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## Current and Emerging Therapies for the Treatment of Multiple Sclerosis: Focus on Cladribine

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**Abstract:** Multiple Sclerosis (MS) is a chronic inflammatory, immune-mediated, demyelinating disorder of the central nervous system with a heterogeneous clinical presentation and pathology in which activated lymphocytes play an important role in mediating tissue damage. Until recently, all first line therapies for MS were injectable. Several oral medications have been studied for preventative treatment of MS. Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside analog that has been used for the treatment of several hematologic neoplasms, with a unique lymphocytotoxic mechanism of action. Cladribine has been investigated as treatment of MS for more than 15 years. A recent placebo-controlled, double-blind study of cladribine, CLARITY, showed decreased relapse rates, risk of disability progression and MRI measures of disease activity at 96 weeks. Cladribine's strengths included high efficacy and convenient, biannual oral dosing. However, concerns about safety prevented the FDA from approving cladribine in 2011. Thus, use of cladribine for treatment of relapsing and remitting multiple sclerosis will remain off-label.

**Keywords:** relapsing and remitting, progressive, multiple sclerosis, treatment, clinical trials, cladribine, methylprednisolone, Interferon beta 1b (Betaseron), Interferon beta 1a (Avonex), Interferon beta 1a (Rebif), glatiramer acetate (Copaxone), natalizumab (Tysabri), mitoxantrone (Novantrone), relapse rate, MRI, EDSS, disability progression, BG12, Laquinimod, Teriflunomide, fingolimod (Gilenya)

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## Introduction

Multiple sclerosis (MS) is a chronic inflammatory, immune-mediated, demyelinating disorder of the central nervous system (CNS) with a heterogeneous clinical presentation and pathology in which activated lymphocytes play an important role in mediating tissue damage. It is marked most commonly by clinical episodes of neurologic impairment. The majority of patients with multiple sclerosis have a relapsing and remitting course, so named Relapsing and Remitting Multiple Sclerosis (RRMS). RRMS is marked most commonly by clinical episodes of neurologic impairment that arise over hours to days, and are not otherwise explained. After an average 15–20 years of relapses, these patients enter a progressive phase of disease, Secondary Progressive Multiple Sclerosis (SPMS). A small subset of patients will present with progressive disease from onset, Primary Progressive Multiple Sclerosis (PPMS). There are no effective treatments for progressive MS.<sup>2</sup>

Treatment of RRMS is two-fold: steroids are used to hasten recovery of exacerbations of disease activity, marked by new onset of neurologic deficits; and disease modifying therapies (DMTs) are used to prevent future relapses. Corticosteroids are the first line treatment for exacerbations. Corticosteroids are recommended to hasten recovery of neurologic deficits from MS exacerbations within 2 weeks of symptom onset, though there may be benefit to extending this treatment window. Prior to the 1990's, subcutaneous ACTH was used primarily. However, within the last 20 years, intravenous methylprednisolone has become the preferred medication. IV methylprednisolone is given once daily at doses of 500–2000 mg for 3–5 days. In exacerbations refractory to steroid treatment, or for severe or multifocal relapses, plasma exchange (PLEX) may be considered.<sup>3</sup> Response rate to PLEX following poor improvement with methylprednisolone was approximately 60% within 6 months if PLEX was initiated within 20 days of symptom onset.<sup>3</sup>

New guidelines for the diagnosis of MS allow for diagnosis of clinically definite MS after one clinical event, if imaging criteria are met.<sup>4</sup> Yet, it is not uncommon for patients to present with one episode of demyelination that does not meet criteria for diagnosis. This is referred to as a clinically isolated syndrome (CIS). Risk of progression to clinically definite MS is largely

based on presence and appearance of asymptomatic white matter lesions. Early prevention studies have indicated a delayed progression to clinically definite MS among patients treated with DMTs.<sup>5–8</sup> Treatment of CIS is currently achieved with the same first line medications used for clinically definite MS.

There are 4 injectable DMTs and one oral DMT approved by the FDA for treatment of patients with clinically definite MS and CIS. These include 3 formulations of beta interferon, glatiramer acetate and fingolimod. The three formulations of interferon beta vary by amino acid sequence, glycosylation, formulation, injection technique and frequency of injections. They each bind to the same heterodimeric receptor resulting in the regulation of hundreds of genes, yet there is no clear relationship between an individual's treatment response and gene expression. In separate pivotal trials, all three formulations decreased annualized relapse rates by approximately 30% over 2 years. They also decreased the development of new inflammatory lesions on MRI by 50%–65%.<sup>9–11</sup> Betaseron<sup>®</sup> (interferon beta 1b) was the first interferon to be released to the market in 1993. Since that time, weekly Interferon beta 1a (Avonex<sup>®</sup>) and three times weekly Interferon beta 1a (Rebif<sup>®</sup>) have become available. Current dosing allows for either low (22 µg) or high (44 µg) dose Interferon beta 1a (Rebif<sup>®</sup>) subcutaneous three times weekly, and one dose of each of Interferon beta 1b (Betaseron) 250 mcg subcutaneous, every other day, and Interferon beta 1a (Avonex<sup>®</sup>) 30 mcg intramuscularly once per week. As a class, the interferons share similar side effects of worsening depressions, possible liver toxicity, and flu-like symptoms following injections (to name a few).

Glatiramer acetate (GA) (Copaxone<sup>®</sup>), released in 1996, is a subcutaneous daily injection that is thought to work by a different mechanism. Glatiramer acetate (GA) is a protein comprised of only 4 amino acids, initially developed to mimic myelin basic protein, a major component of the myelin sheath. The exact mechanism of action is unclear. GA is a daily subcutaneous injection that has been shown to have roughly the same efficacy of the interferons.<sup>8,12–14</sup> The side effect profile of GA includes injection site reactions including pain and inflammation, and possible lipoatrophy with long term use.

Until October 2010, all first line therapies for MS were injectable. With similar efficacies, the



choice of therapy was often determined by patient tolerance of the medication and side effect profile. Each medication was associated with limited long-term treatment adherence for these issues. In October, 2010, fingolimod (Gilenya®) was approved as a first line treatment for relapsing MS. Fingolimod, a long-anticipated oral medication, is an oral sphingosine-1-phosphate analogue which works to block egress of lymphocytes out of secondary lymphoid tissues. There may also be central effects, as fingolimod is lipophilic and able to cross the blood-brain barrier. In the phase III, placebo controlled trial of fingolimod, there were significant relative reductions in relapse rates, sustained disability progression and new and enlarging T2 lesions.<sup>15</sup> When compared to intramuscular interferon beta 1a, there was a significant relative treatment benefit with fingolimod, but no effect on disability over the 12 month study.<sup>16</sup> Two fatalities associated with disseminated VZV and HSV infections were reported. Other common malignancies were reported. It is unclear whether these can be associated with fingolimod exposure. Thus, fingolimod has been approved as first line therapy, yet concerns about its safety profile may limit its use until more post-marketing information about adverse events becomes available.

Natalizumab is a humanized monoclonal antibody that binds to the alpha 4 subunit of alpha 4 beta integrins, and thus limits migration of lymphocytes across the blood brain barrier. A phase III randomized, placebo controlled, double blind trial of natalizumab for patients with RRMS, showed large reductions in relapse rates, sustained disability progression, new or enlarging T2 lesions, and gadolinium enhancing lesions.<sup>17</sup> Enthusiasm for natalizumab waned in February 2005 when the FDA removed natalizumab from the market after 2 patients developed progressive multifocal leukoencephalopathy (PML) while on the drug. In 2006, the drug was reintroduced with national surveillance of adverse effects. To date, approximately one hundred and seventy patients treated with natalizumab have developed PML. Risk of PML appears to be linked with prior exposure to the JC virus, and prior exposure to immunosuppression.<sup>18</sup> The risk is further increased with duration of therapy. After two years of therapy, the risk is 1/1000.<sup>19</sup> A serum assay for antibodies to the JC virus is now available. With the foreknowledge of JC virus exposure status,

use of natalizumab may change from that of second line therapy only, to first line therapy among patients who are JC virus antibody negative. Currently, natalizumab remains a second line therapy.

Several oral medications for treatment of RRMS are under investigation. Laquinimod, a novel oral agent (quinoline-3-carboxamide) alters the balance of Th1 to Th2 cells, resulting in fewer CD8 T cells and NK cells. Phase III trials have been promising.<sup>20</sup> Laquinimod is expected to be approved in 2012.

Teriflunomide is an active metabolite of leflunomide, a drug approved for rheumatoid arthritis since 1998. Teriflunomide decreases T cell proliferation by altering pyrimidine synthesis. Phase III study of teriflunomide showed a 30% reduction in annualized relapse rate (ARR) with 2 doses of the drug when compared to placebo.<sup>21</sup>

BG 12, an oral formulation of dimethyl fumarate inhibits expression of pro-inflammatory adhesion molecules and cytokines. The phase III study of BG12 compared to placebo showed that 240 mg of BG-12, administered either twice or 3 times daily, met the primary study endpoint, demonstrating a highly statistically significant reduction ( $P < 0.0001$ ) in the proportion of patients with RRMS who relapsed at 2 years compared with placebo. The benign side effect profile of BG-12 (similar to that of placebo) suggests that this may be the best tolerated DMT for the treatment of RRMS.<sup>22</sup>

Cladribine has been pursued as another possible oral treatment for RRMS. Cladribine (2-chlorodeoxyadenosine, 2-CdA) is a purine nucleoside analog that has been used in the US for the treatment of several neoplasms, including acute myelogenous leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, cutaneous T cell lymphoma, hairy cell leukemia and non-Hodgkin's lymphoma.<sup>23</sup> Cladribine works preferentially on lymphocytes and monocytes by disrupting cellular metabolism resulting in cell death.<sup>24</sup> Long lasting lymphocyte suppression has been investigated as a means of disease modifying therapy for multiple sclerosis.<sup>25</sup> Indeed, the history of investigation of cladribine for the treatment of multiple sclerosis is long and fraught with many disappointments. The recent (June 2011) Merck decision to withdraw regulatory applications filed with the US Food and Drug Administration (FDA) reflects the most recent event along the path.<sup>26</sup>



The purpose of this article is to review recent efficacy and safety data that might be of help in cases of off-label use of cladribine for the treatment of MS patients.

## Mechanism of Action, Metabolism and Pharmacokinetic Profile

Cladribine enters cells via purine nucleoside transporters.<sup>27</sup> Cladribine is resistant to the action of adenosine deaminase, an enzyme required for adenosine breakdown and the turnover of nucleic acids within the cells. Adenosine deaminase is found in most body cells, particularly lymphocytes and macrophages. In these cells cladribine is phosphorylated into the active triphosphate deoxynucleotide, CdATP. In cell lines with high concentrations of 5'-nucleotidase, CdATP is metabolized. However, lymphocytes, when compared to other cell lines, have high levels of deoxycytidine kinase, and low levels of 5'-nucleotidase and so are unable to metabolize CdATP. CdATP accumulates in the cell and disrupts DNA synthesis and repair, which subsequently leads to apoptosis. Thus, cellular toxicity is limited primarily to lymphocytes.<sup>28</sup> Reduced lymphocyte counts are observed 4–6 weeks after administration, and effects are maintained for at least 6–12 months.<sup>25,28</sup>

One study of cladribine for the treatment of progressive MS showed a dose-dependent decrease in mean levels of CD4+, CD3+, CD8+ and to a lesser degree, CD19+ lymphocytes. Transient decreases in CD16+ and CD56+ cells were also observed.<sup>25</sup> Another study found that at doses of 0.7–2.1 mg/kg a dose-dependent reduction in mean CD4+ T cell counts was sustained for at least 12 months, whereas mean B cell counts decreased during the first 2–7 months, and recovered to near baseline after 10 months.<sup>29</sup> The same study showed that mean natural killer (NK) cell counts dropped during the first months of cladribine treatment, but recovered after 7 months.<sup>29</sup> Cladribine may also impair cellular migration into the CNS.<sup>30</sup> Using an in vitro Boyden chamber and fibronectin layer, Kopadze et al, studied the effect of cladribine on the migratory capacity of immunocompetent cells in both MS patients as well as controls. Fibronectin has previously been identified as a stimulus for migration of mononuclear cells.<sup>31</sup> The group found a significant reduction in migratory capacity of peripheral blood mononuclear cells after treatment with cladribine

in both groups. MMP 2 and MMP 9, two metallo-proteinases required for cell migration, were noticeably reduced in the study, a potential explanation for decreased migration capacity.<sup>30</sup>

Cladribine may also have effects on pro-inflammatory cytokines. Interleukin 2 (IL-2) promotes the proliferation and function of antigen-specific T cells, B cells and natural killer (NK) cells.<sup>32</sup> Significantly lower IL-2 levels were reported in patients with progressive MS 12 months after treatment with cladribine compared to baseline  $P < 0.01$ .<sup>33</sup> Moreover, reduced levels of CXCL8 (IL-8) in the CSF and CCL5 (RANTES) have been reported in the serum and CSF.<sup>34</sup> In vitro studies indicate that cladribine markedly down-regulates secretion of cytokines by human T cells.<sup>35</sup> Further study is required to determine whether this effect exists in vivo, or if the decreased inflammatory profile is the result of reduction of total number of lymphocytes.<sup>32</sup>

Cladribine's efficacy possibly extends beyond its well-known cytotoxic effects as demonstrated by its ability to turn on or off critical genes involved in cell cycle regulation, cell signaling and cellular proliferation. Specifically, cladribine may act as a hypomethylating agent through its inhibition of S-adenosylhomocysteine (SAH) hydrolase. By this mechanism, cladribine indirectly inhibits DNA methylation by decreasing the S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH) ratio through its inhibition of SAM formation. This is achieved by blocking the activity of S-adenosylhomocysteine hydrolase, which leads to the accumulation of SAH. SAH excess, coupled with a deficiency of SAM, prevents further DNA methylation. By inhibiting donation of methyl groups, cladribine may also inhibit methylation of proteins, such as histones. Histone methylation has recently been shown to have an important role in gene silencing in cancer cells.<sup>36</sup>

After administration, cladribine is not extensively metabolized.<sup>27,32</sup> Oral bioavailability of cladribine varies between 37% and 55% whereas bioavailability of subcutaneous injection is 100%.<sup>27,37</sup> Oral bioavailability is not significantly influenced by food intake; although time to reach maximum plasma concentrations may be delayed in the fed state.<sup>32</sup> Cladribine is metabolized in the liver and is 20% protein bound.<sup>37</sup> Cladribine has biphasic half-life elimination. The mean terminal half-life with



normal renal function is 5.4 hours.<sup>37</sup> Cladribine is able to cross the blood brain barrier (BBB).<sup>28</sup> Yet, the concentration in the cerebrospinal fluid is 25% of that in plasma in patients without CNS disease. In patients with disruption of the BBB, the CSF concentration may exceed that of the plasma.<sup>27</sup> There is no correlation between the plasma concentration of cladribine and that of the intracellular metabolites. The renal clearance of cladribine is 51% of total clearance.<sup>27</sup>

## Clinical studies

Study of cladribine for treatment of multiple sclerosis has been ongoing for more than 15 years. Initial studies focused on treatment of progressive multiple sclerosis, either primary progressive multiple sclerosis (PPMS) or secondary progressive multiple sclerosis (SPMS) via intravenous routes. As understanding of cladribine improved, trials changed to focus on efficacy, tolerability and safety of oral formulations for treatment of relapsing and remitting multiple sclerosis (RRMS).

An early randomized double blind trial of cladribine for treatment of chronic, progressive MS administered 4 monthly courses of either 0.7 mg/kg cladribine or placebo through a surgically implanted central line.<sup>38</sup> For the first year, cladribine was administered by continuous 7 day intravenous infusion at the rate of 0.1 mg/kg daily. Fifty one patients with clinically definite or laboratory-supported definite chronic progressive MS for more than 2 years were examined by blinded physicians monthly. Disability scores, as measured via Kurtzke and Scripps scales, and demyelinated volumes on MRI improved in the group receiving cladribine, and continued to decline in the untreated group. At 12 months, the mean paired differences (placebo minus cladribine) in EDSS scores were 1.3 (0.3) with 95% confidence interval 0.6–2. The mean paired difference in demyelinated volumes at 12 months related to baseline was 4.42 (1.10) 95% confidence interval 2.16–6.69.

The number of infusions planned (six) was altered in the course of the trial when severe thrombocytopenia (less than 80,000/ $\mu$ l) was noted in 4 patients receiving cladribine and moderate thrombocytopenia (80,000–100,000/ $\mu$ l) was noted in 3 patients on cladribine.<sup>38</sup> Adverse events included one death from fulminant Hepatitis B liver failure, thought to be unrelated to cladribine; one case of severe Salmonella

enteritidis infection, and a total of 6 cases of mild herpes zoster infections (2 in the first year, 4 in the second year).

In the second year of the study, patients who had received cladribine 2.8 mg/kg in the first 4 months of the study continued to show stabilization of disease for 24 months. However, there was a rapid deterioration thereafter. The patients who received placebo in the first year of the study showed disease progression during that time. There was stabilization of disease for a brief, 8 month period, following infusion of the lower cumulative dose (1.4 mg/kg) of cladribine. This group also had lower occurrence of enhancing lesions on MRI scans. In contrast to the 7 patients who had thrombocytopenia with higher doses of cladribine in the first year, there was only one person with low platelet count in the second year, at the reduced dose. There were no other significant adverse events recorded during the second year of the study, supporting a possible dose-related correlation to adverse events.<sup>39</sup> The results of this small, early study provided incentive for future studies of the efficacy of cladribine and information about dosing, while also raising awareness of safety issues (see Table 1).

Further knowledge about the safety and efficacy of cladribine for the treatment of progressive MS was gleaned from a double-blinded, placebo controlled study in 159 patients with either PPMS or SPMS and a baseline median Kurtzke's Expanded Disability Status Scale (EDSS) score of 6.<sup>25</sup> The primary outcome measure was disability as measured by the EDSS. Patients were randomized to receive placebo or cladribine 0.07 mg/kg/d for 5 consecutive days every 4 weeks for either two or six cycles (total dose 0.7 mg/kg or 2.1 mg/kg, respectively), followed by placebo for a total of 8 cycles. Although the gadolinium enhanced T1 lesions and the mean volume and number of such lesions on MRI was significantly less in the cladribine groups, there was no significant change in disability between the placebo and the treatment groups. Patients who received the higher cumulative dose of cladribine also had fewer T2 lesions. Minor side effects were reported.<sup>25</sup>

Decreases in all blood counts were observed in the treatment arms compared to placebo arm. These included mean leukocyte count, absolute lymphocyte count, absolute neutrophils count, absolute monocyte

**Table 1.** Comparison of early studies of cladribine in multiple sclerosis.

<b>Study</b>	<b>Study type</b>	<b>Patients</b>	<b>Cumulative dose</b>	<b>Duration</b>	<b>AE</b>	<b>Results</b>
Rice, et al. Cladribine and progressive MS: Clinical and MRI outcomes of a multicenter controlled trial	Phase II, Multicenter, randomized, double blind, placebo controlled	159	0.7 mg/kg or 2.1 mg/kg SQ	5 consecutive days every 4 weeks for either two or six cycles	No significant differences between groups	No significant change in EDSS
Romine, et al. A double blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis	18-month, placebo-controlled, double-blind study	52	2.1 mg/kg	0.07 mg/kg/day SQ for 5 consecutive days as six monthly courses	Mild Herpes zoster	Favorable effect on frequency and severity of relapses and magnetic resonance imaging (MRI) findings
Martinez-Rodriguez	Case series	6	0.7 mg/kg–1.4 mg/kg IV	5 consecutive days every 4 weeks for 2–4 monthly courses	None	Improvement in EDSS, mean relapse rate, MRI enhancing lesions
Giovannoni, et al. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis	Phase III, Multicenter, randomized, placebo-controlled, double blind	1326	3.5 or 5.25 mg/kg PO	Once daily for 4–5 days per 28 day period. Low dose: 2 cycles in the first 48 weeks, 2 cycles in the second 48 weeks; High dose: 4 cycles in the first 48 weeks, 2 cycles in the second 48 weeks	Severe neutropenia (3), exacerbation of latent TB, Herpes zoster infections (20), primary varicella (3), neoplasms: melanoma (1), carcinoma of pancreas (1), ovary (1), cervical cancer in situ (1), choriocarcinoma (1); 6 deaths: AML, pancreatic cancer, drowning, cardiopulmonary arrest, suicide, hemorrhagic stroke	Reduced annualized relapse rate; reduced measures of MRI activity



count, platelet count, hemoglobin and hematocrit. Subgroup analysis showed dose-dependent decreases in mean levels of CD4+, CD3+, CD8+ and to a lesser degree, CD19+ lymphocytes. Transient decreases in CD16+ and CD56+ cells were also observed.<sup>25</sup> The lack of treatment effect in this study was hypothesized to be secondary to high level of disability (median score of 6.0 for all three treatment groups) prior to cladribine therapy. The authors hypothesize that at this level of disability, the ability to impact the course of disease is limited. They also report variability in response between the patients with SPMS and those with PPMS.<sup>25</sup> (see Table 1)

The first study of cladribine for patients with RRMS was an 18-month, placebo-controlled, double-blind study to evaluate cladribine in the treatment of 52 patients. At a cumulative dose of 2.1 mg/kg, analysis of results revealed a statistically significant favorable effect of cladribine on the frequency and severity of relapses and magnetic resonance imaging (MRI) findings. MRI-enhancing lesions were completely suppressed in the cladribine patients by the sixth month of treatment. Mild segmental herpes zoster occurred in two cladribine-treated patients and one patient receiving placebo. Otherwise, there were no side effects or adverse events<sup>40</sup> (see Table 1).

Off label use of cladribine for the treatment of aggressive relapsing multiple sclerosis was reported retrospectively by Martinez-Rodriguez, et al in 2007.<sup>41</sup> They reported a series of six patients, four women and two men, who as a group had a median change in EDSS from  $3.2 \pm 2.04$  (range 1.0–5.5) to  $5.25 \pm 0.61$  (range 4.5–5.5), at 12 and 6 months respectively prior to cladribine therapy. The mean relapse rate per year at the initiation of therapy was  $2.67 \pm 0.75$ . Parenteral cladribine was given at 0.07 mg/kg/day for 5 consecutive days monthly. All patients had a slow but sustained recovery in clinical disability following cladribine therapy. After 6 months, mean EDSS was reduced from  $6.42 \pm 0.58$  to  $3.75 \pm 1.64$  ( $P < 0.01$ ). MRI showed a decrease in the number of gadolinium enhancing lesions in 4 patients. Four patients had repeated courses of cladribine ranging from 0.7 to 1.4 mg/kg after relapses between 10 and 24 months after initial dose. In the mean follow-up period of  $49.33 \pm 39.66$  months (range 6–102), the mean relapse rate per year was reduced to  $0.71 \pm 0.55$  ( $P < 0.001$ ). In accordance with the mechanism of

action, there was a decrease in the mean absolute lymphocyte count from  $1358 \pm 557/\mu\text{l}$  prior to therapy to  $452 \pm 248/\mu\text{l}$  after the last course of cladribine. No adverse events occurred in this small series.

In this series of treatment refractory patients with relapsing multiple sclerosis, clinical and radiographic outcomes were improved with cladribine therapy.<sup>41</sup> Five of six patients remained on disease modifying therapy while receiving cladribine, suggesting a potential role of adjunctive therapy. Interestingly, all six patients were young (range 15–38 years) at the time that therapy was initiated. No conclusions can be reached from such a small sample size (see Table 1).

The overall promising results of parenteral cladribine lead to the development of an oral formulation. The 96 week CLARITY (Cladribine Tables Treating MS Orally) study was the first phase III placebo-controlled, double blind, multicenter trial of an oral formulation of cladribine for RRMS. 1326 patients were assigned to one of 3 groups to assess not only efficacy, but also dosing and safety.<sup>42</sup> The study population was divided randomly into a placebo arm, low dose, and high dose regimen. In the first 48 week treatment period, patients received either two courses of cladribine followed by two courses of placebo (total cumulative dose 3.5 mg/kg), four courses of cladribine (total cumulative dose 5.25 mg/kg), or four courses of placebo. In the second 48 week period, both cladribine groups received two courses of cladribine, and the placebo group received 2 courses of placebo. After week 24, rescue therapy with subcutaneous interferon beta-1a was available.<sup>43</sup> The primary end point was rate of relapse at 96 weeks. Secondary Outcome Measures were to assess the effect of cladribine on progression of disability in subjects with RRMS.

The ARR was significantly reduced in both cladribine groups as compared to placebo. Relative reduction of relapse rate, proportion who remained relapse free at 96 weeks, time to first relapse (Hazard ratio), and risk of 3 month sustained progression of disability were all significantly improved in the cladribine treatment groups (see Table 2).

When the study subjects were selected for *Nonresponders*: those who had discontinued interferon beta or GA due to lack of efficacy or suboptimal treatment effect, or disease modifying drug (DMD) *Intolerance*:

**Table 2.** CLARITY clinical efficacy results.

	Annualized relapse rate	Relative reduction	Proportion who remained relapse free at 96 weeks	Time to first relapse Hazard ratio	Risk of 3 month sustained progression of disability
Cladribine (3.5 mg/kg)	0.14	57.6% ( <i>P</i> < 0.001)	79.7% ( <i>P</i> < 0.001)	0.44 (95% CI 0.34–0.58) ( <i>P</i> < 0.001)	33% reduction (Hazard ratio 0.67, 95% CI 0.48–0.93)
Cladribine (5.25 mg/kg)	0.15	54.5% ( <i>P</i> < 0.001)	78.9% ( <i>P</i> < 0.001)	0.46 (95% CI 0.36–0.6) ( <i>P</i> < 0.001)	31% reduction (Hazard ratio 0.69 95% CI 0.49–0.96)
Placebo	0.33		60.9%		

those who recorded a history of adverse reaction or intolerance to interferon beta or GA, similar results were found. Cladribine tablets effectively reduced mean ARR in patients with a history of failed prior disease modifying therapy by 56.1% at high dose, and 41.5% at low dose, and increased the proportion of patients remaining relapse-free over 96 weeks. A significant treatment effect of low dose (3.5 mg/kg) cladribine tablets on EDSS progression was seen in the nonresponder group. Significant reductions in MRI activity were seen in both low and high dose cladribine groups in both nonresponders and DMD intolerant groups.<sup>44</sup>

Lymphocytopenia was reported more frequently among patients receiving cladribine. Three cases of severe neutropenia were reported. Infections were reported in 47.7% of the patients in the low dose cladribine group, 48.9% of those in the high dose cladribine group and 42.5% of those in the placebo group. Twenty patients developed herpes zoster infections: 8 patients in the low dose group and 12 in the high dose group. The occurrence of neoplasms (benign, malignant or unspecified) was reported in 1.4% of patients in the low dose cladribine group and 0.9% of those in the high dose group. There were no cases of neoplasm in the placebo group (see Table 4).

Both dosing regimens of cladribine were associated with clinical and radiographic improvement compared to placebo. There was not a significant difference between the two dosing regimens with respect to benefit; though there was a slight increase in risk of serious adverse events and infections in the high dose group (see Table 4). The authors concluded that the numbers of patients who developed neoplasm during the course of the trial was insufficient to determine the risk of neoplasm with cladribine use.

Interestingly, the baseline relapse rates included in the CLARITY study were less than those reported in trials of interferons and GA for unclear reasons.<sup>28</sup> Yet, when study subjects were selected for high disease activity (HDA) defined as two or more relapses in the year prior to study, with or without high T2 burden of disease or T1 Gd+ lesions, or EDSS score 3.5 or greater, there were highly significant reductions in ARR and MRI lesion activity, and prolonged time to sustained disability at both cumulative doses<sup>45</sup> (see Table 3).

Following the results of CLARITY, and in response to concerns about safety and tolerability, a Phase IIIB extension study was initiated.<sup>42</sup> The primary outcome measures were safety evaluations that include clinical laboratory testing, ECGs

**Table 3.** CLARITY: radiographic efficacy results.

	Lesions per patient per scan		
	Enhancing T1 lesions (mean)	Active T2 lesions (mean)	Combined unique lesions (mean)
Cladribine (3.5 mg/kg)	0.12	0.38	0.43
Cladribine (5.25 mg/kg)	0.11	0.33	0.38
Placebo	0.91	1.43	1.72



**Table 4.** CLARITY: adverse events.

	<b>Infections or infestations</b>	<b>Herpes Zoster infections</b>	<b>Serious adverse events</b>	<b>Neoplasms</b>
Cladribine (3.5 mg/kg)	47.7%	8 (One case defined as serious adverse event)	8.4%	1.4% Including: Melanoma, carcinoma of pancreas and ovary
Cladribine (5.25 mg/kg)	48.9%	12 (2 defined as serious adverse events)	9% Including: 1 patient died following reactivation of latent TB	0.9% Precancerous cervical carcinoma, chorio-carcinoma
Placebo	42.5%	0	6.4%	0

and review of adverse events at each study visit. Secondary outcome measures included efficacy as evaluated on an annual basis and cumulatively over the duration of the 4 year study with neurologic exam for progression of disease and time to disability, as well as burden of disease as demonstrated on MRI. Inclusion criteria include subjects with RRMS who completed the CLARITY trial. The extension study is scheduled for primary completion in September 2011<sup>42</sup> (see Table 5).

Subjects who were randomized to placebo for the 96 week CLARITY study crossed over to receive low dose cladribine for 2 years. Subjects who received either low dose or high dose cladribine were re-randomized in a 2:1 allocation ratio to receive either low dose cladribine or placebo for 2 years.<sup>42</sup>

A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center Clinical Trial of Oral Cladribine in Subjects With a First Clinical Event at High Risk of Converting to MS (ORACLE) is ongoing. The goals are to assess the safety and efficacy of two doses of oral cladribine vs. placebo in subjects who had a first clinical demyelinating event (clinically isolated syndrome). Subjects in either the cladribine or placebo group may also enter treatment periods with open-label interferon-beta or open-label cladribine depending upon the disease status. The primary objective of this study is to evaluate the effect of 2 dosage regimens of oral cladribine vs. placebo on the time to conversion to MS (from randomization) according to the Poser criteria in subjects with a first clinical demyelinating event at high risk of converting to MS.<sup>46</sup> The estimated completion date is July 2011 (see Table 5).

A recently completed study assessed the effect, if any, that pantoprazole (a proton pump inhibitor) has on absorption, distribution, metabolization and excretion of cladribine in the body. Cladribine is sensitive to acidic pH.<sup>47</sup> Subjects were assigned to one of two arms. In arm one, subjects received a single 10 mg dose of cladribine, followed by a 10–25 day washout period. Pantoprazole 40 mg was given for two days following wash out. On the second day, cladribine was given 3 hours after pantoprazole. In the second arm, subjects were given pantoprazole 40 mg daily for 2 days, followed by a single dose of cladribine 10 mg 3 hours after second dose. After a wash-out period of minimum 10 to maximum 25 days, subjects received a single 10 mg tablet of cladribine. Though completed, the results of this study are not yet available (see Table 5).

A Phase II study of safety, tolerability and efficacy is currently underway evaluating cladribine as an adjunctive therapy to Interferon beta 1b in patients in patients with active MS.<sup>48</sup> This study will randomize 200 subjects with multiple sclerosis who have had at least one relapse while taking Interferon-beta within 48 weeks of screening from approximately 50 sites located world-wide. SPMS patients who are still experiencing relapses, and patients who have received DMTs, other than Interferon-beta therapy in the past, but are currently on Interferon-beta therapy may also be enrolled. Subjects will be randomized in a 2:1 fashion to receive up to 4 cycles of oral cladribine or matching placebo in combination with Interferon-beta therapy. Subjects who complete the double-blind portion of the study are invited to participate in an open-label extension phase of matching study design. Subjects will be assessed over 208 weeks.<sup>48</sup> Subjects in the treatment arm will receive up to 4 cycles



Table 5. Comparison of ongoing studies of cladribine for MS.

Study	Study type	Patients	Cumulative dose	Dosing schedule	Primary end points	Secondary outcome measures
CLARITY Extension Trial: NCT00641537	4 year, Phase IIIB, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Extension Trial	1326	3.5 mg/kg	Once daily for 4–5 days per 28 day period. 2 cycles per year	Safety evaluations: – Clinical laboratory testing, – ECGs, – Review of adverse events	Efficacy: – Progression of disease, – Time to disability, – Burden of disease as demonstrated on MRI
ORACLE MS: NCT00725985	Phase III, Randomized, Double blind, placebo-controlled, multicenter	642 Projected	1.75 or 3.5 mg/kg/year	Once/week for 4 weeks at the start of a cycle	Time to conversion to MS	
Study Assessing the Interaction of Pantoprazole With Cladribine in Subjects With Multiple Sclerosis: NCT00938366	Phase I, Open-label, Cross Over Study	18	20 mg	Cladribine 10 mg daily for 2 days, either prior to or following treatment with Pantoprazole	Absorption, distribution, metabolization, excretion of cladribine	
Cladribine as an adjunctive therapy to Interferon-beta (IFN-b) in patients with active MS. ONWARD: NCT00436826	Phase II, Multicenter, placebo controlled, double blind, randomized	Projected 200	1.75 mg/kg/year	Daily over 4 to 5 days, weeks 1, 5, 48, 52	Safety and tolerability of oral cladribine compared to placebo as an add-on therapy to injectable IFN-b treatments in MS subjects with active disease	Efficacy of oral cladribine as an add-on to IFN-b treatments – Lesion activity [MRI]; – Qualifying relapse rate; – Progression of disability
Prospective Observational Long-term Safety Registry of Multiple Sclerosis Patients Who Have Participated in Cladribine Clinical Trials (PREMIERE): NCT01013350	Observational: Case Control	1500 Projected			Long-term safety data on Oral Cladribine in MS by estimating the frequency and risk factors for defined study events over a long period of time extending beyond oral cladribine exposure	Occurrence of selected and severe infections, malignancies, deaths, myelodysplastic syndromes, hematological toxicity, and pregnancies and pregnancy outcomes



of cladribine in combination with their interferon therapy over a period of 2 years. A cycle is defined as daily administration given consecutively over 4 to 5 days. Subjects will receive 0.875 mg/kg/cycle. Cycles will be administered on Study Day 1, Weeks 5, 48, and 52 of the study. The placebo arm is identical to treatment arm #1 with the exception that subjects will receive placebo instead of cladribine.

Primary outcome measures are safety and tolerability measured at 96 weeks. Secondary outcome measures include efficacy of oral cladribine as an add-on to interferon beta treatments compared to placebo as an add-on to interferon beta treatments in MS subjects with active disease as measured by MRI, qualifying relapse rate or progression of disability. The study began in December 2006, and is anticipated to end in November 2013<sup>48</sup> (see Table 5).

## Safety

Cladribine was first used as treatment for patients with malignant disorders in 1981. Most patients treated between 1981 and 1987 had end-stage malignant disease. Unfortunately, given their poor prognosis at the time that cladribine was used, little knowledge was gained on long term side effects of cladribine therapy. In the meantime, several clinical trials have documented safety within the timeframe of each study.<sup>49</sup> Early studies of parenteral dosing of cladribine<sup>25,39,40</sup> demonstrated that the most common adverse events in patients receiving cladribine compared to placebo were upper respiratory tract infections (32% vs. 24%), headaches (28% vs. 38%) and injection-site reactions (24% vs. 25%).<sup>50</sup> Thrombocytopenia occurred in several cases during earliest study of cladribine for multiple sclerosis.<sup>38</sup> This adverse event was not noted in subsequent studies at lower doses.

Reduced lymphocyte counts were observed 4–6 weeks after administration with persistent lymphopenia for 6–12 months after administration.<sup>25</sup> The CLARITY study showed an inverse correlation between the incidence of infection and a patient's lowest absolute lymphocyte count.

The effect of cladribine on human reproduction remains largely unstudied.<sup>32</sup> Parenteral cladribine has been shown to be embryolethal or teratogenic in mice.<sup>28</sup> Accordingly, most studies have mandated that participants and/or their spouses take birth control measures during the study periods.<sup>38,39</sup> Nonetheless,

pregnancies did occur during the CLARITY study. Limited data show various outcomes including abortions, miscarriages and normal-term births.<sup>51</sup> Cladribine has a Pregnancy Category D indicating positive evidence of human fetal risk, for the indication of hairy cell leukemia; yet, a successful pregnancy after cladribine for hairy cell leukemia has been reported.<sup>52</sup>

In addition to the CLARITY extension study, and ONWARD studies evaluating safety and tolerability of Cladribine, a Prospective Observational Long-term Safety Registry of Multiple Sclerosis Patients Who Have Participated in Cladribine Clinical Trials<sup>53</sup> (PREMIERE) is underway to assess long term safety concerns. The goal of PREMIERE is to produce long-term safety data on oral cladribine in MS by estimating the frequency and risk factors for defined study events over a long period of time extending beyond oral cladribine exposure, in a population of subjects previously exposed to oral cladribine in MS clinical studies. Secondary Outcome Measures are to explore the occurrence of selected and severe infections, malignancies, deaths, myelodysplastic syndromes, hematological toxicity, and pregnancies and pregnancy outcomes in relation to the cumulative dose and length of exposure to cladribine. Estimated enrollment is 1500 study participants. The study began in November 2009 and is currently expected to continue until December 2018.

Even following Merck Serono's withdrawal of FDA application for cladribine, it announced that it intends to complete the core 96-week treatment period of the CLARITY EXTENSION (CLADribine Tablets Treating MS Orally Extension), ORACLE MS (Oral Cladribine in Early MS), and ONWARD (Cladribine add-on to Interferon-Beta therapy in MS subjects with active disease) clinical trials and to proceed with the ongoing PREMIERE registry that is following patients who have participated in cladribine studies.

## Conclusion

While most studies of cladribine for the treatment of MS, either progressive or relapsing, note a marked improvement of radiological activity<sup>25,43</sup> the clinical benefit of cladribine has been variable. The earliest studies of cladribine in MS (progressive) showed a reduction in the clinical deterioration.<sup>38,39</sup> However,



Phase III study of cladribine for progressive MS showed no significant effect on disability.<sup>25</sup> Results for patients with RRMS were more promising with lower mean relapse rates when compared to placebo.<sup>54</sup> More recently, CLARITY showed an overall promising effect on ARR, time to first relapse, cumulative number of relapses and time to progression.<sup>43</sup> In addition, high treatment compliance and retention of patients in the CLARITY study may be interpreted as favorable patient perception of efficacy and tolerability.<sup>55</sup> However, despite these promising outcomes, questions of safety remain unanswered. Cladribine was initially granted fast-track status by the FDA in 2006, but questions about tabulation errors and safety concerns prevented the FDA from filing a new drug application in 2009.<sup>26</sup>

Cladribine was approved for use in Russia in July 2010 and Australia in September 2010.<sup>56</sup> In September 2010, and by appeal in January 2011, the European Medicines Agency failed to approve cladribine secondary to concerns about the increase in cancer cases observed in clinical trials. Dosing and expected benefits of treatment were also cited as concerns.<sup>26</sup> Likewise, in March 2011, the US FDA said it wouldn't approve oral cladribine<sup>26</sup> for MS without more safety data.

In light of this disappointment, Merck-Serono announced that it would no longer pursue FDA approval for cladribine tablets for the treatment of relapsing-remitting MS. The company further announced that it would withdraw the drug from Australia and Russia, where it already had achieved approval. This decision was likely influenced not only by the prior release of the first oral medication for the treatment of RRMS, fingolimod; but also by the anticipated approval of BG-12 (dimethyl fumarate) and laquinimod within the next 1–2 years. Thus, it would seem cladribine will be limited to off-label use for the treatment of RRMS.

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