37. Short Form (36) Health Survey (SF-36) and magnetic resonance imaging (MRI) outcomes were not analyzed in the ECT period, as no additional data were collected for these outcomes. Analysis methods for end points were identical to the PAP, unless otherwise noted.

Table 37: Efficacy End Points in Extended Controlled Treatment Period for ORATORIO

Category	End Point
Primary End Point	Time to onset of CDP for at least 12 weeks[a]
Secondary End Points	Time to onset of CDP for at least 24 weeks[a]
	Change in T25FW from baseline to week 144[b]
Exploratory End Points	Change in EDSS score from baseline to week 144[b]
	Change in MSFC score from baseline to week 144[b]
	Time to confirmed composite disability progression sustained for at least 12 weeks (based on EDSS, T25FW, or 9-HPT)[a]
	Time to confirmed composite disability progression sustained for at least 24 weeks (based on EDSS, T25FW, or 9-HPT)[a]
	The time to sustained 20% increase in T25FW and 9-HPT

9-HPT = 9-Hole Peg Test; CDP = confirmed disability progression; EDSS = Expended Disability Status Scale; MSFC = Multiple Sclerosis Functional Composite; T25FW = Timed 25-Foot Walk.

[a] Timing of CDP confirmation differs from the primary analysis period in that it could be ascertained at scheduled open-label extension visits that occurred until the clinical cut-off date of January 20, 2016, as well as at scheduled treatment or safety follow-up visits.

[b] Week 144 was chosen as the last measurement point for these outcomes because at the time of the commencement of patient unblinding and switching to open-label extension visits (October 12, 2015), all patients had been randomized for a minimum of 144 weeks.

Source: Efficacy Data Memo Extended Controlled Treatment Period for ORATORIO.[73]

Efficacy

Confirmed Disability Progression

Results for the primary efficacy end point of CDP for at least 12 weeks and 24 weeks are presented in Table 38. Results from the ECT period were similar to results from the PAP in which ocrelizumab treatment was associated with a reduction in the hazard for CDP for at least 12 weeks (hazard ratio: 0.74; 95% CI, 0.58 to 0.95; $P = 0.0151$). Consistent with the results shown in the PAP, the ECT period results in the ITT population were sensitive to the method of imputation for missing data. Results for 24-week CDP from the ECT period were similar to those from the PAP. Analyses with and without imputation of CDP after 24 weeks of onset favoured ocrelizumab (hazard ratio: 0.70 [95% CI, 0.54 to 0.90] and 0.76 [95% CI, 0.58 to 1.00], respectively). The rates of CDP for at least 12 weeks and 24 weeks are summarized in the Kaplan–Meier survival curves shown in Figure 8. Results from the ECT period are similar to those shown in the PAP. Initial separation of the curves occurs around 12 weeks from baseline, then stabilizes until a second, wider separation of the curves is observed, beginning in the range of 108 weeks to 120 weeks.

Table 38: Time to Onset of Confirmed Disability Progression

	Placebo (N = 244)	Ocrelizumab (N = 488)	Placebo (N = 244)	Ocrelizumab (N = 488)
CDP for at Least 12 weeks				
	With imputation[a]		**Without imputation[b]**	
Patients included in analysis, n (%)[c]	244 (100)	487 (100)	244 (100)	487 (100)
Patients with event, n (%)	106 (43.4)	177 (36.6)	94 (38.5)	168 (34.5)
Patients without event, n (%)	138 (56.6)	310 (63.7)	150 (61.5)	319 (65.5)
Stratified analysis *P* value (log-rank)[d]	0.0151		0.0792	
Hazard ratio (95% CI)[e]	0.74 (0.58 to 0.95)		0.8 (0.62 to 1.03)	
CDP for at Least 24 weeks				
	With imputation[a]		**Without imputation[b]**	
Patients included in analysis, n (%)[c]	244 (100)	487 (100)	244 (100)	487 (100)
Patients with event, n (%)	98 (40.2)	154 (31.6)	82 (33.6)	139 (28.5)
Patients without event, n (%)	146 (59.8)	333 (68.4)	162 (66.4)	348 (71.5)
Stratified analysis *P* value (log-rank)[d]	0. 0056		0.0467	
Hazard Ratio (95% CI)[e]	0.70 (0.54 to 0.90)		0.76 (0.58 to 1.00)	

CDP = confirmed disability progression; CI = confidence interval; EDSS = expanded disability status scale; N = total number of patients in the ITT population; n = number of patients in the analysis; ROW = rest of world.

[a] Patients with an initial disability progression during the treatment period who discontinue the treatment early and do not have a subsequent visit with EDSS measurement are imputed as having a CDP event.

[b] Patients with an initial disability progression during the blinded treatment period who discontinue the treatment early and do not have a subsequent visit with EDSS measurement are censored.

[c] Patient with missing baseline EDSS excluded from analysis.

[d] Stratified by geographic region (US versus ROW) and age (≤ 45 years of age; > 45 years of age).

[e] Hazard ratios estimated by stratified Cox regression.

Source: Efficacy Data Memo Extended Controlled Treatment Period for ORATORIO.[73]

Timed 25-Foot Walk

Results for the secondary end point of change from baseline to week 144 in T25FW are presented in Table 39. The relative reduction in T25FW at 144 weeks was 33% (95% CI, 7% to 53%). Exploratory analyses for a 20% increase in the T25FW after 12 weeks and 24 weeks demonstrated hazard ratios of 0.75 (95% CI, 0.61 to 0.92) and 0.70 (95% CI, 0.56 to 0.87), respectively.[73]

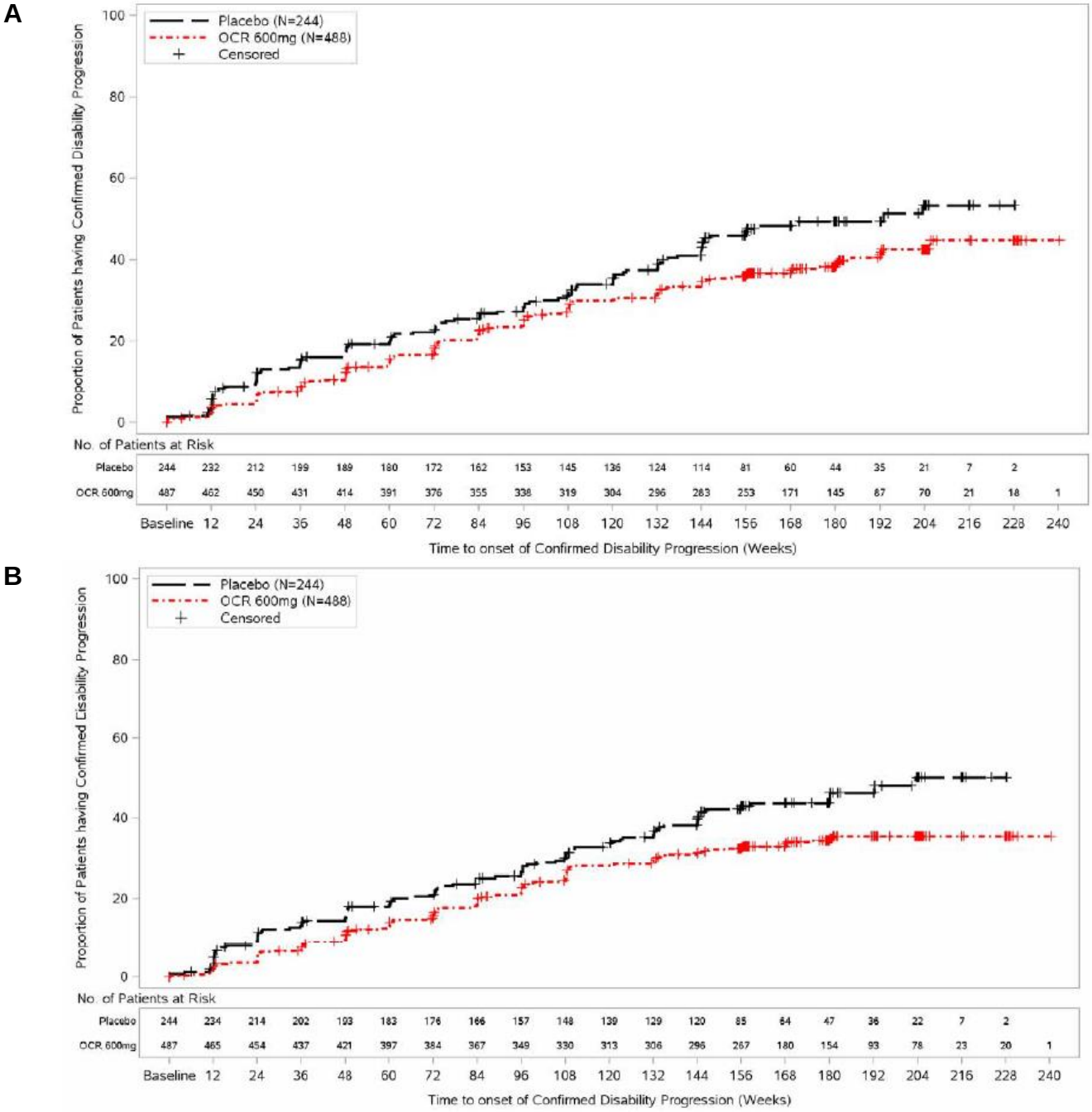
Table 39: Change From Baseline to Week 144 in Timed 25-Foot Walk

Time Point	Parameters	Placebo (N = 244)	Ocrelizumab (N = 488)
Baseline	n	239	473
	Mean (SE)	12.781 (1.00)	14.573 (0.95)
Week 144	n	158	379
	AGM (95% CI)	1.648 (1.483 to 1.832)	1.435 (1.333 to 1.544)
	Percentage change	64.85	43.46
	Ratio of AGM (95% CI)	0.870 (0.768 to 0.986)	
	Relative reduction (%) (95% CI)	32.977 (6.914 to 53.146)	
	P value (Ranked ANCOVA)	0.1004	

AGM = adjusted geometric mean; ANCOVA = analysis of covariance; CI = confidence interval; N = total number of patients in the ITT population; n = number of patients in the analysis; SE = standard error.

Source: Efficacy Data Memo Extended Controlled Treatment Period For ORATORIO.[73]

Figure 8: Kaplan–Meier Curves for Time to Onset of CDP for at Least 12 Weeks (A) and 24 Weeks (B) with Imputation, ITT population



CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; OCR = ocrelizumab.

Note: Patients with missing EDSS were excluded from the analysis; patients with an initial disability progression during the blinded treatment period who discontinued the treatment early and did not have a subsequent visit confirming EDSS measurement were imputed as having a CDP event.

Source: Efficacy Data Memo Extended Controlled Treatment Period for ORATORIO.[73]

Limitations

The limitations identified for the primary analysis also apply to the ECT. In addition, the ECT period was unblinded to the sponsor for approximately four months of the ECT period, and to the centres and patients for approximately three months. Unblinding of the sponsor, investigators, and participants introduces potential bias into the data collection and analysis. Patient exposure and disposition during the ECT period were not reported. Knowledge of exposure and disposition is important, as the population lost to an extension study may enrich the apparent success of the study: those who remain are more likely to be achieving study goals and tolerating treatment, as compared with those who discontinue the treatment and/or the study altogether. Similar to the analyses conducted for the double-blind phase of the ORATORIO trial, ocrelizumab was statistically superior to placebo for 12-week CDP in the analyses where initial progression events that lacked confirmation were imputed as CDP, but not in the analyses conducted without imputation. Only a limited number of efficacy end points were reported for the ECT period. No safety data were reported.

Summary

The ECT period of ORATORIO combined results from the PAP with results collected for up to six months prior to patients receiving their first open-label dose of ocrelizumab in the single-arm extension trial. Approximately half of the six-month period of the ECT period was unblinded to investigators and patients. Results from the ECT period were similar to those reported in the PAP. No additional safety data were presented.

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