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CADTH COMMON DRUG REVIEW

Clinical Review Report

CLADRIBINE (MAVENCLAD)

(EMD Serono)

Indication: As monotherapy for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and delay the progression of disability. Cladribine is generally recommended in RRMS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for RRMS.

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Abbreviations

ARR	annualized relapse rate
CDP	confirmed disease progression
CDR	CADTH Common Drug Review
CI	confidence interval
CrI	credible interval
DAT	disease activity on treatment
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EQ-5D	EuroQoL 5-Dimensions questionnaire
Gd+	gadolinium-enhanced
HLLL	high-dose cladribine/low-dose cladribine
HLPP	high-dose cladribine/placebo
HRA	high relapse activity
IDC	indirect comparison
IFN	interferon
ITT	intention-to-treat population
KFS	Kurtzke Functional Systems
LLLL	low-dose cladribine/low-dose cladribine
LLPP	low-dose cladribine/placebo
MCID	minimal clinically important difference
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSQOL-54	Multiple Sclerosis Quality of Life–54
NEDA	no evidence of disease activity
PML	progressive multifocal leukoencephalopathy
RCT	randomized controlled trial
RRMS	relapsing-remitting multiple sclerosis
SF-36	Short Form (36) Health Survey
TB	tuberculosis
VAS	visual analogue survey

Drug	Cladribine (Mavenclad)
Indication	As monotherapy for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and delay the progression of disability. Cladribine is generally recommended in RRMS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for RRMS.
Reimbursement Request	As per indication
Dosage Form(s)	10 mg tablet
NOC Date	November 29, 2017
Manufacturer	EMD Serono Inc.

Executive Summary

Introduction

Multiple sclerosis (MS) is an immune-mediated inflammatory demyelinating disorder of the central nervous system.[1] It causes disabling motor and sensory symptoms, including mobility problems, vision, issues with coordination, cognitive dysfunction, fatigue, and pain. The condition significantly impairs quality of life, limiting employment and social functioning, and it is a major cause of disability in young adults, with an onset as early as the teenage years.[1] The disease is divided into four subtypes: relapsing-remitting MS (RRMS), primary-progressive MS, secondary-progressive MS, and progressive-relapsing MS. The most common form is RRMS, accounting for up to 90% of cases at first presentation.[2] RRMS is characterized by clearly defined relapses with full recovery or with residual deficit upon recovery, with lack of progression of disability during the periods between relapses. Given the relatively young onset and severity of disability, the disease carries a significant burden on patients, caregivers, and the health care system, and the Multiple Sclerosis Society of Canada estimates that there are currently 100,000 patients with MS in Canada.[1]

There are multiple disease-modifying therapies (DMTs) available for MS, including oral (fingolimod, dimethyl fumarate, and teriflunomide), injectable (interferon beta-1a and 1b, pegylated interferon 1a, glatiramer acetate), and infusion (natalizumab, alemtuzumab, ocrelizumab) formulations, and they tend to be divided into first-line and second-line therapies, with the second-line agents being considered more efficacious but also more toxic (fingolimod, alemtuzumab, natalizumab), and reserved for patients with more active disease. Selection of therapy is guided by various factors: disease activity, disability progression, and findings on MRI, and is highly individualized. Switching between first-line therapies typically occurs to address a tolerability issue, while switching to a second-line drug occurs when there is suboptimal response to a first-line drug.[3] Until recently, daclizumab (previously reviewed by CADTH) was indicated as a second-line therapy for patients with RRMS. However, during writing of this review, it was voluntarily withdrawn from markets worldwide by the manufacturer because of reports of serious inflammatory brain disorders, including immune-mediated encephalitis and meningoencephalitis.[4]

The mechanism of action of cladribine in treating MS is not fully understood. Cladribine inhibits DNA synthesis and has antiproliferative effects on lymphocytes, which likely

mediate the destruction of myelin. It is the loss of myelin that characterizes MS. Cladribine is indicated as monotherapy for the treatment of adult patients with RRMS to reduce the frequency of clinical exacerbations and delay the progression of disability. It is administered orally, and is available as 10 mg tablets. The efficacy and safety of cladribine beyond two years has not been established, thus the recommended cumulative dose is 3.5 mg/kg over the course of two years, with one treatment course of 1.75 mg/kg per year followed by observation for another two years. The treatment course is spread over two weeks each year, one week at the beginning of the first month of that year and the other at the beginning of the second month. During each week, patients receive 10 mg or 20 mg daily (one or two tablets), based on body weight, over the course of four to five days. The following clinical assessments are recommended prior to starting and continuing therapy with cladribine: lymphocyte counts must be normal before initiating cladribine in year 1, and at least 800 cells/mm³ (i.e., grade 0 or 1) before initiating cladribine in year 2. The product monograph for cladribine notes that in year 2 therapy can be delayed for up to six months to allow for recovery of lymphocytes to at least 800 cells/mm^3, but if recovery takes more than six months, the patient should discontinue cladribine.[5]

The objective of this report is to perform a systematic review of the beneficial and harmful effects of cladribine for the treatment of RRMS.

Results and Interpretation

Included Studies

One manufacturer-sponsored double-blind randomized controlled trial (RCT) was included in this systematic review. CLARITY was a multinational trial that randomized patients with RRMS (2005 McDonald criteria) and at least one relapse within 12 months of study entry 1:1:1 to cladribine 3.5 mg/kg (N = 433), cladribine 5.25 mg/kg, or placebo (N = 437), over a treatment course of 96 weeks. The dose of 3.5 mg/kg was the total cumulative dose over the course of the 96-week study, and is the recommended dose in the product monograph. Because it is not the approved dose for cladribine, the 5.25 mg/kg dose was not of interest for this review. The primary outcome was the annualized relapse rate at 96 weeks. Key secondary outcomes included a variety of MRI outcomes (T1- and T2-weighted and combined unique lesions). Other outcomes that were assessed but were not controlled for multiple comparisons included disability progression and health-related quality of life.

Key critical appraisal issues included the lack of an active comparator, as CLARITY was a placebo-controlled study. Only relapse and MRI outcomes were adjusted for multiple comparisons, while key efficacy outcomes such as disability progression and health-related quality of life were not. Additionally there was a significant amount of missing data for the health-related quality of life outcomes, particularly the Multiple Sclerosis Quality of Life–54 (MSQOL-54). All the subgroup analyses of interest to the review, including treatment history with DMTs (naive and frequency of relapses) in the past year were carried out post hoc, and thus should be considered hypothesis-generating. There is a lack of comparative long-term safety data for oral cladribine, and this is an important gap in knowledge, considering the potential risk for malignancies.

Efficacy

There was a lower annualized relapse rate with cladribine (0.14; 95% confidence interval [CI], 0.12 to 0.17) versus placebo (0.33; 95% CI, 0.29 to 0.38) and a statistically significant difference between groups in the rate of relapse over the course of 96 weeks (rate ratio of

0.43; 95% CI, 0.34 to 0.54; *P* < 0.001). This amounts to 19 fewer relapses per 100 patients per year of treatment with cladribine. The proportion of patients who were relapse-free over 96 weeks was higher with cladribine (80%) than with placebo (61%) (odds ratio of 2.53; 95% CI, 1.87 to 3.43; *P* < 0.001). There were fewer events of a three-month sustained progression in Expanded Disability Status Scale (EDSS) scores with cladribine (79%) versus placebo (86%), and the time to sustained progression in EDSS scores was statistically significantly different between groups in favour of cladribine (hazard ratio of 0.67; 95% CI, 0.48 to 0.93; *P* = 0.018). However, this outcome was not adjusted for multiple statistical comparisons and thus should be considered hypothesis-generating. The effect of cladribine on disability appears to be relatively modest compared with its effects on relapses.

Health-related quality of life was assessed using the disease-specific MSQOL-54, the EuroQoL 5-Dimensions questionnaire (EQ-5D), and the Short Form (36) Health Survey (SF-36), although there was a significant amount of missing data for the MSQOL-54 and, to a lesser extent, the EQ-5D, and no baseline data for the SF-36. Due to the lack of baseline data, SF-36 results were not reported in this review. This large amount of missing data is an important gap in knowledge about cladribine, given the importance of health-related quality of life to patients with MS. Only approximately 10% of the randomized population had a baseline and 96-week MSQOL-54 score, and the difference in score between groups at 96 weeks was not statistically significant. EQ-5D scores at baseline and 96 weeks were only available for approximately 80% of the randomized population. EQ-5D index score (difference from placebo of 0.058, *P* < 0.001) and visual analogue score (VAS) (difference from placebo of 4.55, *P* = 0.001) were improved for cladribine versus placebo and this difference was statistically significant, although again not adjusted for multiple comparisons. The difference between cladribine and placebo for EQ-5D index scores appeared to be clinically significant.

MRI results were improved for cladribine versus placebo and these differences were statistically significant for T1-weighted (treatment difference of −0.78; 95% CI, −0.92 to −0.65; *P* < 0.001), T2-weighted (treatment difference of −1.05; 95% CI, −1.22 to −0.87; *P* < 0.001), and combined unique lesions (treatment difference of −1.28; 95% CI, −1.49 to −1.0; *P* < 0.001). A larger proportion of cladribine versus placebo patients had no active T1-weighted or T2-weighted lesions compared with placebo. Cladribine was also superior to placebo for brain atrophy. However, this analysis was post hoc, was not adjusted for multiple comparisons, was missing approximately 20% of the randomized population, and only assessed changes between six and 24 months, not from baseline. The clinical expert consulted for this review considers these to be relatively minor improvements in brain atrophy over placebo. Other efficacy outcomes were not adjusted for multiple comparisons and for these there was a decrease in the proportion of patients using rescue medications with cladribine versus placebo, and an improvement in absenteeism for cladribine versus placebo.

The manufacturer submitted an indirect comparison (IDC) that assessed the relative efficacy and harms of cladribine versus other DMTs for RRMS. This IDC is reviewed in detail in Appendix 7. The IDC included 44 RCTs, and both the “high-efficacy” drugs such as natalizumab, ocrelizumab, fingolimod, and alemtuzumab were included, as well as the interferons, glatiramer, dimethyl fumarate, and teriflunomide. The manufacturer concluded that cladribine had comparable efficacy and harms when compared with these drugs. However, there were several limitations of the IDC, both with transparency of reporting and with methodology, that limits confidence in these conclusions. Lack of comparative data for

cladribine versus the many other DMTs for MS remains a limitation of this CADTH Common Drug Review report.

Harms

With respect to harms, there were numerically more adverse events with cladribine than with placebo (81% versus 73%). The most common adverse events were headache (24% cladribine versus 17% placebo) and lymphopenia (22% versus 2%). According to the manufacturer, transient mild-to-moderate lymphopenia is to be expected with cladribine, given its mode of action. Serious adverse events occurred in 8% of cladribine patients and 6% of placebo patients, and 1% of patients in each group withdrew due to an adverse event. Infections, hematological disorders, and neoplasia were notable harms in this review. Herpes zoster occurred in 2% of cladribine patients and none in placebo, while lymphopenia occurred in 22% of cladribine patients and 2% placebo. Neoplasms that were benign, malignant, or unspecified (including cysts and polyps) occurred in 4% of cladribine and 2% of placebo patients. Neoplasms were a safety concern with cladribine and resulted in an apparent delay in approval of the drug in various jurisdictions, including Canada. An analysis of pooled data from various MS trials, including those using parenteral formulations of cladribine and observational studies, found more cases of cancer with cladribine than with placebo. With respect to CLARITY, the manufacturer attributed the difference in risk of neoplasia between groups to an unusually low risk of neoplasia in the placebo group. The manufacturer also submitted a published meta-analysis, which reported no statistically significant difference between cladribine and other MS drugs or placebo with respect to the risk of developing cancer. Ultimately cladribine was approved by Health Canada, but the reviewers recommend it be used as a second-line therapy, due to these safety concerns. This recommendation is not inconsistent with other DMTs with safety issues. However, these higher-risk drugs are also considered to be more efficacious than the safer alternatives, such as the interferons and glatiramer.

Conclusions

One double-blind RCT met the inclusion criteria for this review. CLARITY was a multinational, manufacturer-sponsored trial that compared cladribine with placebo over a treatment course of 96 weeks. The primary outcome was the annualized relapse rate, and cladribine was superior to placebo at 96 weeks for this outcome. Health-related quality of life was only assessed using the disease-specific MSQOL-54 in a small fraction of the population, and the EQ-5D also had a significant amount of missing data. Disability progression was assessed using the EDSS, and the risk of three-month sustained disability progression was lower with cladribine than with placebo. However, this analysis was not adjusted for multiple comparisons. The lack of health-related quality of life and symptom data is an important limitation in a condition characterized by significant symptoms and quality of life issues. MRI outcomes such as the change in number of T1 gadolinium-enhanced lesions per patient, active T2 lesions, and combined unique lesions, were all superior to placebo. With respect to brain atrophy, cladribine was also superior to placebo, but this post hoc analysis was not adjusted for multiple comparisons. There was a higher proportion of cladribine patients who were free of disease activity, and this difference was statistically significant, although this was a post hoc analysis. A numerically higher proportion of cladribine patients reported an adverse event over the 96-week study, and there was no notable difference in patients with a serious adverse event between groups. Lymphopenia was a common adverse event, and occurred numerically more frequently with cladribine than with placebo. Two per cent of cladribine patients developed herpes zoster

during the study, compared with none in the placebo group. These adverse events, in addition to other potential safety concerns, have made cladribine a second-line therapy in RRMS, based on the indication. There are no long-term comparative safety data for oral cladribine.

Table 1: Summary of Results

Outcome	CLARITY	
	Cladribine 3.5 mg/kg	**Placebo**
Relapses		
Number of qualifying relapses, mean (SD) by week 96	0.25 (0.59)	0.56 (0.88)
Relapse rate, annualized (95% CI)	0.14 (0.12 to 0.17)	0.33 (0.29 to 0.3)]
Relative risk (95% CI)[a]	0.43 (0.34 to 0.54) *P* < 0.001	
Disability - EDSS		
Time to 3-month sustained progression in EDSS score by week 96, n	58	82
Hazard ratio (95% CI)[b]	0.67 (0.48 to 0.93) *P* = 0.018	
Patients without a 3-month sustained change in EDSS score, n (%)	371 (85.7) *P* = 0.02	347 (79.4)
HRQoL		
MSQOL – Overall QoL	N = 47	N = 48
Adjusted mean change[c] in score, baseline to week 96	−2.21	−1.56
Adjusted mean difference from placebo	−0.66 P = 0.840	
EQ-5D	N = 345	N = 340
EQ-5D VAS adjusted mean change[c] in score, baseline to week 96	1.31	−3.24
Adjusted mean difference from placebo	4.55 P = 0.001	
EQ-5D index adjusted mean change[c] in score, baseline to week 96	0.019	−0.039
Adjusted mean difference from placebo	0.058 P < 0.001	
Symptoms	NR	NR
Withdrawals		
Total, n (%)	35 (8)	57 (13)
SAEs		
Total, n (%)	36 (8.4)	28 (6.4)
WDAEs		
Total, n (%)	5 (1.2)	5 (1.1)
Notable harms(s), patients n (%)		
Herpes zoster	8 (1.9)	0
Lymphopenia	93 (21.6)	8 (1.8)
Leukopenia	24 (5.6)	3 (0.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	16 (3.7)	7 (1.6)

CI = confidence interval; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQoL 5-Dimensions questionnaire; HRQoL = health-related quality of life; MSQOL = Multiple Sclerosis Quality of Life; NR = not reported; QoL = quality of life; SAE = serious adverse event; SD = standard deviation; VAS = visual analogue scale; WDAE = withdrawal due to adverse event.

[a] *P* value based on a Wald chi-square test from analysis of end point using a logistic regression model with fixed effects for treatment group and region. Odds ratio and associated 95% CI were estimated using a logistic regression model with fixed effects for treatment group and region.

[b] The hazard ratio, 95% (97.5%) CI and *P* values were estimated using a Cox proportional hazards model with fixed effects for treatment group and region.

[c] QoL: Analysis of covariance (ANCOVA) models on the change in score, including the treatment group, region and score at baseline as covariates.

Introduction

Disease Prevalence and Incidence

Multiple sclerosis (MS) is an immune-mediated inflammatory disorder of the central nervous system that often strikes early in life (15 to 40 years of age) and results in progressive disability.[1] The precise pathophysiology is currently unknown. However, both T- and B-lymphocytes have been implicated in an immune-mediated attack on the myelin sheath that surrounds neurons, resulting in impaired neurotransmission that can affect both sensory and motor neurons.[6,7] According to the McDonald criteria (2010), MS can be diagnosed on the basis of evidence of at least two relapses (clinical and/or MRI), achieved through a detailed medical history and neurological examination. Diagnosis is confirmed by objective clinical evidence of at least two lesions that are disseminated in space and time as demonstrated clinically or by MRI.[8,9] MS is divided into four clinical subtypes: relapsing-remitting MS (RRMS); primary-progressive MS, secondary-progressive MS, and progressive-relapsing MS. By far the most common form is the RRMS, which accounts for up to 90% of all cases of MS.[2] RRMS, as the name suggests, is characterized by relapses and subsequent remissions. Relapses are characterized, and defined, by a worsening of disability that is typically not completely reversed upon recovery, and development of new lesions on MRI. There is a lack of disability progression between relapses. With such an early onset, MS is associated with major financial burden on patients, family, and the health care system. The Multiple Sclerosis Society of Canada estimates that there are currently 100,000 patients with MS in Canada.[1]

Standards of Therapy

The goals of MS therapy are to decrease the number and severity of relapses, limit progression of disability and MRI lesions, both of which are affected by the number of relapses, and ultimately maintain patients' health-related quality of life.[3] Within the past dozen years, beginning with the approval of natalizumab in 2006, the number of disease-modifying drugs available to patients with RRMS has increased dramatically. Prior to natalizumab the options were various interferons and glatiramer, and these have been joined by a variety of oral options (fingolimod, dimethyl fumarate, and teriflunomide), injectables (interferon beta-1a and 1b, pegylated interferon 1a, glatiramer acetate), and infusions (alemtuzumab, ocrelizumab). Drugs such as natalizumab, alemtuzumab, daclizumab, and fingolimod tend to be used as second-line interventions, reserved for patients with more advanced disease, due to toxicities and (to a lesser extent) cost. Otherwise, choice of drug in many cases is guided by patient tolerance for various side effects, such as alopecia for teriflunomide, flushing for dimethyl fumarate, flu-like symptoms for interferon, and injection site reactions for glatiramer. Two newer entrants to the list of therapeutic options for MS include daclizumab and ocrelizumab, both reviewed by CADTH Common Drug Review (CDR). Daclizumab has recently been withdrawn from the Canadian and global markets due to safety concerns.[4]

Selection of therapy is guided by various factors in addition to adverse-event profiles, including disease activity, disability progression, and findings on MRI, and is highly individualized. Switching between first-line therapies typically occurs to address a tolerability issue, while switching to a second-line drug occurs when there is suboptimal response to a first-line drug.[3] The main reason for this is that the second-line drugs tend to have better efficacy but are also likely not as safe as the first-line drugs, particularly older

ones such as the interferons and glatiramer.[10] Although no clinical criteria have been established to identify patients that should discontinue treatment, the Canadian Multiple Sclerosis Working Group suggests that it may be necessary to consider stopping treatment in patients with significant disease progression, determined by an Expanded Disability Status Scale (EDSS) score of higher than 6, who have not experienced a relapse in the preceding two years.[3]

Drug

The mechanism of action of cladribine in treating MS is not fully understood. Cladribine has anti-proliferative effects on lymphocytes, which likely mediate the myelin destruction that characterizes MS. Cladribine appears to carry out these antiproliferative effects through inhibition of DNA synthesis.[11]

Cladribine is indicated as monotherapy for the treatment of adult patients with RRMS to reduce the frequency of clinical exacerbations and delay the progression of disability. The indication states that cladribine should be recommended for patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for RRMS. It is administered orally, and is available as 10 mg tablets. The efficacy and safety of cladribine beyond two years has not been established, thus the recommended cumulative dose is 3.5 mg/kg over the course of two years, with one treatment course of 1.75 mg/kg per year followed by observation for another two years. The treatment course is spread over two weeks each year, one week at the beginning of the first month of that year and the other at the beginning of the second month. During each week, patients receive 10 mg or 20 mg daily, based on body weight, over the course of four to five days. The following clinical assessments are recommended prior to starting and continuing therapy with cladribine: lymphocyte counts must be normal before initiating cladribine in year 1, and at least 800 cells/mm³ (i.e., grade 0 or 1) before initiating cladribine in year 2. The product monograph for cladribine notes that treatment in year 2 can be delayed for up to six months to allow for recovery of lymphocytes to at least 800 cells/mm^3, but if recovery takes more than six months, the patient should discontinue cladribine.[5]

Table 2: Key Characteristics of Various Disease-Modifying Therapies Approved for MS

Approved Drugs[a]	Mechanism of Action	Approved Indications[b]	Route of Administration	Recommended Dose	Serious Side Effects and Safety Issues
Cladribine[5]	Inhibits lymphocyte proliferation	Monotherapy for treatment of adult RRMS patients	Oral	3.5 mg/kg over two years	Lymphopenia, infections (herpes zoster, TB/LTB reactivation, PML), malignancies, teratogenic
Ocrelizumab (Ocrevus)[12]	Reduction in CD20	RRMS	IV infusion	600 mg every six months	Infusion reactions, infections (herpes, respiratory tract) Contraindicated in patients with active/severe infection or PML
Pegylated IFN beta-1a (Plegridy)[13]	Its effects in MS not completely understood; exerts its biological effects by binding to type I IFN receptors on the	RRMS	SC injection	125 mcg every 2 weeks	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection site reactions, depression/suicide

Approved Drugs[a]	Mechanism of Action	Approved Indications[b]	Route of Administration	Recommended Dose	Serious Side Effects and Safety Issues
	surface of human cells				Patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon or any other component of the formulation or the container
Alemtuzumab (Lemtrada)[14]	Binds to CD52	RRMS; patients who have had an inadequate response to interferon beta or other disease-modifying therapies	IV infusion	Initial treatment cycle: 12 mg/day for 5 consecutive days Second treatment cycle: 12 mg/day for 3 consecutive days administered 12 months after the initial treatment course	Autoimmune disorders, infections, infusion reactions Contraindicated in patients who are hypersensitive to alemtuzumab or to any ingredient in the formulation or component of the container; are infected with HIV; have active or latent TB, active severe infections, or active malignancies; are on antineoplastic or immunosuppressive therapies; have a history of PML
Dimethyl fumarate (Tecfidera)[15]	Not completely understood; activates the Nrf2 pathway	RRMS	Oral capsule	240 mg twice daily	PML, reduced lymphocyte count Contraindicated in patients hypersensitive to this drug or to any ingredient in the formulation or component of the container
Fingolimod (Gilenya)[16]	Its effects in MS are not fully known; its active metabolite binds to receptors on lymphocytes, blocks lymphocytes from leaving lymph nodes, reduces the number of lymphocytes in peripheral blood, and reduces lymphocyte migration into CNS	RRMS; generally recommended in MS patients who have had inadequate response to, or are unable to tolerate, one or more therapies for MS	Oral capsule	0.5 mg/day	PML, skin cancer, infections (varicella), heart block Contraindicated in patients who are hypersensitive to fingolimod, who are at risk for an opportunistic infection immunocompromised due to treatment or to disease, have hepatic insufficiency, active severe infections, or known active malignancies. Varicella zoster vaccination recommended

Approved Drugs[a]	Mechanism of Action	Approved Indications[b]	Route of Administration	Recommended Dose	Serious Side Effects and Safety Issues
Glatiramer acetate (Copaxone)[17]	Likely modifies the immune processes responsible for pathogenesis of MS	RRMS; single demyelinating event, accompanied by abnormal MRI scans and considered to be at risk of developing CDMS	SC injection	20 mg/day	Contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol
Interferon beta-1a (Avonex; Rebif)[18]	Its effects in MS not completely understood; exerts its biological effects by binding to specific receptors on the surface of human cells, and inducing the expression of numerous IFN-induced gene products	RRMS; SPMS with relapses; single demyelinating event, accompanied by abnormal MRI scans, with lesions typical of MS	IM injection (Avonex) SC injection (Rebif)	IM: 30 mcg/ week. (increase up to 60 mcg/week if needed) SC: 22 mcg or 44 mcg 3 times/week	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection site reactions, depression/suicide Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, pregnant women
Interferon beta-1b (Betaseron; Extavia)[19]	Its effects in MS not completely understood; exerts its biological effects by binding to specific receptors on the surface of human cells, and inducing the expression of numerous IFN-induced gene products	RRMS; SPMS; single demyelinating event accompanied by at least two clinically silent lesions typical of MS	SC injection (Betaseron, Extavia)	0.25 mg every other day	Hepatic injury, thrombotic microangiopathy, hematologic (abnormal blood cell counts), injection site reactions, depression/suicide Contraindicated in patients with known hypersensitivity to natural or recombinant interferon, patients with liver disease, pregnant women
Natalizumab (Tysabri)[20]	Binds to the alpha 4 subunit of human integrin: blocks interaction of alpha 4 beta-1 integrin with VCAM-1; and blocks the interaction of alpha 4 beta 7 integrin with MadCAM-1	RRMS; generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, other therapies for MS	IV infusion	300 mg every 4 weeks	PML, herpes Contraindicated in patients who have had PML, at risk for PML; hypersensitive to this drug or to any ingredient in the formulation or any component of the drug; immunocompromised, including those immunocompromised due to immunosuppressant or antineoplastic therapies, or immunodeficiencies

Approved Drugs[a]	Mechanism of Action	Approved Indications[b]	Route of Administration	Recommended Dose	Serious Side Effects and Safety Issues
Teriflunomide (Aubagio)[21]	Not completely understood; may reduce numbers of activated lymphocytes available for migration into the CNS	RRMS	Oral tablet	14 mg once daily	Hepatotoxicity Contraindicated in patients who are hypersensitive to this drug or to leflunomide; patients currently treated with leflunomide; severe hepatic impairment; pregnant women or women of child-bearing age who are not using contraception; immunodeficiency states such as AIDS; serious active infection; impaired bone marrow function or with significant anemia, leucopenia, neutropenia, or thromobocytopenia.

CD20 = cluster of differentiation 20 B-lymphocyte antigen; CD52 = cluster of differentiation 52 CAMPATH-1 antigen; CNS = central nervous system; IFN = interferon; IL = interleukin; IM = intramuscular; IV = intravenous; LTB = latent tuberculosis; MadCAM-1 = mucosal addressin cell adhesion molecule-1; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary-progressive multiple sclerosis; TB = tuberculosis; VCAM-1 = vascular cell adhesion molecule-1.

[a] Daclizumab has been voluntarily withdrawn from the Canadian and global market due to safety reports related to serious inflammatory brain disorders during time of drafting this report.[4]

[b] Health Canada indication.

Objectives And Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of cladribine for the treatment of RRMS.

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 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adults with relapsing-remitting multiple sclerosis Subgroups: Disease activity (highly active versus not) Treatment-naive versus experienced
Intervention	Cladribine 10 mg or 20 mg orally once daily for four or five days for one week at the beginning of the first treatment month and one week at the beginning of the second treatment month, over the course of one year. The recommended cumulative dose is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year, followed by observation for another 2 years.
Comparators	Interferon beta-1a (IM or SC, pegylated or non-pegylated) Interferon beta-1b Glatiramer acetate Natalizumab Fingolimod Dimethyl fumarate Alemtuzumab Teriflunomide Daclizumab[a] Ocrelizumab
Outcomes	**Key efficacy outcomes:** Rate of relapse (and proportion of patients relapse-free) Disability progression or improvement (measured by a validated scale)[b] Health-related quality of life[b] Symptoms (e.g., fatigue)[b] **Other efficacy outcomes:** Brain lesions on MRI (number of lesions: Gd+ lesions, new or enlarging T2 lesions) Brain volume on MRI Use of rescue medications Ability to work/attend school[b] No evidence of disease activity
	Harms outcomes:

	Mortality Serious adverse events Non-serious AE Withdrawals (including WDAEs) Notable harms: infection, neoplasia, hematologic, effects in pregnancy, progressive multifocal leukoencephalopathy
Study Design	Published and unpublished phase III RCTs

AE = adverse event; Gd+ = gadolinium-enhancing; IM = intramuscular; MRI = magnetic resonance imaging; RCT = randomized controlled trial; SC = subcutaneous; WDAE = withdrawal due to adverse event.

[a] Daclizumab has since been removed from the Canadian and global markets and is no longer considered an appropriate comparator for this review.

[b] Outcomes identified as important to patients in their input to CADTH Common Drug Review.

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

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

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 January 9, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on May 16, 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 *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 manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

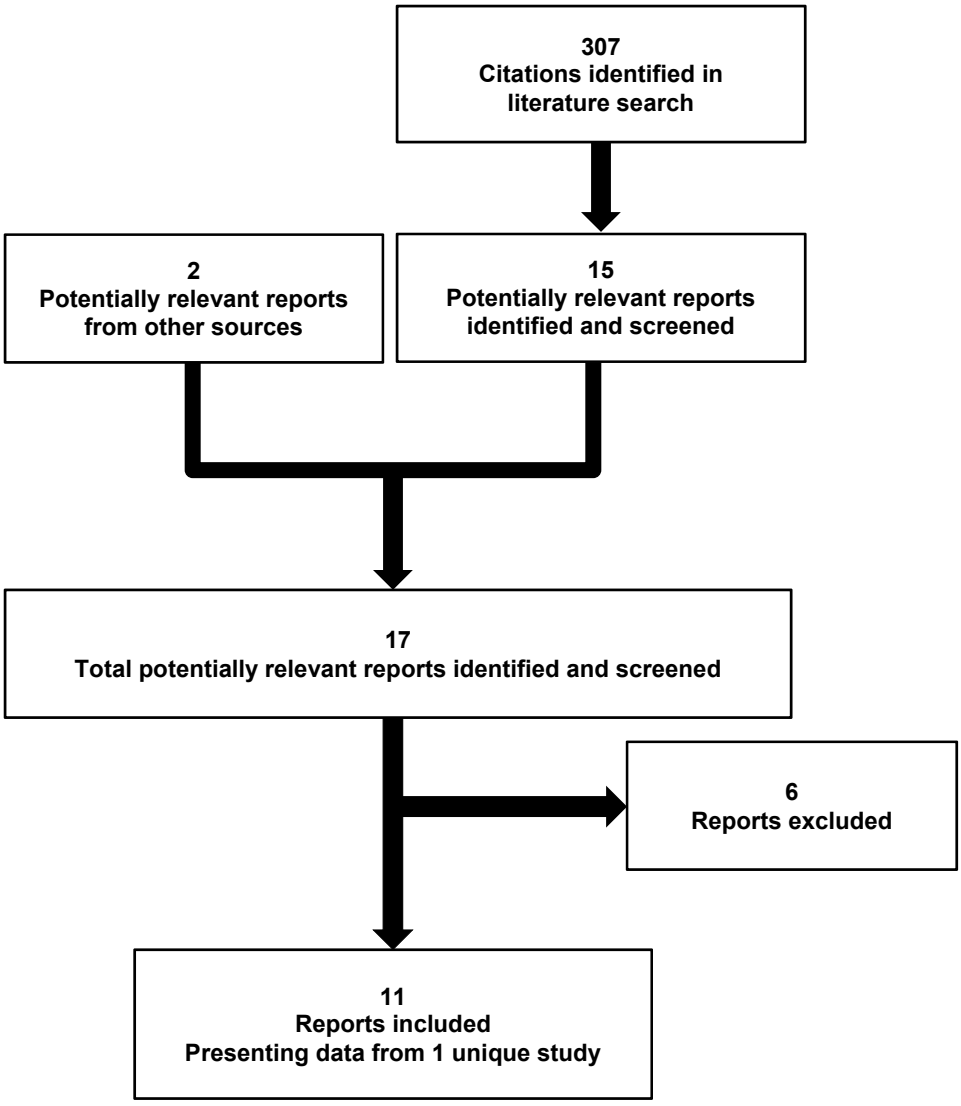


Table 4: Details of Included Studies

		CLARITY
Designs & Populations	**Study Design**	DB RCT
	Locations	155 sites: 32 countries (Canada, US, Europe, South America, Israel, Lebanon, Saudi Arabia, Australia, Tunisia)
	Randomized (N)	1,326
	Inclusion Criteria	Male or female, between 18 and 65 years of age RRMS according to the McDonald criteria (2005) Lesions consistent with MS on MRI according to Fazekas criteria At least one relapse within 12 months before study entry Clinically stable and not had a relapse within 28 days prior to trial day 1 EDSS of no more than 5.5
	Exclusion Criteria	Two or more of their previous DMTs had failed Experienced a relapse within 28 days before the start of the study Any indication of compromised immune function, including systemic disease such as HIV or abnormal hematologic results (e.g., low platelet, neutrophil, or leukocyte count). Received disease-modifying drugs within the last three months prior to trial day 1
Drugs	**Intervention**	Cladribine tablets 3.5 mg/kg (administered p.o. as 0.875 mg/kg/course for two courses plus placebo p.o. for two courses during the first 48 weeks and 0.875 mg/kg/course for two courses during the second 48 weeks), or Cladribine tablets 5.25 mg/kg (administered p.o. as 0.875 mg/kg/course for four courses during the first 48 weeks and 0.875 mg/kg/course for two courses during the second 48 weeks), or
	Comparator(s)	Matching placebo (administered p.o. for four courses during the first 48 weeks and two courses during the second 48 weeks).
Duration	**Phase**	
	Screening	4 weeks
	Double-blind	96 weeks
	Follow-up	4 weeks
Outcomes	**Primary End Point**	Qualifying relapse rate at 96 weeks
	Other End Points	Proportion of patients qualifying relapse-free at 96 weeks Disability progression at 96 weeks (time to sustained change in EDSS ≥ one point, or ≥ 1.5 points if baseline EDSS was 0, over a period of at least three months) Mean number of active T1 gadolinium-enhanced lesions per patient per scan at 96 weeks Mean number of active T2 lesions per patient per scan at 96 weeks Mean number of combined unique lesions defined as 1) new T1 gadolinium-enhancing, or 2) new T2 non-enhancing or enlarging lesions, or 3) both, without double-counting (designated “combined unique lesions”) per patient per scan at 96 weeks **Tertiary endpoints:** Time to first qualifying relapse at 96 weeks Proportion of patients with no active T2 lesions at 96 weeks Proportion of patients with no active T1 gadolinium-enhanced lesions at 96 weeks Mean change in T2 lesion volume from baseline to 96 weeks Mean number of T1 hypointense lesions per patient per scan at 96 weeks Mean change in volume of T1 hypointense lesions from baseline at 96 weeks Proportion of patients rescued at 96 weeks Mean changes in brain atrophy, as measured by mean percentage change in brain parenchymal

		CLARITY
		fraction on MRI scans, from baseline to week 48, from baseline to week 96 and from week 48 to week 96. (Note that analysis pertaining to this end point will be provided as an independent report) Assess the potential impact of treatment with cladribine on patients' health-related quality of life Assess the potential impact of treatment with cladribine on health care resource utilization Change from baseline to 96 weeks in the following MSQOL-54 domains: physical function, role limitations-physical, role limitations-emotional, health perception, mental health and change in health Change from baseline to 96 weeks in the following SF-36 domains: physical functioning, role physical, general health, and mental health. Mean and median number of HRU per patient during the follow-up period.
NOTES	**Publications**	Giovannoni 2010[11], 2011[22], 2017[23], Cook 2011[24], Comi 2013[25], Rammohan 2012[26], Afolabi 2017[27], De Stefano 2017[28]

DB = double-blind; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Score; HRU = health care resource utilization; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSQOL-54 = Multiple Sclerosis Quality of Life–54; p.o.= orally; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis; SF-36 = Short Form (36) Health Survey.

Note: Three additional reports were included (Manufacturer's submission,[29] Clinical Study Report,[30] and Health Canada Reviewers Report[31]).

Source: Clinical Study Report for CLARITY.[30]

Included Studies

Description of Studies

One double-blind RCT was included in this review. CLARITY was a manufacturer-sponsored multinational (155 sites, 32 countries, including Canada) phase III trial. Patients with RRMS (2005 McDonald criteria) and at least one relapse within 12 months before study entry were randomized 1:1:1 to cladribine 3.5 mg/kg, cladribine 5.25 mg/kg, or placebo, over a course of 96 weeks.

Randomization was carried out in a centralized manner using an interactive voice response system and was stratified by study site. Patients were assigned a seven-digit randomization number that corresponded to one of the three treatment groups in the study. An independent blinded evaluating physician performed neurological exams and a blinded central radiological centre assessed MRI.

Subgroup analyses were only planned comparing results in the various regions.

Populations

Inclusion and Exclusion Criteria

Patients had to have a diagnosis of RRMS according to 2005 McDonald criteria and lesions consistent with MS on MRI according to Fazekas criteria. They were to have had at least one relapse in the 12 months prior to study entry, and an EDSS score no greater than 5.5.

Patients who had failed two or more previous disease-modifying therapies (DMTs) were excluded, as were those experiencing a relapse within 28 days of the start of the study. Patients who had received disease-modifying drugs within the three months prior to day 1 of the trial were also excluded.

Baseline Characteristics

Patients were approximately 39 years old on average and the majority were female and white. The mean EDSS score at baseline was approximately 2.9 and most patients (80%) were at a score of 2 or above. A small number of patients (10%) had an EDSS score of 5 or more. All but two patients had a relapse within the past year and 30% had two or more relapses within the past year. Approximately 30% of patients had received prior therapy for MS, most having received some form of interferon. There were no clear differences in baseline characteristics between groups within CLARITY.

Table 5: Summary of Baseline Characteristics

	CLARITY	
	Cladribine 3.5 mg/kg N = 433	**Placebo N = 437**
Age, years, mean (SD)	37.9 (10.3)	38.7 (9.9)
Male, **n (%)**	135 (31.2)	149 (34.1)
Race, n (%)		
White	425 (98.2)	429 (98.2)
Black	2 (0.5)	1 (0.2)
Asian	2 (0.5)	1 (0.2)
Other	4 (0.9)	6 (1.4)
Weight, kg, mean (SD)	68.1 (14.6)	70.3 (15.4)
EDSS		
Mean (SD)	2.8 (1.2)	2.9 (1.3)
EDSS category, n (%)		
0	12 (2.8)	13 (3.0)
1	75 (17.3)	70 (16.0)
2	133 (30.7)	127 (29.1)
3	108 (24.9)	96 (22.0)
4	71 (16.4)	83 (19.0)
≥ 5	34 (7.9)	48 (11.0)
Number T1 gadolinium-enhanced lesions, mean (SD)	1.0 (2.7)	0.8 (2.1)
Number of T1 hypointense lesions, mean (SD)	7.1 (8.2)	7.4 (8.0)
T2 lesion volume (mm^3), mean (SD)	14,828.0 (16,266.8)	14,287.6 (13,104.8)
Time since first attack (years) prior to study day 1, mean (SD)	7.9 (7.2)	8.9 (7.4)
Time since most recent relapse (months) prior to study day 1, mean (SD)	5.4 (2.9)	5.4(2.7)
Number of relapses within the past 12 months prior to study day 1, n (%)		
0	0	0
1	303 (70.0)	306 (70.0)
2	105 (24.2)	110 (25.2)
3	22 (5.1)	19 (4.3)
≥ 4	3 (0.7)	2 (0.5)
Patients who received treatment during the last 3 months prior to study Day 1, n (%)	1 (0.2)	1 (0.2)
Patients with abnormalities related to MS on neurological examination, n (%)	418 (96.5)	425 (97.3)
Patients who have signs and symptoms related to MS, n (%)	416 (96.1)	416 (95.2)
MS therapy taken by patients prior to study day 1, n (%)		
None	320 (73.9)	295 (67.5)

	CLARITY	
	Cladribine 3.5 mg/kg N = 433	Placebo N = 437
Any	113 (26.1)	142 (32.5)
Avonex	44 (10.2)	46 (10.5)
Betaseron	42 (9.7)	56 (12.8)
Copaxone	19 (4.4)	29 (6.6)
Rebif	36 (8.3)	44 (10.1)
Tysabri	0	1 (0.2)
Other	7 (1.6)	17 (3.9)

EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; SD = standard deviation.

Interventions

Patients were randomized to receive placebo, cladribine cumulative dose of 3.5 mg/kg, or cladribine cumulative dose of 5.25 mg/kg over 96 weeks of double-blind treatment. The latter dose was not approved by Health Canada and therefore is out of scope for this review. Cladribine was administered orally as 0.875 mg/kg per course for two courses plus placebo orally for two courses during the first 48 weeks, and 0.875 mg/kg per course for two courses during the second 48 weeks. The placebo group was administered placebo orally for four courses during the first 48 weeks and two courses during the second 48 weeks. Patients were treated with oral cladribine in 10 mg increments based on weight (60 kg to 69.9 kg, 70 kg to 79.9 kg, etc.). The treatment course consisted of a 28-day period during which patients received cladribine on four to five consecutive days. Treatment courses were administered at day 1, weeks 5, 9, and 13 in the first 48-week period, then weeks 48 and 52 in the second 48-week period.

Rescue therapy with interferon beta-1a (Rebif, 44 mcg three times a week) was available beginning at week 24 for patients experiencing more than one qualifying relapse and/or a sustained increase in EDSS of at least one point, or at least 1.5 points if their baseline EDSS was zero (over a period of three months or greater) over the course of a calendar year. Patients were not required to take Rebif as rescue medication and could instead continue on their blinded therapy or take another disease-modifying therapy not supplied by the manufacturer. Patients who took rescue medication, whether it was Rebif or another disease-modifying therapy, were discontinued from study treatment but asked to continue in the trial and adhere to all scheduled assessments.

Corticosteroids (one gram of intravenous methylprednisolone for three days) were permitted for the treatment of acute relapses at the discretion of the treating physician. If not possible to use this intravenous option, oral steroids could be utilized for not more than 14 days following a relapse. Any MRI scans conducted during the trial were to be performed before administration of steroids or at least seven days after the last dose of steroids.

Outcomes

The primary outcome of CLARITY was the qualifying relapse rate at 96 weeks. The annualized relapse rate (ARR) was calculated as the total number of relapses divided by the total number of days on study multiplied by 365.25. A relapse was defined as a two-grade increase in one or more Kurtzke Functional Systems (KFS) or one grade in two or more KFS, not including changes in bowel/bladder function or cognition, in the absence of

fever, and lasting for at least 24 hours, all preceded by at least 30 days of clinical stability or improvement. Relapses were to be documented and followed up through neurological assessments. Patients were told to inform the trial site within 24 hours of a suspected relapse, at which time the trial personnel (with the exception of the evaluating physician) reviewed the symptoms with the patient and determined whether a neurological assessment was indicated. If an assessment was indicated, it was preferred that it be carried out within seven days of the original onset of symptoms. Neurological assessments were to be carried out by the evaluating physician in a blinded manner. Once the assessment was completed, including the EDSS, the treating physician reviewed all the data and determined if the event met the protocol definition of a relapse.

All health-related quality of life questionnaires were administered at day 1, weeks 24, 48, 72, and 96, and at each relapse. In the countries where it was applied, the Short Form (36) Health Survey (SF-36) was also administered in week 13. However, because the SF-36 was added to the study late as a protocol amendment, most baseline assessments were missing.

The Multiple Sclerosis Quality of Life–54 (reviewed in detail in Appendix 5) is a self-reported, disease-specific quality of life instrument, based on the SF-36 instrument and supplemented with 18 disease-specific dimensions measuring: 1) anxiety provoked by the patient's health status (four items); sexual functioning (four items); satisfaction with sex life (one item); overall quality of life (two items); cognitive functioning (four items); energy (one item); pain (one item); and social functioning (one item). There is no single overall score for MSQOL-54. Two summary scores — physical health and mental health — can be derived from a weighted combination of scale scores (ranging from 0 to 100, with a higher scale score indicating improved quality of life).[32] In addition, the multiple-item scales of each of these scores can be analyzed individually to understand more clearly the changes on the composite scores. The physical health composite score is computed from the individual scores of the following scales: physical function, health perceptions, energy/fatigue, role limitations-physical, pain, sexual function, social function, and health distress. The mental health composite score is computed from the individual scores of the following scales: health distress, overall quality of life, emotional well-being, role limitations-emotional, and cognitive function.[32] No minimal clinically important differences (MCIDs) were identified for the summary scores. The MSQOL-54 was only available in three languages (English, Italian, and French-Canadian), and therefore was only used in a limited number of countries (Canada, UK, US, Australia, and Italy).

The EuroQol 5-Dimensions (EQ-5D) questionnaire is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments.[33,34] It is reviewed in detail in Appendix 5. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) by 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[33,34] The second part is a 20 cm visual analogue scale (VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the VAS that best represents their health on that day. The EQ-5D index score

is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) depends on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores below 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for this scale in the general population ranged from 0.033 to 0.074.[35] For patients with MS, the MCID ranged from 0.050 to 0.084.

Disability progression at 96 weeks (time to sustained change in an EDSS score greater than one point, or greater than 1.5 points if the baseline EDSS score was 0, over a period of at least three months) was a secondary outcome of CLARITY. The EDSS evaluation was carried out by a blinded evaluating physician who was not aware of data from the patients' prior evaluations. EDSS is a 10-point ordinal scale commonly used to assess disability in MS. It is reviewed in detail in Appendix 5. EDSS assesses eight different domains of disability: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. Because it is an ordinal scale, changes at the lower end of the scale do not have the same significance for the patient as changes at higher ends of the scale (with the turning point typically thought to be 5.5, the transition to a cane). The MCID from 0 to 5.5 is 1.0, while the MCID from 5.5 to 8.5 is 0.5.

MRI scans were carried out in the pre-trial evaluations, and at weeks 24, 48, and 96. The following MRI parameters were measured and analyzed:

- Combined unique lesions, which were defined as 1) new T1 gadolinium-enhancing or 2) new T2 non-enhancing or enlarging lesions, or 3) both, without double-counting
- T1 gadolinium-enhancing lesions
- T1 gadolinium-enhancing lesion volume
- Active T1 gadolinium-enhancing lesions
- Active T2 lesions
- T2 lesion volume
- Number of T1 hypointense lesions
- T1 hypointense lesion volume
- Brain atrophy, measured by per cent brain volume change (post hoc analysis).

Freedom from disease activity was assessed as a post hoc analysis, and was composed of three outcomes assessed in the pre-planned analysis for CLARITY: patients with no relapses during the study, no three-month sustained change in EDSS score, and no new MRI lesions (no T1 gadolinium-enhancing or active T2 lesions).

Statistical Analysis

Power calculations were performed, providing 90% power to detect what the manufacturer described as a “clinically meaningful” 25% relative reduction in the primary efficacy end point (relapse rate at 96 weeks), comparing both doses of cladribine with placebo. The calculation was performed using a two-sided t-test and assumed 2.1 relapses in the placebo group over 96 weeks, and thus 1.575 relapses over this period in the cladribine groups. The calculation also assumed a standard deviation of 2.02 (which was based on two-year placebo data from the PRISMS study) and a 10% nonevaluable rate and a type I error rate for each cladribine group versus the placebo group of 2.5%. Based on these calculations, there would be 430 patients in each group, for a total sample of 1,290 patients across all three groups.

Relapse rate was analyzed using a Poisson regression model with fixed effects for treatment group and region with log of time on study as an offset variable in the model. Treatment groups were compared using an approximate chi-square test based on Wald statistics and relative risks of developing a qualifying relapse and its associated 95% confidence interval (CI) were estimated for each treatment group comparison. The time to three-month sustained change in EDSS score was analyzed using a Cox proportional hazards model with fixed effects for treatment group and region. An approximate chi-square test based on Wald statistic was used to compare cladribine versus placebo.

Multiplicity

Hochberg’s step-up procedure was used to control for multiple comparisons of the two doses for the primary outcome (ARR). If the cladribine dose group with the largest *P* value when compared with results in the placebo group had a $P \leq 0.05$, then the qualifying relapse rates of both cladribine 5.25 mg/kg and cladribine 3.5 mg/kg groups were considered to be significantly different from the relapse rate of the placebo group. If that *P* value was > 0.05, then the qualifying relapse rate of the other cladribine dose group was only considered to be significantly different from the qualifying relapse rate of the placebo group if its corresponding comparison *P* value was ≤ 0.025.

A hierarchical testing procedure was used to account for multiple statistical comparisons of the secondary outcomes. If both cladribine doses were significant for the primary parameter, then these MRI parameters were tested in this order: T1, T2, and combined unique lesions for cladribine 5.25 mg/kg versus placebo, followed by T1, T2, and combined unique lesions for cladribine 3.5 mg/kg versus placebo in a hierarchical manner at the 5% level. If only one cladribine dose was significant for the primary parameter, then these MRI parameters were tested in the same order for the significant dose of cladribine versus placebo at the 2.5% level. These MRI parameters were analyzed using a non-parametric analysis of covariance model on ranked data with fixed effects for treatment group and region with adjustment for T1 gadolinium-enhancing lesions, as no data were available for baseline T2 or combined unique lesions.

Missing Data

Missing data for MRI and for relapses were imputed using the median across all patients with non-missing values at 96 weeks (or at baseline if baseline data were missing). Patients who received rescue therapy were discontinued from study treatment, but were continued to be followed for assessments, unless they declined to do so.

Subgroups

Pre-planned subgroup analyses were carried out based on region. A number of post hoc subgroup analyses, including those of interest for this review (prior disease-modifying therapy and number of relapses in the year prior to randomization) were published, however, no interaction *P* values were reported.

Analysis Populations

The intention-to-treat population included all randomized patients. The evaluable population consisted of all patients who completed treatment without a major protocol violation and with 96 weeks of data. The safety population included all patients who received at least one dose of study medication, and who had follow-up safety data.

Patient Disposition

Numerically more placebo patients than cladribine-treated patients had discontinued by 96 weeks, 13% versus 8% of patients. Patients experiencing disease progression was the most common reason for discontinuation in the placebo group.

Table 6: Patient Disposition

	CLARITY	
	Cladribine 3.5 mg/kg	**Placebo**
Screened, N	1,641	
Randomized, N	433	437
Completed study, n (%)	398 (92)	380 (87)
Discontinued, n	35 (8)	57 (13)
Adverse event	5 (1)	5 (1)
Protocol violation	4 (1)	10 (2)
Lost to follow-up	8 (2)	4 (1)
Death	1 (< 1)	2 (1)
Disease progression	5 (1)	21 (5)
Other	12 (3)	15 (3)
ITT, N (%)	433	437
Evaluable, N	381 (88)	364 (83)
Safety, N	430 (99)	435 (> 99)

ITT = intention-to-treat.

Exposure to Study Treatments

Six courses of therapy were administered during the study. Of the cladribine-treated patients, 92% completed all their courses of therapy, while in placebo, 86% completed all six courses. The mean (standard deviation) time on treatment was 49.1 (10.7) weeks for cladribine, and 47.1 (13.3) weeks on placebo. Time on treatment was calculated as the time between the last trial administration of study drug and the first trial administration of study drug. The mean time on study was 91.6 (15.9) weeks for cladribine and 88.2 (20.5) weeks for placebo.

Critical Appraisal

Internal Validity

Randomization in CLARITY was carried out using an interactive voice response system to facilitate concealment of treatment allocation. CLARITY was a double-blind study and blinding appears to have been facilitated through the use of a matching placebo. An independent blinded evaluating physician performed neurological exams and a blinded central radiological centre assessed MRI. There was a relatively large difference in the proportion of patients who experienced lymphopenia between cladribine and placebo, and given that this is an expected side effect of cladribine therapy, this may have provided an indication as to which therapy the patient had been assigned.

Power calculations were performed and the manufacturer appeared to enrol the minimum number of patients required for each group, based on its calculations. The manufacturer based the power calculations on a “clinically meaningful” difference of 25% in relapse rate over 96 weeks. However, it is not clear how the manufacturer determined this to be a clinically meaningful difference. According to the clinical expert consulted on this review, a 30% difference is more likely to be considered clinical meaningful.

A Hochberg procedure as well as a hierarchical testing protocol were used to account for multiple statistical comparisons. There were two doses of cladribine in the study, both compared with placebo, therefore adjustments had to be made for the multiple doses as well, and this appears to have been done. However, these adjustments were only made for the primary outcome (relapse rate) and for three MRI outcomes. Disability progression, health-related quality of life, and all other outcomes of interest to this review were not adjusted for multiple comparisons and therefore this data should be considered hypothesis-generating.

There were numerically more withdrawals in the placebo group than in the cladribine group in CLARITY. The most common reason for withdrawal in the placebo group was disease progression. Premature withdrawals may be particularly prone to introducing bias in degenerative conditions like MS as one would expect to see continued decline in the placebo group, in particular.

Missing data were imputed by simply taking the median of the results for patients who had complete data. This method of imputation assumes that the results from the population who had missing data would have been the same as the results from those who had complete data. This approach ignores the impact of lack of treatment on a patient’s results. Fortunately, there appears to have been only a limited amount of missing data for most outcomes, according to the manufacturer’s reporting, thus limiting the impact of the uncertain validity of this method of imputation on the CLARITY data. For example, the manufacturer reported no missing data for the key secondary MRI outcomes (T1- or T2-weighted or combined unique lesions). Data were missing for brain volume (approximately 20% of the randomized population was missing in each group), and disease activity (missing 10% in the cladribine group and 17% in the placebo group). However, these were post hoc analyses and no attempts appear to have been made to impute missing values. As noted below, there was a significant amount of missing data for health-related quality of life (EQ-5D and MSQOL-54). In the case of MSQOL-54, nearly 90% of the randomized population was missing from the analysis, thus clearly no conclusion can be drawn from these data. For the EQ-5D, approximately 20% of the data were missing and, regardless of the method of imputation, confidence in the analysis will be reduced.

No baseline data were collected for the SF-36, because they were added as a late protocol amendment. This makes it impossible to know whether any differences in end-of-study data are attributable to the intervention or due to differences between groups that were evident at baseline and simply continued throughout the study. Therefore, the SF-36 data were not reported in this review. The published post hoc analysis for brain volume by MRI also did not use baseline data. However, according to the authors, this was to account for the fact that there may be an accelerated loss of brain volume in the first six months of anti-inflammatory therapy for MS, a phenomenon known as pseudoatrophy.[28]

Pre-planned subgroup analyses were only performed based on region, therefore all subgroup analyses that were relevant to our review protocol (history of DMT use prior to study [naive or experienced] and frequency of relapses) were post hoc analyses. None of the statistical analyses were adjusted for multiple comparisons. Because randomization was stratified by region, these post hoc subgroup analyses did not follow randomization strata. No interaction *P* values were reported in these post hoc subgroup analyses, therefore one cannot determine if there were differences in response based on subgroup.

Patients in CLARITY were offered rescue therapy with Rebif, per protocol, but the use of other DMTs for rescue was allowed; they were simply not supplied by the manufacturer. Once patients were offered rescue, they were discontinued from their study therapy but remained in the study to be followed for assessments. Although the proportion of patients undergoing rescue was relatively small, numerically more patients in the placebo group underwent rescue (6.2% versus 2.5%) compared with the cladribine group. This may have biased results finding no difference between cladribine and placebo overall. However, due to the small difference in rescue use between groups the impact is likely to be small.

External Validity

Health-related quality of life was only assessed to a limited extent in CLARITY. The MSQOL-54, the only disease-specific instrument used in CLARITY, was administered to a small fraction of the study population — too small to consider it a reliable assessment of health-related quality of life. EQ-5D was also assessed, but data were missing for about 20% of the population, and SF-36 was assessed, but no baseline data were available. The addition of health-related quality of life to CLARITY appears to have been a late protocol amendment, and this helps to explain the lack of baseline data and the low proportion of respondents to the survey instruments. Patients with MS clearly place a large emphasis on quality of life, based on their submission to CDR, and the lack of data for this important outcome is a significant limitation of the data from CLARITY.

Cladribine has only been compared with placebo and not with any of the other approved therapies for MS. Because CLARITY was initiated in 2005 and completed by 2008, the number of active comparators at that time was lower compared with the dramatic increase in DMTs for MS since the time this study was planned. Nevertheless, even a comparison versus one of the interferons or to glatiramer, the two key therapeutic options at the time, would have provided additional context for the efficacy and harms of cladribine.

The manufacturer used the 2005 version of the McDonald criteria to diagnose MS in CLARITY. Although the last two versions (2005 and 2010) are not materially different from each other, it is not clear what the implications would be of using an earlier version of the current 2010 McDonald criteria.

The primary outcome assessed — ARR — is a typical and relevant outcome in MS trials. MRI outcomes received the next highest priority in the statistical analysis hierarchy of outcomes, while disability progression, quality of life, and other outcomes were not part of the statistical hierarchy and therefore no adjustments were made for multiple comparisons of these outcomes. As a result, the results from CLARITY can only be considered as hypothesis-generating when it comes to outcomes of importance to the patient: disability and quality of life.

The demographics of the population enrolled appeared to be consistent with the population one would expect to see treated for RRMS in Canada, according to the clinical expert consulted on this review, and there were Canadian sites in the study. The expert did note that treatment-resistant patients were screened out of the study, as patients failing two or more DMTs were excluded from CLARITY. At the time CLARITY was planned there was a relatively limited number of DMTs, and this is an even larger gap in knowledge today than when CLARITY was originally planned and executed.

The double-blind phase of CLARITY was two years, and for a drug that is dosed in two-year cycles this might not have been long enough to assess either efficacy or safety. There is an extension to CLARITY, reviewed in Appendix 6. However, one of the limitations of the extension was that a varying degree of time, from 0.1 weeks up to 118 weeks, elapsed between the end of the parent trial and the start of CLARITY EXT. Safety data are also available from CLARITY EXT, subject to the same limitation.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 7). See Appendix 3 for detailed efficacy data.

Relapses

There was a lower ARR with cladribine (0.14; 95% CI, 0.12 to 0.17) versus placebo (0.33; 95% CI, 0.29 to 0.38) after 96 weeks and this difference was statistically significant (rate ratio of 0.43; 95% CI, 0.34 to 0.54; $P < 0.001$) (Table 7). This amounts to an absolute difference between groups of 19 relapses per 100 patients per year. The proportion of patients who were relapse-free over 96 weeks was higher with cladribine (80%) than with placebo (61%) (odds ratio of 2.53; 95% CI, 1.87 to 3.43; $P < 0.001$). Note that the proportion of patients relapse-free was not in the statistical hierarchy and thus not controlled for multiple comparisons.

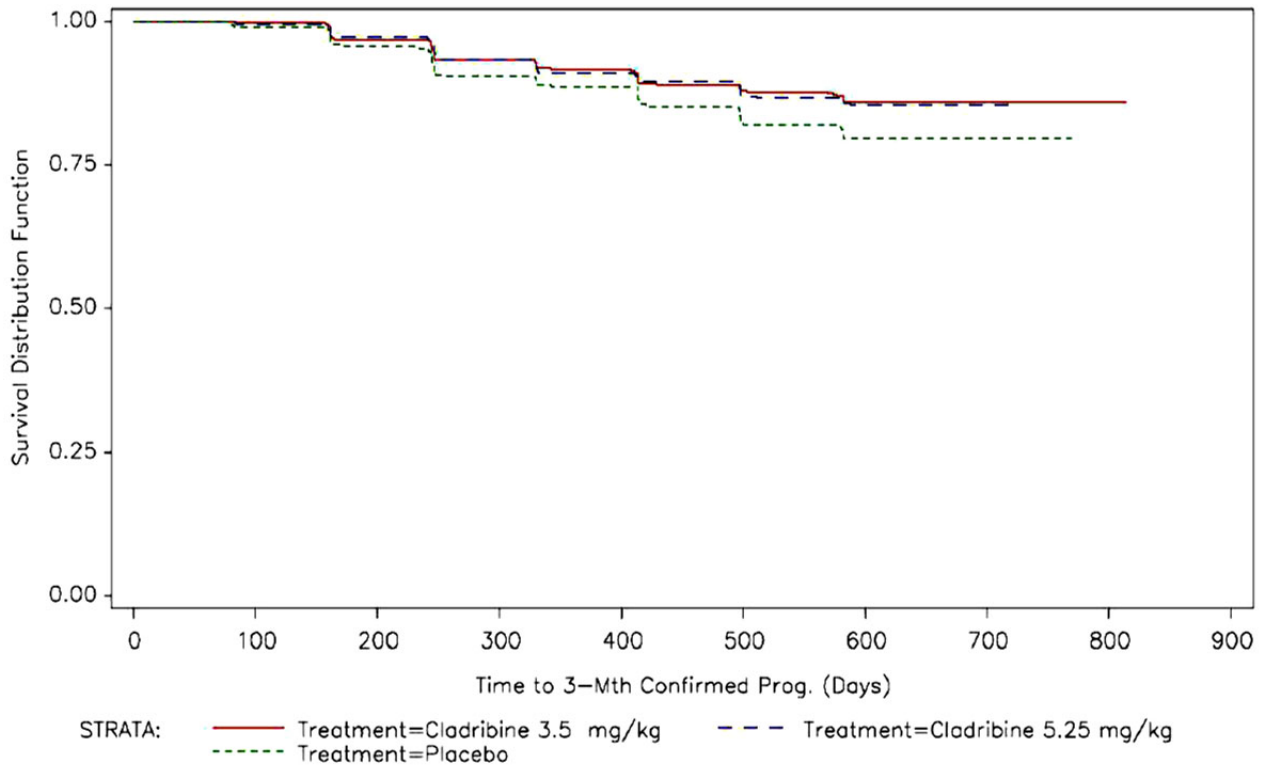
Post hoc subgroup analyses were performed based on prior use of disease-modifying therapy (Table 10). Treatment-naive patients had numerically lower relapse rates in both groups, with statistically significant differences between cladribine and placebo groups in both subgroups. There were statistically significant differences between cladribine and placebo in all subgroups of patients based on prior relapses (1, 2, or 3). None of these results were adjusted for multiple comparisons.

Disability Progression

The time to three-month sustained change in EDSS score was statistically significantly different in favour of cladribine versus placebo (hazard ratio of 0.67; 95% CI, 0.48 to 0.93; $P = 0.018$) (Table 7). This outcome was not part of the statistical hierarchy and thus was not adjusted for multiple comparisons. A larger proportion of cladribine-treated versus placebo-

treated patients went without a sustained three-month change in EDSS score (86% versus 79%, respectively) and this difference was reported as statistically significant (*P* = 0.02), although again not adjusted for multiple comparisons. In a post hoc analysis, similar results were seen for risk of six-month disability progression (hazard ratio of 0.53; 95% CI, 0.36 to 0.78; *P* = 0.0064).

Figure 2: Kaplan–Meier Estimates of Time to Three-Month Sustained Change in EDSS Score by Treatment Group (Intention-To-Treat Population)



EDDS = Expanded Disability Status Scale; Mth = months.

Health-Related Quality of Life

Only approximately 10% of the randomized population had a baseline and 96-week MSQOL-54 score, and the difference in score between groups at 96 weeks was not statistically significant (Table 7). EQ-5D scores at baseline and 96 weeks were available for approximately 80% of the randomized population. EQ-5D index and VAS scores were improved for cladribine versus placebo and this difference was statistically significant (index scores: mean difference of 0.058, *P* < 0.001; VAS: 4.55, *P* = 0.001). No confidence intervals were reported. These outcomes were not part of the statistical hierarchy and therefore no adjustments were made for multiple comparisons. The MCID for EQ-5D index scores in MS is between 0.05 and 0.084, and can be considered clinically significant.

Symptoms

Symptoms were not specifically assessed in CLARITY.

Other Efficacy Outcomes

MRI results were improved for cladribine versus placebo and these differences were statistically significant at 96 weeks for T1-weighted, T2-weighted, and combined unique lesions (Table 9). There were a smaller number of T1 gadolinium-enhanced lesions per patient per scan, with cladribine versus placebo at week 96 (treatment difference of −0.78; 95% CI, −0.92 to −0.65; $P < 0.001$), and a smaller number of active T2-weighted lesions per patient per scan at week 96 (treatment difference of −1.05; 95% CI, −1.22 to −0.87; $P < 0.001$). The number of combined unique lesions per patient per scan at week 96 was also smaller for cladribine versus placebo (treatment difference of −1.28; 95% CI, −1.49 to −1.08]; $P < 0.001$). A larger proportion of cladribine versus placebo patients had no active T1-weighted (87% versus 48%) or T2-weighted lesions (62% versus 28%) compared with placebo. The mean per cent brain volume change from months 6 to 24 was −0.77% for cladribine and −0.95% for placebo, and this difference was reported as statistically significant. However, this was a post hoc analysis and was missing approximately 20% of the randomized population. CDR was unable to find any MCIDs for MRI data (see Appendix 5).

The proportion of patients who were considered free of disease activity was higher with cladribine (47%) than with placebo (17%), and this difference was reported as statistically significant (odds ratio of 4.25; 95% CI, 3.03 to 5.96; $P < 0.0001$). However, this was a post hoc analysis, and data were missing for 10% of the cladribine group and 17% of the placebo group.

A smaller proportion of cladribine-treated patients had to use rescue therapy at some time during the 96-week study compared with placebo (2.5% versus 6.2%) and this difference was statistically significant (odds ratio of 0.40; 95% CI, 0.19 to 0.81; $P = 0.011$), but this analysis was not adjusted for multiple comparisons.

With respect to absenteeism, there was a statistically significant difference between cladribine versus placebo for a number of outcomes, with a smaller number of work days missed by the cladribine-treated patients, a greater degree of productivity for cladribine-treated patients versus placebo, and a smaller number of work days missed by relatives of those treated with cladribine.

Table 7: Key Efficacy Outcomes

	CLARITY	
	Cladribine 3.5 mg/kg n = 433	Placebo n = 437
Relapses		
Number of qualifying relapses, mean (SD)	0.25 (0.59)	0.56 (0.88)
Annualized relapse rate (95% CI)	0.14 (0.12, 0.17)	0.33 (0.29, 0.38)
Rate ratio (95% CI)[a]	0.43 (0.34 to 0.54) $P < 0.001$	
Patients with relapse-free status over 96 weeks, n (%)	345 (79.7)	266 (60.9)
Odds ratio (95% CI)[a]	2.53 (1.87 to 3.43) $P < 0.001$	
Disability – EDSS		
Time to 3-month sustained change in EDSS score by week 96, n	58	82
Hazard ratio (95% CI)[b]	0.67 (0.48 to 0.93) $P = 0.018$	
Patients without a 3-month sustained change in EDSS score, n (%)	371 (85.7) $P = 0.02$	347 (79.4)
Symptoms	NR	NR

	CLARITY	
	Cladribine 3.5 mg/kg n = 433	Placebo n = 437
HRQoL		
MSQOL – Overall QoL	N = 47	N = 48
Adjusted mean change[c] from baseline in score at week 96	−2.21	−1.56
Adjusted mean difference from placebo	−0.66 *P* = 0.840	
EQ-5D	N = 345	N = 340
EQ-5D VAS adjusted mean change[c] from baseline in score at week 96	1.31	−3.24
Adjusted mean difference from placebo	4.55 *P* = 0.001	
EQ-5D index adjusted mean change[c] from baseline in score at week 96	0.019	−0.039
Adjusted mean difference from placebo	0.058 *P* < 0.001	

CI = confidence interval; EDSS = Expanded Disability Status Scale; MSQOL = Multiple Sclerosis Quality of Life; QoL = quality of life; SD = standard deviation; VAS = visual analogue scale.

[a] *P* value based on Wald chi-square test from analysis of end point using a logistic regression model with fixed effects for treatment group and region. Odds ratio and associated 95% CI were estimated using a logistic regression model with fixed effects for treatment group and region.

[b] The hazard ratio, 95% (97.5%) CI and *P* values were estimated using a Cox proportional hazards model with fixed effects for treatment group and region.

[c] QoL: Analysis of covariance (ANCOVA) models on the change in score, including the treatment group, region and score at baseline as covariates.

Source: Clinical Study Report for CLARITY.

Harms

Only those harms identified in the review protocol are reported below (Methods). See Table 8 for detailed harms data.

Adverse Events

There were numerically more adverse events with cladribine than with placebo (81% versus 73%) (Table 8). The most common adverse events were headache (24% cladribine versus 17% placebo) and lymphopenia (22% versus 2%).

Serious Adverse Events

Serious adverse events occurred in 8% of cladribine patients and 6% of placebo patients.

Withdrawal Due to Adverse Events

A similar proportion of patients in the cladribine and placebo groups withdrew due to an adverse event by 96 weeks (1% in each group).

Mortality

Two patients died in each of the cladribine and placebo groups.

Notable Harms

Lymphopenia occurred in numerically more cladribine than placebo patients (22% versus 2%, respectively) over 96 weeks, as did leukopenia (6% versus 1%). According to the manufacturer, transient mild-to-moderate lymphopenia is to be expected with cladribine, given its mode of action. Herpes zoster occurred in 2% of cladribine patients and zero placebo patients by 96 weeks.

Neoplasms — benign, malignant, and unspecified -— occurred in 4% of cladribine versus 2% placebo patients.

Table 8: Harms

	Cladribine 3.5 mg/kg n = 433	Placebo n = 437
Adverse Events		
Adverse events over 96 weeks, n (%)	347 (80.7)	319 (73.3)
Most common, 10% in any group, n (%)		
Headache	104 (24.2)	75 (17.2)
Lymphopenia	93 (21.6)	8 (1.8)
Nasopharyngitis	62 (14.4)	56 (12.9)
Upper respiratory tract infection	54 (12.6)	42 (9.7)
Nausea	43 (10.0)	39 (9.0)
Serious Adverse Events		
Any serious adverse event over 96 weeks, n (%)	36 (8.4)	28 (6.4)
Pneumonia	3 (0.7)	3 (0.7)
Uterine leiomyoma	3 (0.7)	0
Lymphopenia	3 (0.7)	0
WDAE		
Any adverse event leading to study discontinuation, n (%)	5 (1.2)	5 (1.1)
Mortality		
Deaths, n	2 acute MI pancreatic cancer	2 suicide cerebrovascular accident
Notable Harms		
Notable harms, patients over 96 weeks, n (%)		
Infections and infestations	205 (47.7)	185 (42.5)
Nasopharyngitis	62 (14.4)	56 (12.9)
Upper respiratory tract infection	54 (12.6)	42 (9.7)
Urinary tract infection	23 (5.3)	39 (9.0)
Influenza	28 (6.5)	27 (6.2)
Herpes zoster	8 (1.9)	0
PML	0	0
Blood and lymphatic system disorders	114 (26.5)	25 (5.7)
Lymphopenia	93 (21.6)	8 (1.8)
Leukopenia	24 (5.6)	3 (0.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	16 (3.7)	7 (1.6)

	Cladribine 3.5 mg/kg n = 433	Placebo n = 437
Uterine leiomyoma	5 (1.2)	1 (0.2)
Pregnancies during study, n	7	6
Terminated voluntarily	5	2
Spontaneous abortion/miscarriage	1	1
Ectopic pregnancy, terminated	1	0
Normal delivery/baby	0	3

MI = myocardial infarction; PML = progressive multifocal leukoencephalopathy.

Source: Clinical Study Report for CLARITY.

Discussion

Summary of Available Evidence

One manufacturer-sponsored multinational double-blind RCT met the inclusion criteria for this review. CLARITY compared two doses of cladribine, 3.5 mg/kg and 5.25 mg/kg, to placebo, over a double-blind period of 96 weeks. The primary outcome of CLARITY was the ARR at 96 weeks, while secondary outcomes included various MRI measures such as T1-, and T2-weighted and combined unique lesions. Other outcomes that were assessed but not controlled for multiple comparisons included disability progression and health-related quality of life. Other evidence included data from an extension study, CLARITY EXT, and a manufacturer-provided indirect comparison, which are summarized and critically appraised in Appendices 6 and 7, respectively.

Critical appraisal issues in CLARITY included the lack of an active comparator, and the length of comparative follow-up, which may not have been sufficient to assess potential safety issues such as malignancies. Only relapse and MRI outcomes were adjusted for multiple comparisons, while key efficacy outcomes such as disability progression and health-related quality of life were not. Additionally there was a significant amount of missing data for the health-related quality of life outcomes, particularly the MSQOL-54, which was missing 90% of the enrolled population.

Interpretation of Results

Efficacy

The ARR was the primary outcome for CLARITY, and cladribine was superior to placebo at 96 weeks with a greater than 50% reduction in ARR (rate ratio of 0.43; 95% CI. 0.34 to 0.54; $P < 0.001$). This amounted to a reduction of 19 relapses per 100 patients per year. Relapses are a common and clinically relevant outcome used to assess effects of drugs for MS, and it is well established that they do contribute to the pathology of MS, and facilitate the progression of disability. Furthermore, 80% of patients treated with cladribine were relapse-free over the course of the 96-week study, versus 61% of placebo-treated patients. Disability progression sustained for three months was assessed using the EDSS, the standard scale for assessing disability in MS. The outcome assessed was the time to sustained three-month change (worsening) in EDSS score at week 96, and this was also reduced with cladribine versus placebo. However, this outcome was not part of the statistical hierarchy used to account for multiple statistical comparisons and, although the

difference was reported as statistically significant (0.67; 95% CI, 0.48 to 0.93; $P = 0.018$), it was not adjusted for multiple comparisons. This is particularly important in this case because the P value was just below the threshold of $P < 0.05$. Thus, although there appears to be a relatively large reduction in risk of relapses with cladribine, this did not appear to translate into a proportional reduction in disability progression sustained for three months. As the clinical expert consulted by CADTH on this review pointed out, CLARITY does not assess improvement in disability — a more ambitious, but also likely a much more meaningful, outcome for patients with MS. The clinical expert also noted that the relatively modest effects on disability seen in CLARITY are disappointing for a second-line therapy.

Health-related quality of life and symptoms such as fatigue are key concerns of patients with MS. Symptoms, including fatigue, were not assessed in CLARITY, health-related quality of life was assessed using the disease-specific MSQOL-54 in only a small fraction of the population, and approximately 20% of the population was missing for assessment by the EQ-5D. The manufacturer also assessed the SF-36, but this was such a late protocol amendment that no baseline data were available, and so these data were not reported by CDR. There was some evidence of improvement with cladribine versus placebo on the EQ-5D, with a statistically significant difference between groups. However, this was not adjusted for multiple comparisons, and should be considered hypothesis-generating. The difference between groups in EQ-5D index scores of 0.058 fell within the range of what is considered to be clinically significant (0.05 to 0.084), but the large amount of missing data reduces confidence in this analysis. As far as its role in MS, the EQ-5D, reviewed in Appendix 5, may also lack construct validity for patients with MS, as it is missing certain domains, such as mobility and mood, that are important in the disease, and the instrument had difficulty differentiating between different levels of disability. Therefore, with no baseline data for the SF-36, almost no data at all for the MSQOL-54, and a large amount of missing data and lack of adjustment for multiple comparisons for the EQ-5D, very little can be concluded about the impact of cladribine on health-related quality of life in patients with RRMS.

Cladribine has a unique treatment regimen in that it is administered in cycles for two years, and, per the product monograph, its efficacy beyond two years has not been established. This raises the question of how cladribine will be used in practice: will patients be switched to another therapy after two years or will they be continued on therapy? There is an extension to CLARITY (CLARITY EXT), summarized in Appendix 6, that continues therapy beyond two years. In CLARITY EXT, patients who were on placebo in CLARITY were assigned to cladribine, while patients in both cladribine groups were re-randomized to either cladribine 3.5 mg/kg or placebo, resulting in three comparison groups: cladribine/cladribine (i.e., cladribine in both the parent trial and the extension) or placebo/cladribine (placebo in the parent trial and cladribine in the extension) or cladribine/placebo (cladribine in the parent trial and placebo in the extension). All efficacy outcomes in the study were exploratory, and there were no statistically significant differences between groups for ARRs or for disability progression, both defined the same way they were in the parent trial. The group that switched from cladribine to placebo in the extension had worse MRI results for T1 gadolinium-enhanced lesions, but not for T2 or combined unique lesions. Interestingly, there were no differences in relapse rates or disability progression between the patients who received cladribine throughout CLARITY and CLARITY EXT, and those who switched from cladribine to placebo in the extension.

MRI outcomes were featured prominently in CLARITY, as the number of T1 gadolinium-enhanced lesions, number of active T2 lesions, and number of combined unique lesions were the only key secondary outcomes included as part of the statistical hierarchy and thus adjusted for multiple comparisons. Cladribine demonstrated superiority over placebo for all these MRI outcomes, as well as post hoc outcomes such as change in per cent brain volume and patients free of disease activity. This latter outcome has become standard in MS trials, but as this was not likely the case when CLARITY was being planned, it was added after the study had been completed. Thus data from CLARITY for brain atrophy and freedom from disease activity, which today would likely be considered of utmost importance among MRI outcomes for MS, should only be considered hypothesis-generating. MRI outcomes and their relation to relapses and disability in MS are reviewed in Appendix 5. A number of studies have investigated the correlation between MRI findings and key disease outcomes such as relapses and disability, but the findings from these studies have not been entirely consistent. The clinical expert consulted on this review noted that the brain volume data for cladribine was relatively modest compared with higher-efficacy DMTs.

No active comparator studies were included in this systematic review. The manufacturer submitted an indirect comparison of cladribine versus other DMTs in RRMS, reviewed in Appendix 7. The manufacturer concluded that cladribine demonstrated similar efficacy and safety versus other DMTs. However, there were a number of methodological flaws with the manufacturer's indirect comparison, including a significant amount of heterogeneity between studies, both with respect to populations excluded and risk of bias. At the time of CLARITY the options for DMTs were quite limited, and almost all patients who had tried a therapy prior to CLARITY had been on either glatiramer or an interferon. The clinical expert consulted by CADTH on this review noted that this limits knowledge of the effects cladribine would have on patients who had failed other DMTs, most notably other orally administered agents, none of which were available at the time of CLARITY.

Harms

Cladribine has a relatively long history as a potential treatment for MS, with the initial studies dating back to the late 1990s, conducted using a parenteral route of administration.[36,37] CLARITY was designed over a decade ago, and the initial double-blind phase was completed in 2008. [redacted][31] Cladribine has a longer history as an anti-cancer drug. Extensive long-term follow-up data were sought before cladribine was approved by regulators in Canada and in other jurisdictions for the MS indication. During the double-blind phase of CLARITY there was a numerically higher proportion of patients with any neoplasia or with uterine leiomyoma, specifically. These differences appeared to be maintained in the extension, although no groups remained on placebo into the extension phase, and all groups had been exposed to cladribine. The manufacturer suggested that the difference was exaggerated because the occurrence of malignancies in the CLARITY placebo group was lower than that observed in other clinical trials. In support of this, the manufacturer provided a meta-analysis[38] that pooled data from 11 trials (including CLARITY) of approved DMTs (dimethyl fumarate, fingolimod, teriflunomide, natalizumab, alemtuzumab, and glatiramer acetate) for the treatment of RRMS. The meta-analysis found that the rate of cancer was significantly lower in the CLARITY placebo treatment group compared with other placebo groups (0% and 1.19%, respectively; $P = 0.0159$). The meta-analysis also reported no significant difference in the rate of cancer with cladribine (in CLARITY, 0.34%) compared with trials that included placebo or active comparators (0.67%;

P = 0.3669) or when compared with placebo-controlled trials only (0.6%; *P* = 0.4631). There are several limitations with this meta-analysis, including (but not limited to) the fact that the comparisons were essentially indirect comparisons that did not apply the appropriate statistical analyses to maintain randomization and account for the increased variance with such comparisons. As well, it was assumed that the studies were similar enough to compare. However, there is an important degree of statistical heterogeneity (I^2 greater than 50% for the pooled malignancy risk differences), and limited assessment of clinical and methodological heterogeneity was reported. It is also unclear whether the length of follow-up in these studies was sufficient to assess risk of cancer, as most cancers take many years to develop. As a result, the meta-analysis is intriguing but insufficient on its own to provide evidence on the risk of malignancy with cladribine, or other DMTs for MS.

[redacted][31] and the European Medicines Agency also noted the potential increased risk of malignancies with cladribine.[31,39] As mentioned, there are likely not enough long-term data to determine what the true association between cladribine and cancer is.

Like many drugs for MS, cladribine has immunosuppressant effects, and therefore there is an elevated risk of infection. There was a numerically higher proportion of cladribine-treated versus placebo patients with lymphopenia (22% versus 2%). Of particular concern with immunosuppressants used in MS is the risk of progressive multifocal leukoencephalopathy (PML), most commonly seen with natalizumab. There were no cases of PML reported in CLARITY or in the extension, and while there have been rare reports of PML occurring with the injectable form of cladribine, none of these four cases involved the use of cladribine for MS and the regimens were different than would be used for MS.[40] The manufacturer noted that from various clinical trials of cladribine in MS, and from the PREMIERE registry, no cases of PML have been reported over an observation period of 8,500 patient-years.[41] The most frequently occurring opportunistic infection that poses a potential safety risk arising out of CLARITY was herpes, as there were 2% of patients treated with cladribine with cases of herpes zoster versus zero with placebo. Data regarding herpes were inconsistent in the extension phase, as there was a numerically higher proportion of patients with herpes in the group that switched from cladribine to placebo compared with the group that stayed on cladribine throughout both studies. The only conclusion that can be drawn from the extension is that the risk of herpes does not appear to increase for those who continue on cladribine relative to other groups (those switching from placebo to cladribine or vice versa). This is the case despite the fact that in the extension phase there is a large numerical difference in the proportion of patients with reports of grade 3 or 4 lymphopenia with cladribine throughout the double-blind phase and extension versus those who switched from placebo to cladribine in the extension (41% with cladribine/cladribine versus 5% placebo/cladribine). [redacted][31] Health Canada also reported that its comprehensive safety analysis identified three patients exposed to cladribine who were diagnosed with tuberculosis (TB) infection and/or latent TB reactivation, including one TB-related death. TB screening was not part of the CLARITY entry protocol. TB screening prior to initiating treatment with cladribine is included in the product monograph, which is consistent with other immune modulatory DMTs used for RRMS.

Health Canada expressed concern with the highlighted important harms to the point that the second-line indication was largely based on potential impact on patients with RRMS. The Health Canada review states, "At this point in time, considering the above safety issues identified during the review, the benefit-risk profile for oral cladribine in the treatment of RRMS is favourable when MAVENCLAD is not used as a first-line agent in the treatment of RRMS as described in the Product Monograph."[31] This is not unusual for DMTs used for treating MS, with several other drugs receiving similar benefit-to-harm assessments from Health Canada.

Potential Place in Therapy[1]

The clinical expert consulted by CADTH noted several unmet medical needs for patients with RRMS: a treatment that results in reversal or improvement of disability; improvement in health-related quality of life; preventing relapses; preventing disability worsening (progression); a safe and convenient option. Cladribine meets some of these needs.

Cladribine is an oral medication for relapsing forms of MS that offers good convenience for MS patients with good overall safety and a low monitoring burden. Based on one phase III trial in RRMS (CLARITY), cladribine is superior to placebo with respect to annualized relapses and disability progression sustained for three months. There are no comparative head-to-head studies of cladribine with the currently approved injectable or oral DMTs for RRMS.

Indirect comparison across the published phase III trials of the oral DMTs can only provide a very limited and cautious impression of comparative efficacy because of the heterogeneity in the patient and trial characteristics.[42-47] In the absence of head-to-head data, no consistent or robust indirect evidence suggests that cladribine is more efficacious than other oral DMTs (i.e., dimethyl fumarate, teriflunomide or fingolimod).

Overall, CLARITY did not appear to raise any serious tolerability and safety concerns, with the most common side effect being lymphopenia. There is a higher rate of herpes infections compared with placebo, ranging from 2% (CLARITY randomized phase) to more than 6% (CLARITY extension). Gastrointestinal tolerance appears good, which has been an issue for dimethyl fumarate. No hair loss is reported, as has been an issue for teriflunomide. There is no cardiac monitoring or concerns, as has been an issue for fingolimod. Similar to teriflunomide, there have been no reported cases of PML in MS. There have been four case reports of PML with parenteral cladribine.[40]

Despite certain safety concerns, cladribine would be attractive for patients who cannot tolerate any of the other oral medications due to gastrointestinal side effects or who have a contraindication, such as cardiac concerns. It should be used with caution in those with recurrent herpes infections. As a second-line therapy, there is reasonable evidence from CLARITY that patients who failed interferon or Copaxone would benefit. However, there is no evidence that patients who failed another oral DMT or monoclonal antibody DMT would benefit and it may not be an adequate DMT for those treatment failures. The dosing and monitoring schedule will be of interest for patients and clinicians.

A major concern is the borderline-to-modest impact on disability progression and brain atrophy relative to some of the higher-efficacy DMTs. We can expect that 40% to 50% of patients treated with cladribine will meet treatment failure criteria for escalation (20% have a relapse within two years, 14% to 25% have disability progression, 40% have new MRI activity

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

within two years), so sequencing becomes an issue. The product monograph for cladribine notes: “The efficacy of taking Mavenclad for treatment duration beyond 2 years has not been established.”[5] It is highly unlikely that two years of cladribine ("induction") would be sufficient for the long-term management of the majority of relapsing onset MS patients. The use of cladribine as a first-line or second-line treatment would require ongoing subsequent treatment with either cladribine or another agent. Unlike all other oral DMTs, there is no long-term chronic exposure data on the safety of cladribine or on the safety of sequencing. There is some potential concern that exposure to cladribine leading to prolonged lymphopenia could delay escalation to a presumed higher-efficacy DMT, such as ocrelizumab or alemtuzumab that often requires lymphocytes to be about 0.8 x 10^9/L. This may take several months after cladribine dosing. There could be safety concerns using natalizumab after cladribine in the patients seropositive for the John Cunningham (or “JC”) virus, as prior exposure to “chemotherapy” is a known risk factor for natalizumab related PML.[48] The ongoing PREMIERE registry captures data on the safety of sequencing, and to date no issues have been identified with respect to sequencing of high-efficacy DMTs after cladribine therapy, according to the manufacturer.[41]

Overall, cladribine will be an option for relapsing onset MS patients and likely more attractive to patients and clinicians than the injectables and other oral DMTs that may have similar efficacy. The dosing and tolerability are the most attractive features and potential advantage for patients rather than the overall efficacy. Cladribine does lack long-term safety and efficacy data with prolonged continuous exposure. The current data from CLARITY and CLARITY EXT are insufficient to fully inform the benefits versus risks of ad hoc dosing versus continuous dosing. While it is reasonable to consider, there is no evidence that cladribine would be superior or adequate for patients that fail another oral DMT, ocrelizumab, natalizumab, or alemtuzumab.

Conclusions

One double-blind RCT met the inclusion criteria for this review. CLARITY was a multinational, manufacturer-sponsored trial that compared cladribine with placebo over a treatment course of 96 weeks. The primary outcome was the ARR, and cladribine was superior to placebo at 96 weeks for this outcome. Health-related quality of life was only assessed using the disease-specific MSQOL-54 in a small fraction of the population, and the EQ-5D also had a significant amount of missing data. Disability progression was assessed using the EDSS, and the risk of three-month sustained disability progression was lower with cladribine than with placebo, but this analysis was not adjusted for multiple comparisons. The lack of health-related quality of life and symptom data is an important limitation in a study of a condition characterized by significant symptoms and quality of life issues. MRI outcomes such as the change in number of T1 gadolinium-enhanced lesions per patient, active T2 lesions, and combined unique lesions, were all superior to placebo. With respect to brain atrophy, cladribine was also superior to placebo, but this post hoc analysis was not adjusted for multiple comparisons. A higher proportion of cladribine patients were free of disease activity, and this difference was statistically significant, although this was a post hoc analysis. A numerically higher proportion of cladribine patients reported an adverse event over the 96-week study, and there was no notable difference in patients with a serious adverse event between groups. Lymphopenia was a common adverse event, and occurred numerically more frequently with cladribine than with placebo. There were 2% of cladribine patients that developed herpes zoster during the study, and none in the placebo group. These issues, in addition to other potential safety concerns, have placed cladribine as second-line therapy in RRMS, based on the indication. There are no long-term comparative safety data for oral cladribine.

Appendix 1: Patient Input Summary

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

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

One patient group, the Multiple Sclerosis (MS) Society of Canada, provided patient input for this CDR.

The MS Society of Canada is an organization that aims to be a leader in finding a cure for MS and enabling people affected by MS to enhance their quality of life. This mission is accomplished by the organization's support for research on the cause, treatment, and cure of MS, and programs and services that assist people with MS and their families. The MS Society of Canada has contributed more than $140 million toward MS research since its inception in 1948. The MS Society of Canada has received financial payment from the following companies and organizations: Bayer, Biogen, EMD Serono, Novartis, Roche, Pfizer, Sanofi Genzyme, Allergan, and Teva Neuroscience.

2. Condition-Related Information

The MS Society of Canada collected condition-related patient input from a sample of individuals assumed to be Canadian through an online survey posted to the main page of its national website (www.mssociety.ca) and Facebook page. The survey was available in English and French and open from December 4, 2017, to December 18, 2017. Data were collected from 190 respondents with the majority (n = 134) identified as being diagnosed with relapsing-remitting MS.

MS is a disease of the central nervous system that causes damage to the myelin (protective covering wrapped around nerve fibres) resulting in the interruption or loss of the usual flow of nerve impulses. MS is typically diagnosed between the ages of 15 and 40 and results in a number of symptoms, including fatigue, difficulty walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain. Other symptoms may include issues with balance, sexual dysfunction, spasticity, tremor, weakness, and difficulty speaking and swallowing. The most common type of MS is relapsing-remitting, which affects 85% to 90% of patients with MS. Relapsing-remitting MS is characterized by bouts of inflammation in the central nervous system, resulting in "attacks," followed by full or near-complete recovery. Half of people with relapsing-remitting MS will transition to secondary-progressive MS, a form of the disease that steadily worsens over time and is marked by fewer or no attacks and advanced disability. Approximately 10% of people with MS are diagnosed with primary-progressive MS, which differs from relapsing-remitting MS in that it is characterized by a steady worsening of the disease.

The relapses, symptoms, medication side effects, and disability progression of MS create barriers in a multitude of areas, including employment, education, physical activity, family commitments, interpersonal relationships, and social and recreational life. MS has a pronounced effect on caregivers, as they play an instrumental role in the overall care management plan of people living with MS. The role of caregivers may include providing emotional support and assistance with medication administration, helping with activities of daily living such as personal care, feeding and transportation to and from appointments. One caregiver stated, *"[The] demanding nature of caring for a patient with a chronic illness is harder on the caregiver than people realize, it is a 24/7 commitment."*

3. Current Therapy-Related Information

The MS Society of Canada collected current therapy-related patient input from an online survey.

There are currently 10 first-line and five second-line therapies approved in Canada for the treatment of relapsing forms of MS. From the patients surveyed, about half (n = 48) felt that their current therapy was effective in managing their disease, while 31 did not know if their medication was effective, and 18 felt their medication was not effective at all. Common side effects associated with current therapy included injection site reactions, flushing, hair thinning, skin rash or hives, joint or musculoskeletal pain, gastrointestinal symptoms, and flu-like symptoms. One survey respondent reported progressive multifocal leukoencephalopathy, a rare and potentially fatal side effect associated with treatment with some of the MS therapies.

Current therapies for treatment of MS include oral, injected, and infusion routes of administration. The majority (65%) of survey respondents indicated that the route of administration of the drug was "very important," while 32% stated that they did not care about administration as long as the medication worked. The administration of drugs and dosing schedules affects patients' adherence, ability to travel, and employment. Patients may need time off work/school to attend appointments or to deal with side effects post-administration.

While several therapies are available to patients with MS, it is important to note that the course of the disease and the response to therapy differs greatly among patients. One patient stated, *"… each person responds differently to meds, and each MS patient is unique, I think it is important that different avenues of treatment are available."*

4. Expectations About the Drug Being Reviewed

The MS Society of Canada collected drug expectation–related patient input from an online survey.

The experience of MS and the response to therapy varies among patients with MS. The importance of having a choice and a selection of therapy is highlighted in the following quotes extracted from the online survey:

"We need to be able to provide multiple different therapies to people with MS because people react differently to the same medication. Also because there is no 'one size fits all' for MS we need to have different meds available."

"I think any drug is worth trying and everyone is affected differently. I am so happy to hear so many drugs are available to try out. It at least gives us an opportunity to better our lives from this disease."

The MS Society of Canada did not receive feedback from patients who had experience with Mavenclad. However, the need for new therapies was evident, and echoed in the following statement made by one patient: *"Nothing else has helped me so far. I need something new to try."*

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to January 8, 2018 Ovid MEDLINE(R) ALL 1946 to January 08, 2018 Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 9, 2018
Alerts:	Bi-weekly search updates until May 16, 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
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
#	**Searches**	**Results**
1	Cladribine/	7416
2	(biodribin or cladribine or cladarabine or Chlorodeoxyadenosine or intocel or leustat or leustatin or leustatine or litak or litax or mavenclad or movectro or mylinax or rwj 26251 or rwj26251 or HSDB 7564 or HSDB7564 or NSC 105014 or NSC 105014 or CCRIS 9374 or CCRIS9374 or "BRN 0624220" or BRN0624220 or 47M74X9YT5 or 4291-63-8 or 24757-90-2).ti,ab,kf,ot,hw,rn,nm.	8262
3	1 or 2	8262
4	exp Multiple sclerosis/	168101
5	(multiple scleros* or disseminated scleros* or chariot disease* or insular scleros* or sclerosis multiplex).ti,ab,kf.	169278
6	(MS or PPMS or RRMS or SPMS).ti,kf.	82291
7	or/4-6	270270
8	3 and 7	1126
9	8 use medall	249
10	*cladribine/	2591
11	(biodribin or cladribine or cladarabine or Chlorodeoxyadenosine or intocel or leustat or leustatin or leustatine or litak or litax or mavenclad or movectro or mylinax or rwj 26251 or rwj26251 or HSDB 7564 or HSDB7564 or NSC 105014 or NSC 105014 or CCRIS 9374 or CCRIS9374 or "BRN 0624220" or BRN0624220).ti,ab,kw,dq.	4386
12	10 or 11	4823
13	Multiple sclerosis/	161946
14	(multiple scleros* or disseminated scleros* or chariot disease* or insular scleros* or sclerosis multiplex).ti,ab,kw,dq.	171605
15	(MS or PPMS or RRMS or SPMS).ti,kw.	102657
16	or/13-15	290313
17	12 and 16	641
18	17 use oemezd	415
19	18 not conference abstract.pt.	261
20	9 or 19	510
21	remove duplicates from 20	307

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:	January 3, 2018
Keywords:	Mavenclad, Cladribine, multiple sclerosis
Limits:	No date or language limits used

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

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

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
STELMASIAK et al. Mult Scler 2009;15(6):767-70	Injection
WAGNER et al. Eur Neurol 2000;43(4):194-200	
ROMINE et al. Proc Assoc Am Physicians 1999;111(1):35-44	
SIDDIQUI et al. Curr Med Res Opin 2017;1-11	Network meta-analysis
DE STEFANO et al. Mult Scler 2018;:1352458517748476, 2018 Jan 01	Letter
SCHIFFMANN et al. Mult Scler 2018;:1352458517749895, 2018 Jan 01	

Appendix 4: Detailed Outcome Data

Table 9: Other Efficacy Outcomes

	CLARITY	
	Cladribine 3.5 mg/kg n = 433	Placebo n = 437
MRI		
Number T1 gadolinium-enhanced lesions, mean (SD) baseline	1.0 (2.7)	0.8 (2.1)
Mean (SD) number of active T1 gadolinium-enhanced lesions per patient per scan, week 96	0.09 (0.30)	0.86 (1.78)
LSM (SE)[a] week 96	0.12 (0.05)	0.91 (0.05)
Treatment difference (95% CI)[b]	−0.78 (−0.92 to −0.65) *P* < 0.001	
Mean (SD) number of active T2 lesions per patient per scan at week 96	0.35 (0.66)	1.38 (2.11)
LSM (SE)[a] week 96	0.38 (0.07)	1.43 (0.06)
Treatment difference (95% CI)[b]	−1.05 (−1.22 to −0.87) *P* < 0.001	
Mean (SD) number of CU lesions per patient per scan at week 96	0.39 (0.71)	1.65 (2.55)
LSM (SE)[a] week 96	0.43 (0.08)	1.72 (0.08)
Treatment difference (95% CI)[b]	−1.28 (−1.49 to −1.08) *P* < 0.001	
Patients with no active T1 gadolinium- enhanced lesions at week 96, n (%)	376 (86.8)	211 (48.3)
Odds ratio[c] (95% CI)	7.57 (5.37 to 10.67) *P* < 0.001	
Patients with no active T2 lesions at week 96, n (%)	267 (61.7)	124 (28.4)
Odds ratio[c] (95% CI)	4.17 (3.13 to 5.55) *P* < 0.001	
Mean PBVC, months 6 to 24	−0.77% (0.94) N = 336 *P* = 0.02	−0.95% (1.06) N = 338
Patients disease activity–free[d] for weeks 0-96, n (%),	183 (46.8) N = 391	63 (17.4) N = 363
Odds ratio (95% CI)	4.25 (3.03 to 5.96), *P* < 0.0001	
Rescue Meds		
Rescue status: Yes	11 (2.5)	27 (6.2)
Rescue status: No	422 (97.5)	410 (93.8)
Odds ratio (95% CI)	0.40 (0.19 to 0.81) *P* = 0.011	
Absenteeism		
Mean number of days patient missed from work over 96 weeks	[redacted]	[redacted]
Mean difference in the number of days missed by patient	[redacted]	
Mean number of hours patient missed from work over 96 weeks	[redacted]	[redacted]
Productivity achieved (%)	[redacted]	[redacted]
Mean difference in productivity (%)	[redacted]	
Mean number of days relatives missed from work over 96 weeks	[redacted]	[redacted]

	CLARITY	
	Cladribine 3.5 mg/kg n = 433	Placebo n = 437
Mean difference in the number of days missed by relatives	[redacted]	

ANCOVA = analysis of covariance; CI = confidence interval; CU = combined unique; LSM = least squares mean; PBVC = per cent brain volume change; SD = standard deviation; SE = standard error.

[a] LSM (SE), treatment difference, point estimate (SE) and 95% CI estimated using parametric ANCOVA model on raw data with fixed effects for treatment group and region and baseline T1 gadolinium-enhanced lesion as a covariate.

[b] *P* values calculated based on non-parametric ANCOVA model on ranked data with fixed effects for treatment group and region and baseline T1 gadolinium-enhanced lesion as a covariate.

[c] *P* value based on Wald chi-square test from analysis of end point using a logistic regression model with fixed effects for treatment group and region. Odds ratio and associated 95% CI were estimated using a logistic regression model with fixed effects for treatment group and region.

[d] Disease activity–free is defined as having no relapses, no six-month sustained change in Expanded Disability Status Scale score, no new T1 gadolinium-enhancing lesions and no active T2 lesions.

Source: Clinical Study Report for CLARITY.

Table 10: Subgroup Analysis of the Primary Outcome (Annualized Relapse Rate)

	CLARITY	
	Cladribine 3.5 mg/kg n = 433	Placebo n = 437
Previous Treatment Status		
DMT-naive (n = not reported)	0.12	0.31
Relative risk (95% CI)	0.39 (0.29 to 0.51) *P* < 0.001	
Prior DMT therapy (n = not reported)	0.22	0.40
Relative risk (95% CI)	0.55 (0.38 to 0.79) *P* < 0.001	
Previous Relapses		
≤ 1 (n = not reported)	0.14	0.27
Relative risk (95% CI)	0.50 (0.37 to 0.66) *P* < 0.001	
2 (n = not reported)	0.14	0.45
Relative risk (95% CI)	0.32 (0.21 to 0.50) *P* < 0.001	
≥ 3 (n = not reported)	0.23	0.67
Relative risk (95% CI)	0.34 (0.16 to 0.73) *P* = 0.006	

CI = confidence interval; DMT = disease-modifying therapy

Source: Clinical Study Report for CLARITY.

Appendix 5: Validity Of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Expanded Disability Status Score (EDSS)
- Multiple Sclerosis Quality of Life–54 (MSQOL-54)
- EQ-5D (EuroQoL 5-Dimensions questionnaire)
- MRI outcomes

Findings

Instrument	Type	Evidence of Validity	MCID	References
EDSS	Ordinal scale (0 to 10)	YES	1.0 point change when the score was between the EDSS 0 to 5.5 range; 0.5 point change when the EDSS score was between the 5.5 to 8.5 range	33-35,37,49-51
MSQOL-54	54-item tool with Likert scales and multiple choice items	YES	UNKNOWN	32,52
EQ-5D	Descriptive system and visual analogue scale	MIXED	0.05 to 0.084	33,34,53,54
SF-36[a]	Multiple dimensions (eight subscales, two summary scores) with individual scales (0 to 100)	YES	2 points for the physical component summary score, and 3 points for the mental component summary score (not specific to patients with MS)	32,55-60
MRI Outcomes	MRI	YES	UNKNOWN	32,52,58-62

EDSS = Expanded Disability Status Scale; EQ-5D = EuroQoL 5-Dimensions questionnaire; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSQOL-54 = Multiple Sclerosis Quality of Life–54; SF-36 = Short Form (36) Health Survey.

[a] SF-36 was used as a measure of health-related quality of life in the CLARITY trial. However, data for this outcome measure were not extracted or interpreted for this review because of missing baseline data.

Expanded Disability Status Scale

The EDSS is an ordinal scale used to measure disability in multiple sclerosis (MS). It has been shown to be a valid tool for patients with multiple sclerosis (MS).[50] The EDSS addresses disability in eight functional systems: 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 functional system grades as well as the degree of functional disability and ambulation (Table 11).[49] 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 two or three points, and six or seven 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 for the individual functional systems between 0.23 to 0.58 were reported),[49] offers poor assessment of upper limb and cognitive function, and lacks linearity between score difference and the clinical severity.[33-35,53] Other limitations include that it relies heavily on

the evaluation of motor function and the ability to walk — 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,[51] the clinically important difference was determined to be a 1.0 point change when the EDSS score was in the 0 to 5.5 range, while it was determined that this value decrease to 0.5 points when the EDSS score was between 5.5 and 8.5.

Table 11: Scoring of Expanded Disability Status Scale

	Normal Neurological Exam (All Grade 0 in Functional Systems; Cerebral Grade 1 Acceptable)
1	No disability, minimal signs in one FS (i.e., grade 1 excluding cerebral grade 1)
1.5	No disability, minimal signs in more than one FS (more than one grade 1 excluding cerebral grade 1)
2.0	Minimal disability in one FS (one FS grade 2; other 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 metres
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 assistances; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest for some 300 metres
5.0	Ambulatory without aid or rest for about 200 metres; disability severe enough to impair full daily activities (e.g., to work full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)
5.5	Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0)

FS = functional systems.

Multiple Sclerosis Quality of Life–54 items

The MSQOL-54 is a self-reported, disease-specific quality of life instrument developed in the US in 1995.[32,52] It is based on the SF-36 instrument and supplemented with 18 disease-specific dimensions measuring: 1) anxiety provoked by the patient's health status (four items); sexual functioning (four items); satisfaction with sex life (one item); overall quality of life (two items); cognitive functioning (four items); energy (one item); pain (one item); and social functioning (one item). The instrument has Likert scales and multiple choice items.[52] There is no single overall score for MSQOL-54. Two summary scores — physical health and mental health — can be derived from a weighted combination of scale scores (scale scores range from 0 to 100, with a higher scale score indicating improved quality of life).[32] In addition, the multiple-item scales of each of these scores can be analyzed individually to understand more clearly the changes on the composite scores. The physical health composite score is computed from the individual scores of the following scales: physical function, health perceptions, energy/fatigue, role limitations-physical, pain, sexual function, social function, and health distress. The mental health composite score is computed from the individual scores of the following scales: health distress, overall quality of life, emotional

well-being, role limitations-emotional, and cognitive function.[32] No minimal clinically important differences (MCIDs) were identified for the summary scores. Psychometric properties in MS patients are provided below:

Reliability: MSQOL-54 has good internal consistency reliability (Cronbach's alpha 0.75 to 0.96 scale items).[32] Intra-class coefficients ranged from 0.67 and 0.96.[32]

Construct validity: Statistically significant differences between patients with mild versus patients with moderate symptoms were found for physical function, health distress, and physical health composite. The role limitations due to emotional problems and the cognitive function scales were the least sensitive to group differences.[32]

EuroQol 5-Dimensions Questionnaire

The EQ-5D is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments.[33,34] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) by 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (index score) to self-reported health states from a set of population-based preference weights.[33,34] The second part is a 20 cm visual analogue scale (VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

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

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) depends on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores below 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for this scale in the general population ranged from 0.033 to 0.074.[35] For patients with MS, the MCID ranged from 0.050 to 0.084.

One study assessed the EQ-5D as well as the validated Patient Determined Disease Steps scale and the 12-Item Multiple Sclerosis Walking Scale in patients with MS. Moderately strong correlations between the EQ-5D and the Patient Determined Disease Steps and Multiple Sclerosis Walking Scale were observed (Spearman's r = −0.56 and −0.59, respectively; $P < 0.0001$ for both).[54] In addition, a review determined a lack of content validity for patients with MS for the EQ-5D as it was found to be missing certain domains (i.e., mobility and mood) that were important to the disease and showed difficulty in

differentiating between levels of disability.[50] Test-retest reliability in the MS population was determined to be good (intra-class correlation coefficient = 0.81).[50]

Magnetic Resonance Imaging Outcomes

MRI techniques play an important role in the diagnosis of multiple sclerosis. In addition, they are valuable in monitoring treatment response and predicting disease progression. However, the correlation between the burden of lesions observed on MRI scans and the clinical manifestations of the disease remains controversial.[58-60]

In CLARITY, the following MRI outcomes were measured between treatment groups: active T1 lesions, gadolinium-enhanced lesions, and active T2 lesions. These are conventional MRI outcomes that are widely used to monitor treatment effects in clinical trials of MS. Their roles as a surrogate for clinical outcomes such as relapses and disability progression in relapsing-remitting MS have been investigated in previous research. Findings from systematic reviews and large randomized controlled trials reporting the correlations between the treatment effect on relapses and disability progression and the treatment effect on MRI lesions are presented in Table 12. In these studies, relapsing-remitting MS patients received interferon, cladribine, fingolimod, placebo, or no drug treatment. The correlations between MRI outcomes and clinical outcomes (relapses and disability progression) varied across studies.

Table 12: Summary of Correlations Between MRI Outcomes and Clinical Outcomes

Study	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
Sormani 2013[62]	• 31 RCTs of all available DMTs for RRMS; published from 2008 to 2012	• Number of MRI lesions • ARR • MRI effect: ratio between the average number of MRI lesions per patient in the experimental arm and in the control arm • REL effect: ratio between the relapse rate in the experimental arm and in the control arm • Coefficient of determination (R^2): used to assess the goodness of fit for a regression equation in which the treatment effect on relapses was predicted by MRI results	Data from 31 RCTs were used in deriving regression equation. $R^2 = 0.71$, suggesting a good degree of prediction of REL effect using MRI effect.	The effect of a treatment on relapses can be accurately predicted by the effect of that therapy on MRI lesions.
Sormani 2011[63]	• 3 RCTs enrolling RRMS patients (cladribine vs. placebo; fingolimod versus placebo; fingolimod vs. interferon) • Follow-up: 12 to 24 months	• MRI effect: ratio between the average number of new and enlarging T2 lesions/patient in the experimental arm and in control arm • REL effect: ratio between the annualized relapse rate in the experimental arm and in the control arm • DIS effect: ratio between % of patients with disability progression (≥ 1 point on EDSS at month 3) in experimental and control arm • Regression equations from previous meta-analyses were used to predict the drug effect on relapse (REL effect) and disability progression (DIS effect) based	92% of observed effects of oral drugs (cladribine and fingolimod) on clinical outcomes resulted close to those predicted by MRI active lesions. From the regression lines provided in the article, 10 out of 12 observed effects on the clinical variables were very close to those predicted by the lines.	MRI markers were able to predict treatment effects on clinical endpoints in RRMS patients treated with novel oral agents.

Study	Population and Interventions	Outcomes Examined	Correlations Between MRI Outcomes and Clinical Outcomes	Author's Conclusion
		on MRI effect		
Sormani 2010[64]	• The PRISMS study enrolling 560 RRMS patients: subcutaneous interferon versus placebo • Follow-up: 2 years	• PTE on relapses that was accounted for by the effect of treatment on the MRI marker	New T2 lesions and relapses were significantly correlated: compared with placebo, interferon significantly ↓ new T2 lesion number by 60% over 2 years, and the number of relapses ↓ by 30%. PTE on relapses accounted for by the effect of treatment on new T2 MRI lesions was 53% in RRMS patients. A pooled PTE of 62% was found when meta-analysis was performed on data from PRISMS and 2 other trials of DMTs.	The study provides evidence that new T2 MRI lesion count is a surrogate for relapses in MS patients treated with interferon or drugs with similar mechanism of action.
Kappos 1999[61]	• Patients in natural-course studies or were treated with placebo or observed in the pre-treatment phase of controlled clinical trials • 77% of the patients had RRMS; 23% had secondary-progressive MS • Follow-up: 6 to 24 months	• Change in disability: assessed by EDSS • Relapse • MRI data	Relapse rate in the first year was predicted with moderate ability by mean number of Gd+ lesions: RR 1.13, *P* = 0.023. The mean of Gd+ lesion counts in the first 6 monthly scans was weakly predictive of EDSS change after 1 year: OR 1.34, *P* = 0.082; and 2 years: OR 1.65, *P* = 0.049.	Gd+ MRI was not a strong predictor of the development of cumulative impairment or disability.

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

Conclusion

A summary of the characteristics of instruments was provided; one measuring disability (i.e., EDSS) and three measuring health-related quality of life (i.e., MSQOL-54, EQ-5D, SF-36). In addition, the correlation between MRI outcomes and clinical outcomes such as relapses and progression in disability in patients with relapsing-remitting MS 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 change when the score was between the EDSS 0 to 5.5 range, and a 0.5 point change when the EDSS score was between 5.5 and 8.5.
- The MSQOL-54 has good internal consistency reliability, test-retest reliability, and construct validity in patients with MS. No minimal clinically important difference specific to patients with MS was identified.

- The EQ-5D was determined to have a range in MCID of 0.050 to 0.084 in patients with MS. The tool was determined to be reliable (intra-class correlation coefficient for test-retest reliability = 0.81), but may not have construct validity for patients with MS.
- Findings from the studies investigating the correlations of MRI outcomes and clinical outcomes suggested that conventional MRI scans may be a tool of predicting disease relapses and disability progression for patients with relapsing-remitting MS. However, the correlations between MRI outcomes and clinical outcomes were not consistent across studies.

Appendix 6: Summary Of Extension Study

Objective

To summarize the efficacy and safety results from the 96-week CLARITY EXT study.[65] CLARITY EXT was considered to be a non-pivotal supportive study for Health Canada's review of cladribine.[30]

Findings

Study Design

Patients with relapsing-remitting multiple sclerosis (RRMS) were enrolled in CLARITY EXT if they completed all scheduled clinic visits in the 96-week CLARITY trial and had a normal lymphocyte count and other normal hematological results within 28 days of the first planned dose. CLARITY was a 96-week, double-blind, placebo-controlled study in which patients received cladribine at either 3.5 mg/kg or 5.25 mg/kg.

CLARITY EXT was a double-blind, placebo-controlled, multi-centre, parallel-group extension study designed to assess the long-term safety and efficacy of oral cladribine. A summary of study characteristics is presented in Table 13 and a diagram of the study design in Figure 3. Patients who were enrolled in the placebo group in CLARITY were assigned to receive cladribine 3.5 mg/kg (PPLL), while patients in both cladribine groups in CLARITY were re-randomized 2:1 to receive cladribine 3.5 mg/kg (LLLL) or placebo (LLPP) with blinding maintained. The focus of the following summary of CLARITY EXT is on the patients who originally received either cladribine 3.5 mg/kg or placebo in the CLARITY trial because the other studied dose, cumulative 5.25 mg/kg, is not approved by Health Canada.

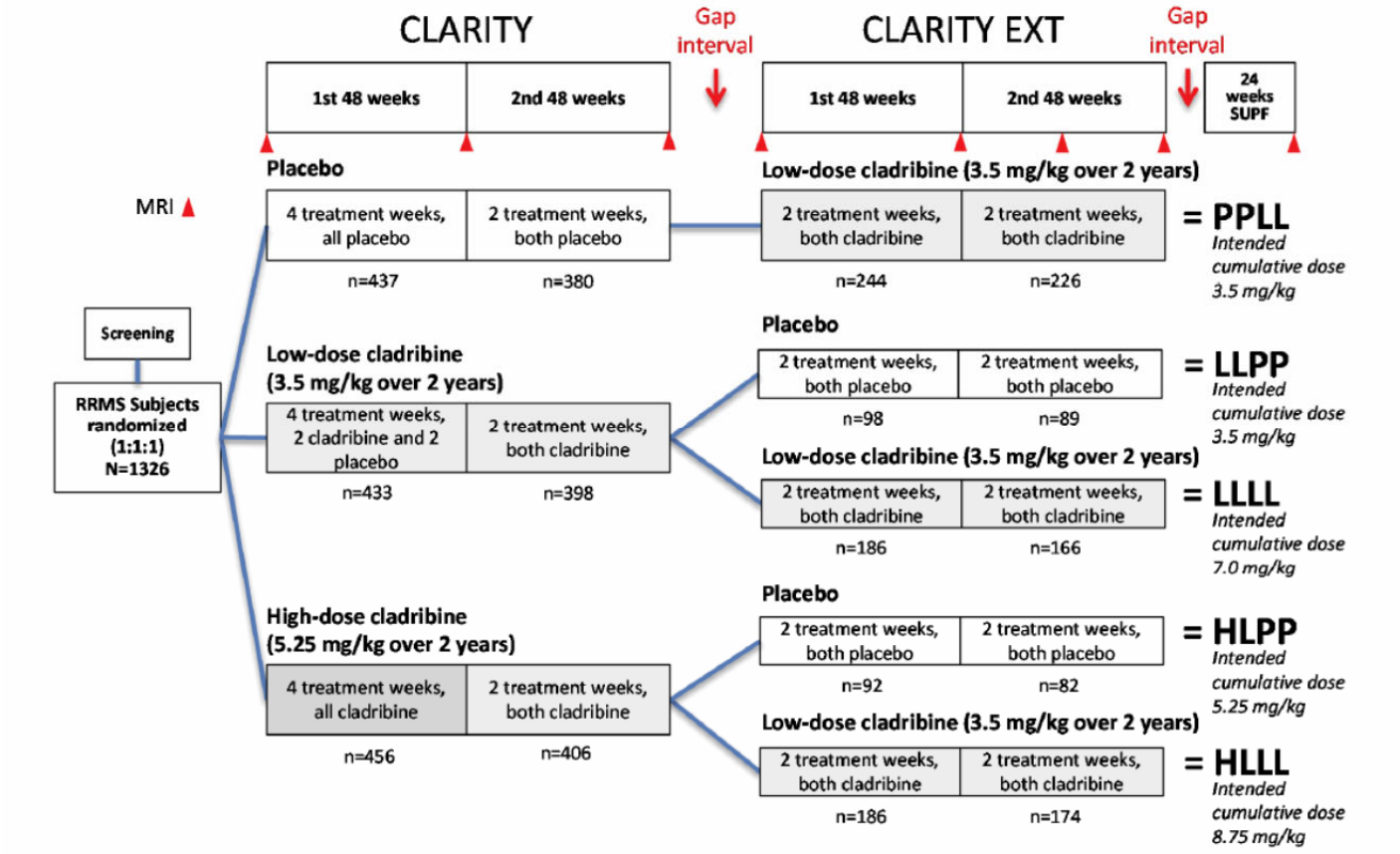
CLARITY EXT was conducted in 133 of the 155 sites involved in the CLARITY study. CLARITY EXT was not pre-planned; as a result, the gap in time prior to patients entering CLARITY EXT was variable (median gap = 40.3 weeks; range = 0.1 to 118 weeks).

Table 13: Study Characteristics

Patient Population	Adults with relapsing-remitting multiple sclerosis who were eligible to enrol from CLARITY
Intervention	Cladribine 10 mg to 20 mg orally once daily for four or five days for one week at the beginning of the first treatment month and one week at the beginning of the second treatment month, over the course of one year. Cumulative dose of 3.5 mg/kg body weight over 2 years.
Comparators	Placebo Low cladribine dose (cumulative dose of 3.5 mg/kg body weight over 2 years)
Outcomes	**Key efficacy outcomes:** Rate of disease progression (e.g., EDSS) MRI measures of disease activity Clinical relapses Health-related quality of life **Harms outcomes:** Mortality Serious adverse events Withdrawals
Study Design	Phase III RCT

EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; RCT = randomized control trial.

Figure 3: Trial Design Diagram for CLARITY and CLARITY EXT



HL = high-dose cladribine; LL = low-dose cladribine; MRI = magnetic resonance imaging; PP = placebo; RRMS = relapsing-remitting multiples sclerosis; SUPF = supplemental follow-up period.

Note: The high-dose groups (HLPP and HLLL) are not included in the data presentation as they are not Health Canada–approved doses.

Source: Clinical Study Report for CLARITY EXT.[65]

Assessment

The assessment of safety and efficacy of cladribine were the primary objectives of the CLARITY EXT study. The safety of cladribine with an emphasis on cardiac repolarization was assessed by changes in QT interval. Exploratory efficacy end points included the following variables:

- Annualized relapse rate (ARR).
- The proportion of patients free of qualifying relapses.
- The time to first qualifying relapse.
- Expanded Disability Status Scale (EDSS) progression.
- MRI outcomes (T1 Gd+, T2, combined unique lesions).

Results

Eight hundred and sixty-seven (73.2%) entered the CLARITY EXT trial out of 1,184 patients who completed the CLARITY trial. In CLARITY EXT, 244 (28%) were from the former

placebo group, 278 (31%) were from the former high-dose group (cladribine 5.25 mg/kg), and 284 (32%) were from the former low-dose group (cladribine 3.5 mg/kg). The most common reason for discontinuation was "other." Table 14 presents the detailed patient disposition for CLARITY EXT.

Table 14: Patient Disposition for CLARITY EXT

	LLLL Cladribine 3.5 mg/kg – Cladribine 3.5 mg/kg (N = 186)	PPLL Placebo – Cladribine 3.5 mg/kg (N = 244)	LLPP Cladribine 3.5 mg/kg – Placebo (N = 98)	HLLL[a] Cladribine 5.25 mg/kg – Cladribine 3.5 mg/kg (N = 186)	HLPP[a] Cladribine 5.25 mg/kg – Placebo (N = 92)
Screened, N	883				
Randomized, N	186	244	98	186	92
Discontinued, N (%)	20 (10.8)	17 (7.0)	9 (9.2)	12 (6.5)	10 (10.9)
Adverse Event	3 (1.6)	2 (0.8)	0	0	1 (1.1)
Lost to Follow-up	2 (1.1)	4 (1.6)	3 (3.1)	(1.1)	1 (1.1)
Protocol Violation	0	0	0	(0.5)	1 (1.1)
Death	1 (0.5)	0	2 (2.0)	0	0
Other	14 (7.5)	11 (4.5)	4 (4.1)	(4.8)	7 (7.6)
ITT, N	186	244	98	186	92
Safety, N	186	244	98	186	92

HLLL = cladribine high/low dose; HLPP = cladribine high dose/placebo; ITT = intention-to-treat; LLLL = cladribine low/low dose; LLPP = cladribine low/placebo; PPLL = placebo/cladribine low dose.

[a] These groups received unapproved doses of oral cladribine and are presented for completeness only; safety and efficacy data are not reported for these groups.

Source: Clinical Study Report for CLARITY EXT.[65]

Safety Outcomes

The safety analysis set was composed of 806 patients. Table 15 presents harms data for patients during the CLARITY EXT study. Between 75.5% and 80.1% of patients in the intervention groups of interest experienced a treatment-emergent adverse event. The most common adverse events included blood and lymphatic system disorders (17.3% to 41.9%), musculoskeletal and connective tissue disorders (23.7% to 27.6%), nervous system disorders (18.8% to 23.4%), gastrointestinal disorders (21.5% to 27.6%), general disorders, and administration site conditions (17.2% to 20.4%).

Adverse events occurred less frequently in the placebo (LLPP) group for the blood and lymphatic system disorders; specifically for lymphopenia, 1.0% of patients in the LLPP group were affected compared with 36.6% of patients in the LLLL group and 28.3% of patients in the PPLL group. In the LLPP group, 5.1% of patients had any grade 3 or 4 lymphocyte count decrease compared with 40.9% and 25.0% in the LLLL and PPLL groups, respectively. Any malignant or unspecified tumour was identified in 2.0% of patients in the LLPP group compared with 3.8% and 0.8% of patients in the LLLL and PPLL groups, respectively.

Serious adverse events occurred in 16.3% of patients in the LLPP group compared with 13.4% and 9.0% in the LLLL and PPLL groups, respectively. Discontinuation of treatment due to treatment-emergent adverse events was reported in 3.1% of patients in the LLPP group compared with 14.0% and 10.2% in the LLLL and PPLL groups, respectively. The most common reason for treatment discontinuation was lymphopenia. Throughout

CLARITY EXT three patients died due to reasons unrelated to the study drug. [redacted]

[redacted]

Table 15: Harms

	LLLL Cladribine 3.5 mg/kg – Cladribine 3.5 mg/kg (N = 186)	PPLL Placebo – Cladribine 3.5 mg/kg (N = 244)	LLPP Cladribine 3.5 mg/kg – Placebo (N = 98)
AEs, N (%)[a]	149 (80.1)	194 (79.5)	74 (75.5)
Blood And lymphatic system disorders	78 (41.9)	81 (33.2)	17 (17.3)
Leukopenia	19 (10.2)	12 (4.9)	1 (1.0)
Lymphopenia	68 (36.6)	69 (28.3)	9 (9.2)
Neutropenia	7 (3.8)	7 (2.9)	2 (2.0)
Ear and labyrinth disorders	9 (4.8)	7 (2.9)	7 (7.1)
Vertigo	6 (3.2)	5 (2.0)	5 (5.1)
Gastrointestinal Disorders	40 (21.5)	53 (21.7)	27 (27.6)
Diarrhea	6 (3.2)	14 (5.7)	7 (7.1)
Nausea	11 (5.9)	10 (4.1)	8 (8.2)
Toothache	5 (2.7)	4 (1.6)	4 (4.1)
Vomiting	5 (2.7)	4 (1.6)	1 (1.0)
General disorders and administration site conditions	33 (17.7)	42 (17.2)	20 (20.4)
Fatigue	8 (4.3)	12 (4.9)	5 (5.1)
Influenza-like illness	14 (7.5)	11 (4.5)	5 (5.1)
Infections and infestations	91 (48.9)	110 (45.1)	48 (49.0)
Bronchitis	1 (0.5)	17 (7.0)	6 (6.1)
Influenza	16 (8.6)	17 (7.0)	11 (11.2)
Nasopharyngitis	22 (11.8)	45 (18.4)	19 (19.4)
Upper respiratory tract infection	17 (9.1)	19 (7.8)	8 (8.2)
Urinary tract infection	17 (9.1)	17 (7.0)	6 (6.1)
Musculoskeletal and connective tissue disorders	44 (23.7)	61 (25.0)	27 (27.6)
Arthralgia	5 (2.7)	13 (5.3)	5 (5.1)
Back pain	16 (8.6)	28 (11.5)	9 (9.2)
Pain in extremity	10 (5.4)	11 (4.5)	8 (8.2)
Nervous system disorders	35 (18.8)	57 (23.4)	21 (21.4)
Headache	21 (11.3)	38 (15.6)	20 (20.4)
Psychiatric Disorders	14 (7.5)	29 (11.9)	14 (14.3)
Anxiety	4 (2.2)	7 (2.9)	5 (5.1)
Depression	6 (3.2)	9 (3.7)	6 (6.1)
Vascular Disorders	7 (3.8)	11 (4.5)	5 (5.1)
Hypertension	5 (2.7)	7 (2.9)	4 (4.1)
Notable AEs			
Any grade 3 or 4 lymphocyte count decrease	76 (40.9)	61 (25.0)	5 (5.1)
Any malignant or unspecified tumour	7 (3.8)	2 (0.8)	2 (2.0)

	LLLL Cladribine 3.5 mg/kg – Cladribine 3.5 mg/kg (N = 186)	PPLL Placebo – Cladribine 3.5 mg/kg (N = 244)	LLPP Cladribine 3.5 mg/kg – Placebo (N = 98)
Any herpes viral infection	6 (3.2)	11 (4.5)	6 (6.1)
Any viral infectious disorder	28 (15.1)	39 (16.0)	20 (20.4)
Any opportunistic infection	9 (4.8)	15 (6.1)	8 (8.2)
SAE	25 (13.4)	22 (9.0)	16 (16.3)
Any Discontinuation of Treatment Due to TEAE, N (%)	26 (14.0)	25 (10.2)	3 (3.1)
Death, N (%)	1 (0.5)	0	2 (2.0)

AE = adverse event; HLLL = cladribine high/low dose; HLPP = cladribine high dose/placebo; LLLL = cladribine low/low dose; LLPP = cladribine low/placebo; SAE = severe adverse event, TEAE = treatment-emergent adverse event; PPLL = placebo/cladribine low dose.

[a] Frequency ≥ 5% during CLARITY EXT.

Source: Clinical Study Report for CLARITY EXT.[65]

Exploratory Efficacy Outcomes

Table 16 presents results from the exploratory efficacy analysis for the intervention groups of interest. The mean number of qualifying relapses ranged from 0.23 to 0.35, with qualifying relapse defined as follows: a two-grade increase in one or more Kurtzke Functional Systems (KFS) neurological examination, or a one-grade increase in two or more KFS, excluding changes in bowel/bladder function or cognition, in the absence of fever, lasting for greater than or equal to 24 hours, and preceded by at least 30 days of clinical stability or improvement. Compared with the placebo group (LLPP), neither active intervention group (LLLL, PPLL) differed significantly for the relative risk of annualized relapses. The number of patients who qualified as relapse-free ranged from 75.6% to 81.2%, with no significant differences associated with the odds ratio when compared with the LLPP group. The time to the first qualifying relapse for the 10th percentile ranged from 313 days to 483 days, with no significant differences associated with the odds ratio when compared with the LLPP group. Overall, outcomes pertaining to relapses did not show statistically significant advantages for either intervention group.

Disability was assessed using three-month confirmed EDSS progression from baseline; the range of patients that met this end point was 72.4% to 77.4%. Compared with the LLPP group, neither intervention groups showed statistically significant differences in the hazard ratio.

MRI outcomes were for new T1 gadolinium-enhanced (Gd+) T2, and combined unique lesions were assessed. The mean number of new T1 Gd+ lesions per patient per scan ranged from 0.03 to 0.28; compared with the LLPP group, both intervention groups showed statistically significant differences ($P < 0.001$). The mean number of active T2 lesions per patient per scan ranged from 0.31 to 1.21; compared with the LLPP group, neither intervention group showed statistically significant differences. The mean number of combined unique lesions per patient per scan ranged from 0.88 to 1.49; compared with the LLPP group, neither intervention group showed statistically significant differences. Overall, the only MRI outcome pertaining that showed statistically significant advantages for the intervention groups related to the new T1 Gd+ lesions.

Table 16: Exploratory Efficacy Outcomes

	LLLL Cladribine 3.5 mg/kg – Cladribine 3.5 mg/kg (N = 186)	PPLL Placebo – Cladribine 3.5 mg/kg (N = 244)	LLPP Cladribine 3.5 mg/kg – Placebo (N = 98)
Relapses			
Number of qualifying relapses, mean (SD)	0.23 (0.56)	0.25 (0.57)	0.35 (0.79)
Relapse rate, annualized (97.5% CI)	0.10 (0.06 to 0.13)	0.10 (0.07 to 0.13)	0.15 (0.09 to 0.21)
Relative risk-point estimate (97.5% CI)[a]	0.65 (0.39 to 1.08)	0.68 (0.42 to 1.11)	
***P* value[b]**	0.059	0.078	
Relapse-free status, n (%)	134 (81.2)	180 (79.6)	68 (75.6)
Odds ratio (97.5% CI)[c]	1.41 (0.69 to 2.88)	1.27 (0.65 to 2.47)	
***P* value[d]**	0.275	0.421	
Time to first qualifying relapse (days) 10th percentile (95% CI)[e]	483 (304 to 663)	313 (185 to 527)	411 (132 to 749)
Hazard ratio (97.5% CI)[f]	0.73 (0.39 to 1.37)	0.84 (0.47 to 1.50)	
***P* value**	0.262	0.493	
EDSS			
3-Month confirmed EDSS-progression free, N (%)[g]	144 (77.4)	185 (75.8)	71 (72.4)
Hazard ratio (97.5% CI)[f]	0.62 (0.30 to1.27)	0.91 (0.48 to 1.71)	
***P* value**	0.134	0.728	
MRI[h]			
Number of new T1 Gd+ lesions per patient per scan, mean (SD)	0.03 (0.08)	0.07 (0.38)	0.28 (0.87)
Point estimate (97.5% CI)[i]	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	
***P* value[j]**	< 0.001	0.003	
Number of active T2 lesions per patient per scan, mean (SD)	0.31 (0.65)	1.21 (1.65)	0.34 (0.53)
Treatment difference point estimate (97.5% CI)[i]	0.00 (−0.17 to 0.00)	0.00 (−0.17 to 0.00)	
***P* value[k]**	0.260	0.470	
Number of CU lesions per patient per scan, mean (SD)	0.88 (1.63)	1.08 (1.86)	1.49 (3.82)
Treatment difference point estimate (97.5% CI)[i]	0.00 (−0.20 to 0.00)	0.00 (−0.17 to 0.00)	
***P* value[k]**	0.214	0.387	

CI = confidence interval; CU = combined unique; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhanced; HLLL = cladribine high/low dose; HLPP = cladribine high dose/placebo; LLLL = cladribine low/low dose; LLPP = cladribine low/placebo; MRI = magnetic resonance imaging; PPLL = placebo/cladribine low dose; SD = standard deviation.

[a] Relative risk, relative reduction and associated 97.5% CIs were estimated using a Poisson regression model with fixed effects for treatment group and region and with log of time on study during weeks 0 to 120 as an offset variable.

[b] *P* value based on Wald chi-square test from analysis of number of qualifying relapses using a Poisson regression model with fixed effects for treatment group and region and with log of time on study during weeks 0 to 120 as an offset variable.

[c] Odds ratio and associated 97.5% CI were estimated using a logistic regression model with fixed effects for treatment group and region.

[d] *P* value based on Wald chi-square test of log odds ratio for treatment from logistic regression model with fixed effects for treatment group and region.

[e] The percentiles are estimated from a Kaplan–Meier survival curve.

[f] Hazard ratio, 97.5% CI and *P* values estimated using a Cox proportional model with fixed effects for treatment group and region.

[g] Patients with no observed EDSS progression, but incomplete assessments, are considered to have unknown progression status, and are included in the denominator.

[h] Scans at weeks 24, 48, 72, and 96 during double-blind period, and day 1 and week 24 during supplemental follow-up period contribute to the mean value, as available.

[i] Treatment difference (location shift) point estimate, standard estimate, and 97.5% CI estimated using Hodges–Lehmann estimate.

[j] *P* value calculated based on non-parametric ANCOVA model on ranked data with fixed effects for treatment group and region and baseline T1 Gd+ lesion as a covariate.

[k] *P* values calculated based on non-parametric analysis of covariance (ANCOVA) model on ranked data with fixed effects for treatment group and region. Scans at weeks 24, 48, 72, and 96 during double-blind period, and day 1 and week 24 during supplemental follow-up period contribute to the mean value, as available.

Note: The CLARITY EXT data in this table covers the 96-week double-blind and the 24-week supplemental follow-up period (including the gap between periods).

Source: Clinical Study Report for CLARITY EXT.[65]

Limitations

The main limitations of CLARITY EXT relate to the gap in time between CLARITY and CLARITY EXT, the associated impact on MRI outcomes, selection bias, and the absence of a true placebo group. The gap in time between CLARITY and CLARITY EXT varied resulting in heterogeneity for the total duration of observation and interventions assigned during CLARITY EXT. During this gap in time, data were not collected prospectively; they were captured retrospectively, potentially introducing recall bias. The variable gap may have potentially influenced the efficacy results, but this was explored in subgroup analysis. Patients who were treated with other disease-modifying therapies during this gap were required to discontinue treatment for at least three months prior to the start of CLARITY EXT. The MRI outcomes for patients that had a gap of four weeks or more between CLARITY and CLARITY EXT were assessed using new baseline scans. It is also possible that T1 Gd+ lesions that occurred during the gap would not be detected or accounted for as they are transient. The CLARITY EXT study was also limited in terms of statistical power, as the sample size was dependent on the number of patients from CLARITY that wanted to enroll; the study-wide alpha level was therefore not controlled at 5%. The inclusion criteria for CLARITY EXT required patients to have completed the CLARITY trial; this may have introduced selection bias, as patients who discontinued CLARITY due to adverse events would not have been eligible to participate in CLARITY EXT. Finally, this trial did not include a true placebo group, as patients in the placebo group in CLARITY were not randomized in CLARITY EXT, but assigned to the low dose group.

Discussion

It appeared that the safety results were similar across the CLARITY and CLARITY EXT studies, with lymphopenia reported as one of the most common associated adverse events occurring more frequently in the intervention groups compared with the placebo group. Notable adverse events included patients with any grade 3 or 4 lymphocyte count decrease, and patients with any malignant or unspecified tumour. Fewer patients in the LLPP group experienced grade 3 or 4 lymphocyte count decrease compared with the intervention groups, and patients in the LLLL group experienced the greatest proportion of malignant or unspecified tumours. The most common reason for treatment discontinuation was lymphopenia and this was also consistent with CLARITY. Three deaths occurred during CLARITY EXT, with none related to the treatment. Additionally, there was one death due to bile duct adenocarcinoma that occurred 14 months after discontinuing from the supplemental follow-up phase of the trial. This death was considered possibly related to the study medication.

Efficacy results were exploratory. When compared with the placebo group (LLPP), the intervention groups (LLLL, PPLL) showed no statically significant differences for the relapse or EDSS outcomes. MRI outcomes for lesions (T1 Gd+, T2, and combined unique) showed statistically significant improvements for only the T1 Gd+ lesions for the LLLL group compared with the LLPP group.

Summary

The safety of cladribine 3.5 mg/kg was similar in both the CLARITY and CLARITY EXT studies. The majority of patients experienced adverse events, the most common being blood and lymphatic system disorders, musculoskeletal and connective tissue disorders, nervous system disorders, gastrointestinal disorders, general disorders, and administration site conditions. A total of four deaths occurred in CLARITY EXT with one possibly related to the study drug. Limitations to CLARITY EXT included the variable gap in time between CLARITY and CLARITY EXT, the associated impact on MRI outcomes, and the potential for selection bias. These limitations highlight the need for caution when interpreting the results of this study.

Appendix 7: Summary Of Indirect Comparisons

Introduction

Background

There is limited data from head-to-head randomized controlled trials (RCTs) that have compared oral cladribine 10 mg or 20 mg to other therapies in patients with relapsing-remitting multiple sclerosis (RMSS). The purpose of this appendix is to summarize and critically appraise the literature for the comparative efficacy and safety of oral cladribine (10 mg or 20 mg) and other therapies for RRMS through indirect comparisons (IDCs).

Methods

An IDC submitted by the manufacturer was reviewed. In addition, a literature search was undertaken to identify any additional relevant published IDCs.

Description of IDCs Identified

One IDC submitted by the manufacturer was included for critical appraisal. Table 17 summarizes the key aspects of the IDC. The IDC included was sponsored by the manufacturer of cladribine.

Table 17: Overview of Included Indirect Comparisons

Population	Intervention	Comparators	Outcomes	Study Design
Adult patients with RRMS, or patient population with ≥ 80% RRMS patients	Cladribine 3.5 mg/kg[a]	• Placebo • Best supportive care • IFN beta-1a • IFN beta-1b • Glatiramer acetate • PEG-IFN beta-1a • Natalizumab • Alemtuzumab • Fingolimod • Dimethyl fumarate • Teriflunomide • Daclizumab • Ocrelizumab	• Annualized relapse rate • Confirmed disease progression at 3 and 6 months • Proportion relapse-free at 24 months • Proportion with no evidence of disease activity at 24 months • Total adverse events	• RCTs

IFN = interferon; PEG = pegylated; RCT = randomized control trial; RRMS = relapsing-remitting multiple sclerosis.

[a] Cladribine as a cumulative dose of 0.875 mg/kg over a course of four or five consecutive days of a 28-day period at weeks 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during a treatment period of 96 weeks.

Review and Appraisal of IDC

The manufacturer-submitted IDC[66] was critically appraised in part using recommendations from the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons as a guide.[67]

Manufacturer's IDC[66]

Objectives and Rationale

The manufacturer provided a clear rationale for the IDC, stating that the efficacy and safety of cladribine had not been directly compared with different disease-modifying treatments

(DMTs) in head-to-head trials. This IDC aimed to investigate the relative treatment efficacy and safety of cladribine tablets compared with alternative DMTs in patients with active RRMS and in a high disease activity subgroup of patients with high relapse activity (HRA) plus disease activity on treatment (DAT). Patients with high disease activity were defined as having two or more relapses in the previous year whether on disease-modifying drug treatment or not, plus patients with one relapse and one T1 gadolinium-enhanced (Gd+) lesion or nine T2 lesions in the previous year while on therapy with other disease-modifying drugs. An additional subgroup analysis was provided in the clinical summary supporting the manufacturer's clinical file and in the economic analysis, based on previous treatment with DMTs. Because this analysis was not reported in the main IDC published report, it was considered post hoc.

Methods for the Manufacturer's IDC[66]

Study Eligibility, Selection Process, and Data Extraction

Studies for the manufacturer's IDC were identified via systematic literature review based on a systematic search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The literature was searched for studies published in English indexed on multiple electronic databases (i.e., MEDLINE, Embase, MEDLINE In-Process, CENTRAL) from the date of database inception to January 2017. Conference websites, trial registries, and the FDA and European Medicines Agency (EMA) websites were also searched.

The manufacturer provided clear eligibility criteria for the inclusion of studies in the IDC. Studies were included if they were RCTs of DMTs that were approved by the FDA or EMA. Studies were included if they had an adult population with RRMS or if the study had a subgroup of 80% or more RRMS patients.

Studies were screened for inclusion in the IDC by two independent reviewers using a standard two-stage process. Discrepancies between reviewers in either the screening or extraction process were evaluated by a third independent reviewer.

Comparators

The comparators for the IDC were placebo, best supportive care, and DMTs approved by the FDA or EMA. DMTs included the following: interferon (IFN) beta-1a, IFN beta-1b, glatiramer acetate, PEG-IFN beta-1a, natalizumab, alemtuzumab, fingolimod, dimethyl fumarate, teriflunomide, daclizumab, and ocrelizumab.

Outcomes

The IDC evaluated the following three efficacy outcomes: annualized relapse rate (ARR), confirmed disease progression (CDP) at three and six months, relapse-free at 24 months, and no evidence of disease activity (NEDA) at 24 months. The definitions for ARR and CDP varied by trial. However, most trials defined relapse as new or worsening symptoms that lasted at least 24 hours and occurred in the absence of fever or infection, and defined disability progression as an increase in Extended Disability Status Scale (EDSS) score of one or more points, or half or more points for baseline EDSS or equal to 5.5. Disease progression was confirmed during two subsequent neurological examinations separated by three to six months free of relapses. NEDA was defined as no activity on EDSS, relapse, or lesion imaging.

Quality Assessment of Included Studies

Risk of bias in the trials was assessed using checklists (i.e., National Institute for Health and Care Excellence, Germany's Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, and France's Haute Autorité de Santé) and study grade. The Jadad score was used to assess study quality and study reporting. Studies were included in the IDC regardless of quality; no exclusion criteria based on methodology (i.e., exclude early-phase/unclear-phase RCTs, exclude studies with high risk of bias) was applied to this IDC.

Indirect Comparison Methods

The manufacturer used a series of Bayesian network meta-analyses. Random and fixed-effects models were fit for each outcome assessment; the best-fitting model was based on residual deviance and deviance information criteria. Each analysis (ARR, CDP, relapse-free, NEDA, and safety) used three independent Monte Carlo Markov chains with a burn-in of 20,000 and 100,000 simulations. Study-level treatment effects, baseline outcomes, and between-study heterogeneity parameters were based on vague prior distributions. Between-study heterogeneity was assessed using the posterior of the between-trial standard deviation, and the consistency between direct and indirect evidence was tested using the loop-specific approach.

The analysis for ARR utilized relapse rate ratio, the CDP analysis used hazard ratios, and the relapse-free, NEDA, and safety end points used odds ratios. Statistical significance was determined using a Bayesian *P* value (below 0.05).The efficacy analyses were performed on the intent-to-treat (ITT) populations of included studies and on the subgroup for patients with high disease activity when feasible. Due to an absence of data, safety analysis was only preformed on the ITT population. The ITT population was defined as all patients with one or more relapses in the previous year, or two or more relapses in the previous two years. If data for patients in the high disease activity subgroup were not reported, subgroups for patients with HRA or patients with DAT were used and generalized to the full high disease activity population.

Potential treatment-effect modifiers were accounted for using meta-regression analysis for the following covariates: mean age, percentage female, mean baseline EDSS score, study duration, disease duration, and mean number of relapses in prior one year and two years.

Sensitivity analyses were conducted for the ARR and CDP outcomes based on the following main areas of heterogeneity: diagnostic criteria (exclusion of studies that used Poser diagnostic criteria and studies for which diagnostic criteria was unclear), year of publication (exclusion of studies published prior to the year 2000), study blinding (exclusion of open-label studies and studies for which blinding status was unclear), and study phase (exclusion of phase II studies). Additional end point–specific sensitivity analyses were also performed excluding specific studies that may have had inappropriate influence on results. The impact of potential sources of heterogeneity was assessed through meta-regression using mean age, percentage female, mean baseline EDSS score, study duration, disease duration, and mean number of relapses in the previous year and two years as covariates. Meta-regression was conducted only if the number of studies in a given network was ≥ 10.

Results

Out of a total of 10,825 articles identified from the systematic literature search, 44 trials were included in the IDC. The adult patient populations included in the trials were not restricted by geographic region, gender, race, or line of therapy. Variability was noted for a number of study characteristics. The publication dates for the studies were between 1987 and 2017, this included six studies published prior to 2000. The sample size was between 31 and 2,244 patients. Variation for the mean duration of disease was determined with as the studies ranged between 1.2 and 9.1 years. The mean age of patients was between 27.4 and 40.8 years and the proportion of female patients ranged from 33% to 81%. The IDC included 27 phase III trials, six phase II trials, three phase IV trials, and eight studies that did not report the phase. Blinding status varied by study: 33 studies were double-blinded, nine studies were assessor-blinded, one study was open-label, and one study did not report the method of blinding. The diagnostic criteria varied between studies as 30 studies utilized McDonald's diagnostic criteria, nine utilized Poser's diagnostic criteria, one used both criteria, and four were unclear. The majority of trials enrolled patients with a baseline EDSS score equal to or less than 6 who had at least one or two relapses in the past year or two, respectively. The mean EDSS score at baseline ranged from 0.1 to 3.7.

Annualized Relapse Rate

Forty-one trials contributed data to the ARR analysis, and 11 trials contributed data to the subgroup analysis for patients with high disease activity. Table 18 summarizes the rate ratios between various DMTs and cladribine tablets. Cladribine was statistically more efficacious for the ARR outcome when compared with glatiramer acetate 20 mg, pegylated IFN beta-1a 125 mcg, IFN beta-1a 44 mcg, teriflunomide 14 mg, glatiramer acetate 40 mg, IFN beta-1b 250 mcg, IFN beta-1a 22 mcg, teriflunomide 7mg, IFN beta-1a 30 mcg, and placebo ($P < 0.05$). Cladribine was not statistically significant different from other DMTs. Publication year was negatively correlated with ARR.

Table 18: Summary of Annualized Relapse Rate Results in the ITT Population for Cladribine Tablets Versus Disease-Modifying Therapies for Relapsing-Remitting Multiple Sclerosis

Drug	RR[a]	95% CrI
Cladribine tablets	Reference	NA
Alemtuzumab 12 mg q.d.	1.30	0.93 to 1.83
Natalizumab 300 mg q.4.w.	1.22	0.89 to 1.68
Ocrelizumab 600 mg once every 6 months	1.14	0.81 to 1.6
Daclizumab HYP 150 mg q.4.w	0.92	0.66 to 1.25
Fingolimod 0.5 mg q.d.	0.91	0.67 to 1.22
DMF 240 mg b.i.d.	0.78	0.57 to 1.07
Glatiramer acetate 20 mg q.d.	0.64	0.48 to 0.85[b]
PEG-IFN beta-1a 125 mcg q.2.w.	0.64	0.44 to 0.92[b]
IFN beta-1a 44 mcg t.i.w.	0.63	0.47 to 0.84[b]
Teriflunomide 14 mg q.d.	0.62	0.46 to 0.84[b]
Glatiramer acetate 40 mg t.i.w.	0.62	0.44 to 0.87[b]
IFN beta-1b 250 mcg e.o.d.	0.62	0.47 to 0.83[b]
IFN beta-1a 22 mcg t.i.w.	0.58	0.42 to 0.81[b]

Drug	RR[a]	95% CrI
Teriflunomide 7mg q.d.	0.54	0.4 to 0.72[b]
IFN beta-1a 30 mcg q.1.w.	0.52	0.39 to 0.68[b]
Placebo	0.42	0.32 to 0.54[b]

b.i.d.= twice daily; CrI = credible interval; DMF = dimethyl fumarate; e.o.d. = every other day; HYP = high-yield process; IFN = interferon; ITT = intention-to-treat; NA = not applicable; PEG = pegylated; q.d. = once per day; q.1.w. = once weekly; q.2.w. = every 2 weeks; q.4.w. = every four weeks; RR = risk ratio; t.i.w. = three times weekly.

[a] Rate ratio versus cladribine tablets; random-effects model.

[b] Statistically significant difference from cladribine tablets indicated by 95% CrI.

Source: Siddiqui et al. (2017).[66]

Results from subgroup analyses for high disease activity patients and treatment-experienced patients are shown in Table 19.Tabular data and evidence networks were not presented in the published report for the IDC, but data tables were included in the manufacturer's clinical summary and economic submission to CADTH Common Drug Review (CDR) for the comparisons of cladribine with placebo and DMTs for which subgroup data were available. [redacted] It was reported in the published article for the IDC that cladribine was associated with 49% to 56% relative reductions in ARR versus teriflunomide 7 mg, IFN beta-1a 30 mcg, IFN beta-1a 44 mcg and glatiramer acetate 20 mg in the high disease activity subgroup. However, these data were not presented and could not be found in the clinical or economic submission to CDR. It was reported that no comparisons between cladribine versus ocrelizumab and daclizumab were possible for the high disease activity subgroup because no published data were identified for the subgroup.

Table 19: Comparative Efficacy of Cladribine Versus Select DMTs and Placebo for Annualized Relapse Rate in subgroups in Relapsing-Remitting Multiple Sclerosis

Drug	High Disease Activity		Treatment-Experienced	
	Rate ratio[a]	95% CrI	Rate ratio[a]	95% CrI
Placebo	[redacted]			
Alemtuzumab 12 mg q.d.				
Natalizumab 300 mg q.4.w				
Fingolimod 0.5 mg q.d				
Daclizumab HYP 150 mg q.4.w.				

ARR = annualized relapse rate; CrI = credible interval; DMT = disease-modifying therapy; HYP = high-yield process; NE = not estimated; q.d. = per day; q.4.w. = every four weeks.

[a] Model not specified. A rate ratio greater than 1 favours the comparator and less than 1 favours cladribine tablets.

Source: Manufacturer's submission.[29]

Confirmed Disease Progression Sustained for Three and Six Months at 24 Months

Twenty studies contributed to the IDC for CDP sustained for six months at 24 months while four studies contributed to the high disease activity subgroup analysis. Eighteen studies formed the network for CDP sustained for three months at 24 months; the number of studies contributing to the high disease activity subgroup analysis was not reported. Table 20 summarizes the hazard ratios between various DMTs and cladribine tablets for CDP sustained for three and six months at 24 months. Cladribine was statistically more efficacious for CDP sustained for three and six months when compared with placebo only

(hazard ratio at three months = 0.60; 95% CI, 0.38 to 0.95; and at 6 months = 0.54; 95% CI, 0.29 to 0.99).

Table 20: Summary Of Confirmed Disease Progression Sustained for Three and Six Months at 24 Months in the ITT Population for Cladribine Tablets Versus DMTs for RRMS

Drug	CDP for 3 Months		CDP for 6 Months	
	HR[a]	95% CrI	HR[a]	95% CrI
Cladribine tablets	Reference	NA	Reference	NA
IFN beta-1b 250 mcg e.o.d.	0.68	0.39 to 1.26	1.79	0.65 to 4.73
Alemtuzumab 12 mg q.d.	2.25	0.81 to 6.49	1.37	0.58 to 3.32
Ocrelizumab 600 mg once every 6 months	1.50	0.7 to 3.26	1.26	0.51 to 2.98
Natalizumab 300 mg q.4.w	1.10	0.58 to 2.07	1.21	0.52 to 2.77
Daclizumab HYP, 150 mg, q.4.w.	0.92	0.41 to 2.04	1.07	0.42 to 2.65
DMF 240 mg b.i.d.	0.94	0.54 to 1.66	0.85	0.41 to 1.81
Glatiramer acetate 20 mg q.d.	0.84	0.49 to 1.47	0.81	0.37 to 1.73
Fingolimod 0.5 mg q.d.	0.78	0.45 to 1.35	0.79	0.37 to 1.64
IFN beta-1a 30 mcg q.1.w.	0.78	0.39 to 1.54	0.79	0.37 to 1.64
IFN beta-1a 44 mcg t.i.w.	0.93	0.47 to1.83	0.76	0.35 to 1.61
Teriflunomide 14 mg q.d.	0.82	0.47 to 1.43	0.66	0.31 to 1.38
Teriflunomide 7 mg q.d.	0.67	0.38 to 1.16	0.57	0.27 to 1.18
Placebo	0.60	0.38 to 0.95[b]	0.54	0.29 to 0.99[b]

b.i.d. = twice daily; CDP = confirmed disease progression; CrI = credible interval; DMF = dimethyl fumarate; DMT = disease-modifying therapy; e.o.d. = every other day; HR = hazard ratio; HYP = high-yield process; IFN = interferon; ITT = intention-to-treat; NA = not applicable; q.d. = per day; q.1.w. = once weekly; q.4.w. = every four weeks; RRMS = relapsing-remitting multiple sclerosis; t.i.w. = three times weekly.

[a] Hazard ratio versus cladribine tablets; random-effects model. A hazard ratio greater than 1 favours the comparator and lower than 1 favours cladribine tablets.

[b] Statistically significant difference from cladribine tablets indicated by 95% CrI.

Source: Siddiqui et al., 2017.[66]

Results from the subgroup analyses for high disease activity patients and treatment-experienced patients for CDP sustained for six months were reported in the text of the IDC report only; results for this subgroup for CDP sustained for three months were not reported in the IDC report. Data tables for these subgroups for the CDP outcomes were presented in the manufacturer's clinical summary and economic report for the cladribine CADTH Common Drug Review (CDR) submission. The results are shown in Table 21 and Table 22. It was reported in the published IDC report that cladribine showed a statistically significant reduction in CDP sustained for six months at 24 months of 82% versus placebo, and 61% to 68% reductions versus alemtuzumab and IFN beta-1a 44 mcg. However, the reduction versus alemtuzumab was not statistically significant and the data for the comparison with IFN beta-1a 44 mcg were not reported in the data tables. [redacted]

Table 21: Comparative Efficacy of Cladribine Versus Select DMTs and Placebo for Confirmed Disability Progression for Three Months at 24 Months (Subgroups)

Drug	High Disease Activity		Treatment-Experienced	
	Hazard ratio[a]	95% CrI	Hazard ratioa	95% CrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab 300 mg q.4.w.	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5 mg q.d.	[redacted]	[redacted]	[redacted]	[redacted]

CrI = credible interval; DMT = disease-modifying therapy; NE = not estimated; q.d. = per day; q.4.w. = every four weeks.

[a] Model not specified. A hazard ratio greater than 1 favours the comparator and less than 1 favours cladribine tablets.

Source: Manufacturer's submission.[29]

Table 22: Comparative efficacy of Cladribine Versus Select Disease-Modifying Therapies and Placebo for Confirmed Disability Progression for 6 Months at 24 Months (Subgroups)

Drug	High Disease Activity		Treatment-Experienced	
	Hazard ratioa	95% CrI	Hazard ratioa	95% CrI
Placebo	[redacted]	[redacted]	[redacted]	
Alemtuzumab 12 mg q.d.	[redacted]	[redacted]		

CrI = credible interval; q.d. = per day.

[a] Model not specified. A hazard ratio greater than 1 favours the comparator and less than 1 favours cladribine tablets.

Source: Manufacturer's submission.[29]

Proportion of Patients Relapse-Free

The IDC network for the proportion of patients relapse-free at 24 months comprised 25 RCTs. A significantly larger proportion of cladribine-treated patients remained relapse-free versus those who received placebo, teriflunomide 7 mg or 14 mg, or IFN beta-1a 30 mcg (Table 23). However, a significantly larger proportion of patients remained relapse-free when treated with alemtuzumab compared with cladribine. [redacted]

Table 23: Proportion of Patients Relapse-Free at 24 Months in the ITT Population for Cladribine Versus Disease-Modifying Therapies for Relapsing-Remitting Multiple Sclerosis

Drug	Odds ratio[a]	95% CrI
Cladribine tablets	Reference	NA
Alemtuzumab 12 mg q.d.	0.47	0.25 to 0.81
Ocrelizumab 600 mg once every 6 months	0.61	0.32 to 1.06
Natalizumab 300 mg q.4.w.	0.90	0.53 to 1.54
Fingolimod 0.5 mg q.d.	1.04	0.65 to 1.65
Daclizumab HYP 150 mg q.4.w.	1.11	0.64 to 2.02
IFN beta-1a 44 mcg t.i.w.	1.17	0.67 to 1.88
DMF 240 mg b.i.d.	1.25	0.78 to 1.97
Glatiramer acetate 20 mg q.d.	1.35	0.84 to 2.1
IFN beta-1b 250 mcg e.o.d.	1.36	0.83 to 2.22
IFN beta-1a 22 mcg t.i.w.	1.43	0.75 to 2.61
Teriflunomide 14 mg q.d.	1.71[b]	1.07 to 2.73
Teriflunomide 7 mg q.d.	1.90[b]	1.12 to 3.18

Drug	Odds ratio[a]	95% CrI
IFN beta-1a 30 mcg q.1.w.	2.14 [b]	1.36 to 3.49
Placebo	2.62 [b]	1.79 to 3.82

b.i.d. = twice daily; CrI = credible interval; DMF = dimethyl fumarate; e.o.d. = every other day; IFN = interferon; ITT = intention-to-treat; NA = not applicable; NR = not reported; q.d. = once per day; q.1.w. = once weekly; q.2.w. = every two weeks; q.4.w. = every four weeks; t.i.w. = three times weekly.

[a] Odds ratio versus cladribine. Random-effects model. An odds ratio greater than one favours cladribine tablets and lower than one favours the comparator.

[b] Statistically significant difference in favour of cladribine tablets indicated by 95% CrI.

Source: Siddiqui et al., 2017.[66]

Proportion with No Evidence of Disease Activity

Five studies contributed to the IDC for the proportion of patients achieving NEDA at 24 months. No studies (besides CLARITY) were available for the high disease activity subgroup analysis. Table 24 summarizes the odds ratios between various DMTs and cladribine tablets. Cladribine was statistically more efficacious for the NEDA outcome when compared with teriflunomide 14 mg, DMF 240 mg, teriflunomide 7 mg, glatiramer acetate 20 mg, and placebo. No subgroup analyses were conducted for NEDA due to lack of data.

Table 24: Summary of No Evidence of Disease Activity at 24 Months in the ITT Population for Cladribine Tablets Versus DMTs for Relapsing-Remitting Multiple Sclerosis

Drug	OR[a]	95% CrI
Cladribine tablets	Reference	NA
Natalizumab 300 mg q.4.w.	0.64	0.35 to 1.12
Teriflunomide 14 mg q.d.	2.00	1.2 to 3.32[b]
DMF 240 mg b.i.d.	2.72	1.77 to 4.21[b]
Teriflunomide 7 mg q.d.	2.84	1.7 to 4.76[b]
Glatiramer acetate 20 mg q.d.	3.39	2.17 to 5.35[b]
Placebo	4.69	3.35 to 6.65[b]

b.i.d. = twice daily; CrI = credible interval; DMF = dimethyl fumarate; DMT = disease-modifying therapy; e.o.d. = every other day; ITT = intention-to-treat; NA = not applicable; OR = odds ratio; q.d. = once per day; q.1.w. = once weekly; q.4.w. = every four weeks.

[a] Odds ratio versus cladribine tablets; fixed-effects model. An odds ratio greater than one favours cladribine tablets and lower than one favours the comparator.

[b] Statistically significant difference from cladribine tablets indicated by 95% CrI.

Source: Siddiqui et al., 2017.[66]

Sensitivity Analyses

Sensitivity analyses indicated that the point estimates for the relative efficacy treatment differences between cladribine and comparators for ARR and CDP at 24 months outcomes did not change direction. However, the 95% credibility intervals (CrIs) were sensitive to the various analyses and it was reported that "in some instances the significance level of findings changed."[66] It was not reported which assumptions, comparisons and outcomes to which the 95% CrIs were sensitive in the various scenarios tested. For the proportions of patients relapse-free at 24 months, an effect on the findings for cladribine tablets versus teriflunomide 14 mg and alemtuzumab was found as between-intervention significance was lost in some sensitivity analyses. Additionally, when two trials were excluded due to inconsistent findings compared with other trials, it appeared that the treatment difference for cladribine versus certain comparators changed.

It was reported that univariate meta-regression analyses suggested covariates did not affect results in a meaningful way, although data were not presented for these analyses. However, EDSS score was reported as having a significant ($P < 0.05$) negative correlation with ARR and the percentage of females was significantly correlated with ARR in a positive

direction. These correlations were considered unlikely to be clinically significant because the effect size and 95% CrIs were close to zero. It was also reported that the number of relapses in the previous two years had a significant negative correlation with CDP sustained for six months at 24 months, yet no interpretation regarding the clinical significance of this finding was reported.

Adverse Events

Table 25 summarizes the results of the safety comparison for cladribine versus DMTs for any adverse event. Twenty-five studies were included in the network for adverse events. Collectively, no statistical differences between cladribine and DMTs or placebo were identified for the overall odds of any adverse event. The manufacturer provided additional information regarding harms analyses in the IDC that were not reported in the main published IDC report. The clinical summary states that [redacted][29] The manufacturer notes the following regarding comparisons with cladribine and other DMTs with respect to lymphopenia and malignancy:

[redacted][29]

In addition, the clinical summary states that [redacted]

Table 25: Summary of Adverse Events in the Intention-To-Treat Population for Cladribine Tablets Versus Disease-Modifying Therapies for Relapsing-Remitting Multiple Sclerosis

Drug	OR[a]	95% CrI
Cladribine tablets	Reference	NA
Natalizumab 300 mg q.4.w.	2.70	0.96 to 7.93
Glatiramer acetate 20 mg q.d.	2.23	0.89 to 5.69
Placebo	1.59	0.76 to 3.34
Daclizumab HYP 150 mg q.4.w.	1.53	0.62 to 4.16
Teriflunomide 7 mg q.d.	1.38	0.55 to 3.43
Fingolimod 0.5 mg q.d.	1.31	0.52 to 3.06
Teriflunomide 14 mg q.d.	1.21	0.48 to 3.05
IFN beta-1a 30 mcg q.1.w.	1.13	0.49 to 2.81
DMF 240 mg b.i.d	1.02	0.39 to 2.7
IFN beta-1b 250 mcg e.o.d.	0.81	0.04 to 15.52

Drug	OR[a]	95% CrI
Glatiramer acetate 40 mg t.i.w.	0.98	0.35 to 2.75
Ocrelizumab 600 mg once every 6 months	0.67	0.12 to 3.31
IFN beta-1a 44 mcg t.i.w.	0.67	0.13 to 3.03
PEG-IFN beta-1a 125 mcg q.2.w.	0.51	0.17 to 1.51
Alemtuzumab 12 mg q.d.	0.27	0.05 to 1.47

b.i.d. = twice daily; CrI = credible interval; DMF = dimethyl fumarate; e.o.d. = every other day; HYP = high-yield process; IFN = interferon; NA = not applicable; OR = odds ratio; q.d. = once per day; q.1.w. = once weekly; q.2.w. = every two weeks; q.4.w. = every four weeks; RR = risk ratio; t.i.w. = three times weekly.

[a] Odds ratio versus cladribine tablets; random-effects model. An odds ratio greater than one favours cladribine tablets and lower than one favours the comparator

Source: Siddiqui et al., 2017.[66]

Critical Appraisal

The rationale and objectives for the IDC were clearly stated. The systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the inclusion and exclusion criteria allowed for the identification of studies with relevant outcomes. Four databases, multiple clinical trial registers, key regulatory agency websites, and conference websites were searched for relevant publications. The criteria and key terms used in the literature search were provided and it was clear that the literature screening and data extraction were conducted in duplicate with methods in place to assess discrepancies. However, the potential for publication bias was not reported and the literature search was limited to English-language trials. The population, intervention, comparators, and outcomes evaluated in the systematic review for the IDC were similar to the Patient-Intervention-Comparator-Outcomes approach for CDR review for cladribine; of note, daclizumab was removed from the Canadian market late in the course of the CDR review and is no longer considered a relevant comparator. Key efficacy outcomes for health-related quality of life or symptoms were not included in the analysis. Other efficacy items (brain lesions on MRI, brain volume on MRI, use of rescue medications, ability to work/attend school) identified in the CDR review protocol were not evaluated in the IDC. Safety outcomes (i.e., total adverse events) were assessed, but mortality, serious adverse events, withdrawals and withdrawals due to adverse events, and notable harms were not reported. For most of the studies included in the IDC, the risk of bias was low according to most checklists. Some studies had unclear or high risk of bias, primarily attributed to studies that were open-label or had a single assessor. Evidence network diagrams for the main outcomes (ARR, CDP at three and six months, NEDA) were presented.

The dose for cladribine was determined to be consistent as the following dose specifications were stated: a cumulative dose of 0.875 mg/kg over a course of four or five consecutive days of a 28-day period at weeks 1, 5, 48, and 52, resulting in a total cladribine dose of 3.5 mg/kg during a treatment period of 96 weeks.

Clinical heterogeneity was present in the analysis due to varying study phase, blinding, diagnostic criteria, publication date, and mean duration of disease. In addition, the definitions for “relapse” and “disease progression” were inconsistent across studies. Heterogeneity may have been reduced by specifying additional inclusion criteria for studies, such as requiring data on the study phase, blinding status, diagnostic criteria, follow-up duration and mean duration of disease. Rationale for the inclusion of early-phase or unclear-phase trials were not provided. In addition, ambiguity with the composition of the high disease activity subgroup was present, as the IDC stated that 11 studies were of high disease activity patients. However, only two of the studies actually contained data for both the HRA and DAT groups to form the high disease activity subgroup. The remaining eight

studies only examined one of the two groups, and thus do not accurately capture high disease activity as it is by definition composed of criteria for both HRA and DAT. The analysis for the high disease activity subgroup was presented in text only, and evidence networks were not available. Tabular data for this subgroup were presented in the economic report submitted to CDR, but the results were restricted to comparisons between DMTs and placebo (effect estimates were not reported for between-drug comparisons), seemingly only select DMTs were included, as the text in the report made reference to comparisons that were not included in the tables, and only ARR and CDP outcomes were reported. It was unclear if the individual studies with the high disease activity subgroup randomized patients within the subgroup. These subgroups were not post hoc subgroup analyses for the CLARITY study, requested by the EMA. Therefore, the poor reporting of methods and results for this subgroup, as well as the apparent limited power (sparsely populated networks) and potential issues with subgroup definitions (in terms of the actual definitions and whether their formation in the individual trials maintained equal distribution of characteristics through randomization), there is a high degree of uncertainty as to the validity of the results for the high disease activity subgroup analyses. Moreover, the relevance of this subgroup is unclear in light of the Health Canada indication for cladribine.

It was clear that covariate analysis in the form of meta-regression was performed for a number of variables for the RRMS efficacy analysis. However, meta-regression was not conducted if fewer than 10 studies contributed to the analysis (which is appropriate), therefore meta-regression was not performed for the NEDA outcome. There was minimal information provided regarding the methodology for modelling and choosing the covariates to model using meta-regression. Insufficient data were presented to actually assess the impact of adjustment on the treatment-effect differences.

To explore some of the potential sources of heterogeneity, sensitivity analyses were conducted for the ARR and CDP outcomes but not for the NEDA outcome. While it was stated that between-study heterogeneity was explored, the statistical results were not reported in the IDC.

Criteria for adverse events were not specified for this IDC, increasing the risk of heterogeneity. It was also unclear if all adverse events were accounted for. Moreover, specific adverse events (e.g., infection) and serious adverse events were not reported in the main IDC report, although the manufacturer provided an overview of analyses on lymphopenia, malignancies, and infections in its clinical summary. Insufficient data and methodology details were reported to assess these analyses.

Consistency between direct and indirect evidence was determined for the ARR and the CDP outcomes, but statistical results were not provided. The direct evidence was not presented separately from the indirect evidence. Rationale for the use of fixed versus random-effects models and goodness-of-fit results were not presented (i.e., deviance information criterion were not reported).

Conclusion

In conclusion, the evidence from the IDC is difficult to interpret due to a lack of transparency in the reporting of methods and results, and where these are reported there are important methodological and analytical limitations. Thus, the conclusion with respect to comparative effectiveness and safety between cladribine tablets and other DMTs compared in this IDC cannot be made with absolute certainty. There is no definitive evidence that cladribine is superior to any other DMT used to treat patients with RRMS.

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