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REVIEW ARTICLE

The Development of Cladribine Tablets for the Treatment of Multiple Sclerosis: A Comprehensive Review

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Abstract
Cladribine is a purine nucleoside analog initially developed in the 1970s as a treatment for various blood cancers. Due to the molecule's ability to preferentially reduce T and B lymphocytes, it has been developed into an oral formulation for the treatment of multiple sclerosis (MS). The unique proposed mechanism of action of cladribine allows for the therapy to be delivered orally over two treatment-week cycles per year, one cycle at the beginning of the first month and one cycle at the beginning of the second month of years 1 and 2, with the potential for no further cladribine treatment required in years 3 and 4. This review summarizes the clinical development program for cladribine tablets in patients with MS, including the efficacy endpoints and results from the 2-year phase III CLARITY study in patients with relapsing–remitting MS (RRMS), the 2-year CLARITY EXTENSION study, and the phase III ORACLE-MS study in patients with a first clinical demyelinating event at risk for developing MS. Efficacy results from the phase II ONWARD study, in which cladribine tablets were administered as an add-on to interferon-β therapy in patients with RRMS, are also summarized. A review of all safety data, including lymphopenia, infections, and malignancies, is provided based on data from all trials in patients with MS, including the initial parenteral formulation studies. Based on these data, cladribine tablets administered at 3.5 mg/kg over 2 years have been approved across the globe for various forms of relapsing MS.

1 Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, immune-mediated demyelinating and neurodegenerative disease of the central nervous system (CNS). It is one of the most common causes of serious neurological disability in young adults, and one of the most prevalent neurological disorders in the world [1]. In 2016, the estimated global prevalence of MS was 2.2 million, an increase of 10.4% from the age-standardized MS prevalence in 1990 [2]. Among the more than 2 million people with MS, more than 900,000 are thought to reside in the United States (US) [3]. About 85% of patients with MS present with relapsing–remitting MS (RRMS), which is characterized by periodic acute exacerbations of disease activity (relapses) punctuated by periods of clinical stability. Relapses may be associated with partial or complete recovery [4].

MS is associated with poor health-related quality of life and can have a profound effect on social functioning, employment status, and healthcare costs [5, 6]. The mean age at onset of symptoms is 30 years, and approximately 75% of patients are female [7]. Therefore, many patients are women of childbearing age, and MS can impact family planning due to risks associated with treatments that may affect pregnancy [8]. While there are no adequately controlled studies of disease-modifying drugs (DMDs) and pregnancy, there is a significant body of evidence on the safety of DMDs during pregnancy, generated primarily

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Key Points

Multiple sclerosis (MS) is a neurodegenerative disease that affects more than 2 million people globally and is associated with poor quality of life. MS involves an aberrant immune system attacking the central nervous system, and disease-modifying drugs are thought to act by suppressing or modulating the immune system.

Cladribine tablets are the first oral therapy with a short-course, limited cycle dosing schedule approved for patients with relapsing forms of MS (RMS). In clinical studies, cladribine tablets have demonstrated efficacy in patients across the RMS spectrum.

The safety profile of cladribine tablets monotherapy at the recommended dosage of 3.5 mg/kg includes data from > 3700 patient-years of cladribine exposure at this dose, and from > 2200 patient-years of placebo exposure in clinical trials. The most common adverse events reported with cladribine tablets include headaches and lymphopenia. Additional adverse events examined include malignancy and infections.

from clinical experience and pregnancy registries. Large interferon (IFN)-β registry studies have found no evidence for differences in infant size [9], congenital anomalies, or miscarriages [10], and recently updated IFN-β Summaries of Product Characteristics recommend to continue treatment during pregnancy and while breastfeeding if clinically needed [11, 12]. Glatiramer acetate is also generally considered to be safe for use during pregnancy [13, 14]. However, the labels for the majority of DMDs for patients with MS either state to use 'only if clearly needed' [15], to avoid these therapies unless the benefits outweigh the risks [16–19], or not to use at all, and a washout period is recommended prior to pregnancy [20–26]. Longitudinal studies indicate that life expectancy is shorter for patients with MS compared with the general population (approximately 7 years shorter in a Norwegian population studied over a 60-year period) [27], but rising prevalence without parallel changes in incidence, and a shift in peak age towards older age groups, suggest that survival is improving (based on Canadian data collected over 2 decades) [28]. An aging MS population may be associated with significant disability; in a self-reporting postal survey conducted in a Canadian cohort of MS patients aged > 55 years who had been living with MS for a mean of approximately 33 years, 28% either required a wheelchair or were bedridden [29].

Lymphocytes play a central role in the pathogenesis of MS, with the actions of both B and T cells in the periphery and in the CNS implicated from an early stage in the disease process. Immune cells activated in the periphery enter the CNS, facilitated by chemokines [30, 31]. Autoreactive T cells are present in acute CNS lesions in early MS [30, 32]; their reaction to myelin protein-derived antigens [32] contributes to direct cytotoxic effects and stimulation of macrophages [31, 33]. B cells have a role in the proliferation and reactivation of T cells, acting as antigen-presenting cells, and fully differentiated B cells further contribute to demyelination via the production of antibodies to myelin by plasma cells [30, 31, 33, 34]. Thus, the combined actions of T cells, B cells, and macrophages contribute to demyelination and axonal damage, triggering neurodegenerative processes from disease onset [30, 31]. Later in the course of the disease, chronic CNS inflammation drives ongoing neurodegeneration, possibly via neurotoxic inflammatory mediators produced by activated microglia and astrocytes [32].

Treatment options for relapsing forms of MS (RMS) comprise a number of immunosuppressive and immunomodulatory agents. The first DMD, IFN-β-1b, was approved by the US Food and Drug Administration (FDA) for RMS in 1993 [19] and by the European Medicines Agency (EMA) in 1995 [35]. Alternative forms of IFN-β (subcutaneous [SC] and intramuscular [IM] IFN-β-1a) and glatiramer acetate entered the market between 1996 and 2002, becoming standard treatment over the ensuing years [36]. The introduction of natalizumab, a recombinant monoclonal antibody against cell adhesion molecule α4-integrin [23] (initially approved in 2004, withdrawn from the market, then reintroduced in 2006 [37]), marked a shift in the treatment paradigm for MS [38]. While this molecule was perceived to be more effective than the IFNs and glatiramer acetate [39], it is associated with greater risks, including progressive multifocal leukoencephalopathy (PML), which is rare but carries significant morbidity and a mortality rate of approximately 23% [40]. After a span of nearly 20 years of injectable therapies, oral DMDs became available. While patients have generally preferred oral DMDs over injections when given the choice [41], most approved oral DMDs, including fingolimod, teriflunomide, dimethyl fumarate and siponimod, require regular and ongoing dosing once- or twice-daily [20–22].

More recently, therapies with different hypothesized mechanisms of action (MOA) that require less frequent dosing have become available. Ocrelizumab is an anti-CD20 antibody, administered via intravenous (IV) infusion every 6 months (after the initial dose, which is split across two infusions 2 weeks apart) [25, 42]. Alemtuzumab is an anti-CD52 antibody with an infrequent dosing regimen, involving infusions over a course of 5 days in year 1, followed by 3 days in year 2, with further 3-day courses administered as needed thereafter, separated by intervals of at least 12 months [24, 43]. Both antibodies are thought to deplete lymphocytes via cytolysis and complement-mediated lysis, with different profiles based on expression of their respective

target antigens on B cells, T cells, and other immune cells [24, 25, 44–46].

Cladribine tablets are the first oral therapy with an infrequent dosing schedule, administered in two yearly treatment courses, each divided into two treatment cycles comprising 4–5 days of treatment [12, 26]. Cladribine tablets are thought to exert their clinical effects via a transient reduction of selective lymphocyte subtypes, followed by a recovery period during which cell numbers return to the normal range [47, 48]. While immune function is restored as cell numbers recover, cell subtype ratios are thought to be altered, resulting in a reduction in autoreactive lymphocytes [47–49]. Thus, a short dosing period is thought to achieve sustained effects on lymphocytes that persist for an extended period after the treatment period has ended.

Cladribine tablets have been approved worldwide by many different regulatory authorities, including the EMA in 2017 [50] and the FDA in 2019 [51]. In this review, we provide an overview of the development of cladribine tablets as a therapy for patients with MS, from initial discovery and development of the molecule to its putative MOA in MS. We also review the pertinent efficacy data from clinical studies, and an integrated safety analysis of > 3700 patient-years' clinical trial experience with cladribine tablets monotherapy at the recommended dosage.

1.1 Discovery and Development

Cladribine (2-chlorodeoxyadenosine [2-CdA]) was first synthesized nearly 50 years ago [52] (Fig. 1). It is a synthetic purine nucleoside analog of deoxyadenosine that was developed to selectively target lymphocytes in lymphoproliferative diseases (e.g. hairy cell leukemia) and autoimmune disorders [53–55]. The design of cladribine was inspired by the consequences of adenosine deaminase (ADA) deficiency in children [55, 56]. The selective vulnerability of lymphocytes in this autosomal recessive genetic disorder was described by Carson and colleagues as resulting from the preferential accumulation of cytotoxic deoxyadenosine nucleotides in lymphocytes, causing lymphocytopenia [54, 57]. Based on this understanding, several nucleoside analogs were synthesized, including cladribine in the early 1970s [54, 58, 59]. Following the efficacy observed in lymphoid leukemias and the ability of cladribine to selectively target lymphocyte populations, the drug was considered for potential use in MS [53].

1.2 Mechanism of Action

Cladribine (2-CdA) is a small molecule (molecular mass 285.7 g/mol [60]) prodrug that is taken up by cells via nucleoside transporter proteins and becomes active in certain cells upon phosphorylation to 2-chlorodeoxyadenosine triphosphate (2-Cd-ATP). 2-CdA undergoes sequential intracellular phosphorylation, first to 2-chlorodeoxyadenosine monophosphate (2-Cd-AMP) mediated by deoxycytidine kinase (DCK), and subsequently to 2-chlorodeoxyadenosine diphosphate (2-Cd-ADP) and 2-Cd-ATP by other kinases. De-phosphorylation by 5′-nucleotidases (5′-NTases) prevents accumulation of 2-Cd-ATP in most cells [31]. Phosphorylation preferentially occurs in B and T lymphocytes due to their unique constitutively high DCK and relatively low 5′-NTase levels, compared with other cell types. DCK is a rate-limiting enzyme in the nucleoside salvage pathway that provides deoxyribonucleosides (dNTPs). The high DCK level is thought to be important for lymphocyte clonal expansion during development and immune reactions [61, 62]. Lymphocytes are therefore susceptible to accumulation of 2-Cd-ATP (Fig. 2). In cells where 2-Cd-ATP accumulates, it incorporates into deoxyribonucleic acid (DNA) strands, disrupting DNA synthesis and cell cycle progression, and inhibits enzymes involved in DNA synthesis, leading to cell death in both proliferating and quiescent lymphocytes [31, 59, 63].

While the precise mechanisms by which cladribine exerts its therapeutic effects in patients with MS is not known, its effects on B and T lymphocytes are thought to play a central role. Cladribine preferentially reduces cells of the adaptive immune system, while leaving the innate immune system relatively spared. Absolute lymphocyte counts (ALC) and B- and T-cell subset counts rapidly reach nadir following administration of cladribine tablets, and gradual lymphocyte count recovery begins soon after treatment and continues for months afterwards [64]. In the phase III CLARITY and CLARITY Extension studies [65, 66], median ALC reached nadir, at the lower limit of normal (LLN) at week 13, and was followed by recovery of cell counts back to the normal range (Fig. 3). In year 2, median ALC fell below the LLN but recovered into the normal range by week 84, or approximately 30 weeks postdose after completion of the second treatment cycle in year 2. Reduction of CD19+ B cells in year 1 also reached nadir at about week 13 (below LLN and approximately 80% change from baseline), followed by recovery towards baseline values (Fig. 4). CD19+ B-cell counts also fell below LLN in year 2, and recovered to LLN by week 84. CD4+ T-cell median counts showed a lesser decline from baseline to nadir (approximately 50% change from baseline, also reached at week 13) in year 1, followed by a more gradual recovery towards baseline (Fig. 5). While CD4+ T cells did not reach the LLN in year 1, they fell below the LLN in year 2 and reached threshold values for recovery by week 96, approximately 43 weeks post last therapy dose. Median CD8+ T cells never dropped below LLN (Fig. 6) [64]. Analysis of CD4+ T-cell subtypes in ORACLE-MS showed that subpopulations displayed different repopulation dynamics, leading to changes in the

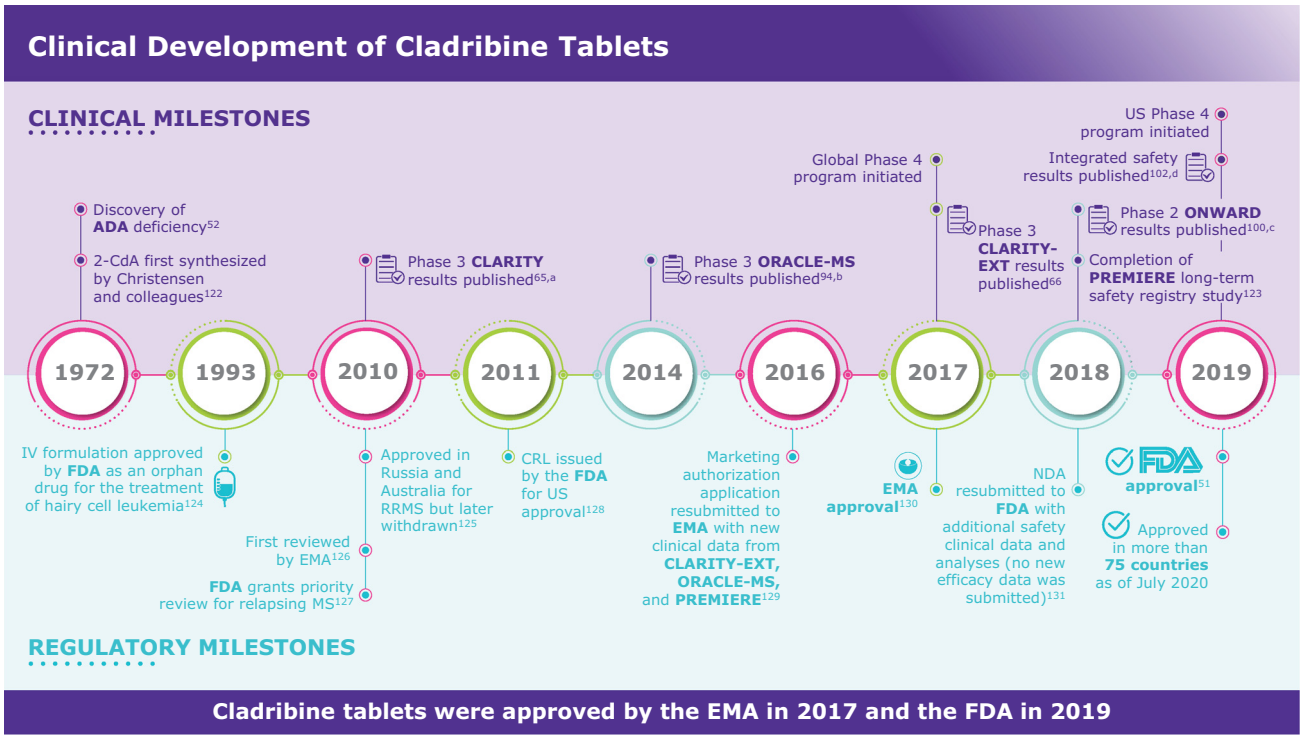

Fig. 1 Cladribine tablets development milestones [51, 52, 65, 66, 94, 100, 102, 122–131]. [a]Naive and treatment-experienced patients with RRMS. [b]Treatment-naive patients at high risk for developing MS. [c]Patients with active RRMS in combination with IFN-β. [d]Including patients from CLARITY, CLARITY–EXT, ORACLE-MS, and PREMIERE. *ADA* adenosine deaminase, *2-CdA* 2-chlorodeoxyadenosine deaminase, *CRL* complete response letter, *EMA* European Medicines Agency, *FDA* Food and Drug Administration, *IFN* interferon, *IV* intravenous, *MS* multiple sclerosis, *NDA* new drug application, *RRMS* relapsing–remitting MS

relative proportions of the CD4+ T-cell subpopulations [67]. Median monocyte and neutrophil counts remained within the normal range throughout the CLARITY and CLARITY Extension studies (Figs. 7, 8), while the effects on natural killer (NK) cells were moderate and transient, with a 30–44% median decrease in NK cells followed by a recovery towards pretreatment levels by week 24 (Fig. 9). These findings support the view that the impact of cladribine on the innate immune system is relatively minor [67]. The preferential reduction of lymphocyte subpopulations, followed by the pattern of lymphocyte count recovery (termed immune reconstitution), may 'reset' the immune system to a less autoreactive state [64], a putative mechanism with considerable potential in the long-term treatment of MS [48].

1.3 Approvals

Cladribine tablets were developed as a potential treatment for MS in response to the efficacy seen in early studies of parenteral cladribine and the need for additional treatment options [53, 68, 69]. The pivotal CLARITY trial was completed in 2009 and published in 2010; however, some regulatory authorities indicated in 2011 that improved understanding of safety risks and the overall benefit–risk profile was required. Phase II and III studies that were ongoing at the time were completed, and a long-term safety registry was continued. The additional data served to support the thorough characterization of the safety profile of cladribine tablets in MS. Evaluation of these additional data and analyses of the compound's longer-term benefit–risk profile supported new submissions to regulatory authorities. Cladribine tablets received EMA approval in August 2017 [50] and FDA approval in March 2019 [26]. As of July 2020, cladribine tablets have gained marketing authorization in more than 75 countries for the treatment of patients with various forms of RMS.

1.4 Dosing Schedule

Two dosages were investigated during the clinical development of cladribine tablets: 3.5 mg/kg and 5.25 mg/kg (cumulative doses over 2 years). In addition, in certain study arms, patients received retreatment in years 3 and 4 (cumulative doses over 4 years of 7.0 mg/kg and 8.75 mg/kg). The 3.5 mg/kg and 5.25 mg/kg doses appeared to be equally efficacious, but the 5.25 mg/kg dose was associated with an increased rate of higher-grade lymphopenia [65]. The 3.5 mg/kg dose was considered to have the most favorable benefit–risk profile.

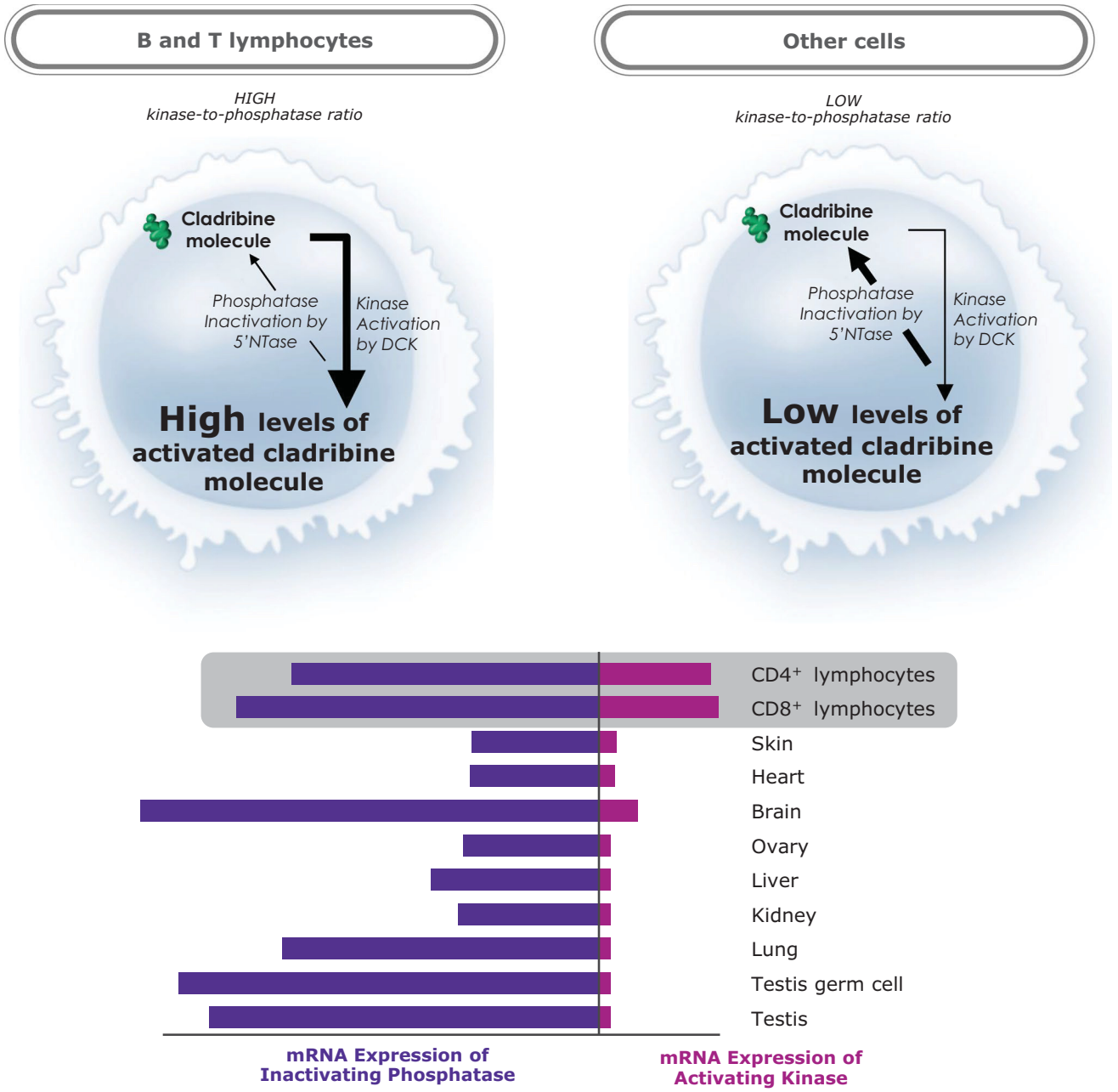

Fig. 2 Ratios of DCK to 5′-NTase mRNA expression in T cells and various non-hematologic cells [58]. *5′-NTase* 5′-nucleotidases, *DCK* deoxycytidine kinase, *mRNA* messenger RNA. *Calculated using data from the BioGPS website (available at https://biogps.org/#goto=welcome). Adapted with permission from Giovannoni [58]

In countries where approved, the recommended cumulative dose of cladribine tablets is 3.5 mg/kg given over 2 years (one treatment course is 1.75 mg/kg/year) [12, 26]. Each course consists of two treatment weeks or cycles—one cycle at the beginning of the first month and one cycle at the beginning of the second month. Each treatment cycle lasts 4 or 5 consecutive days, depending on the patient's weight, and patients receive one or two 10 mg tablets per day. Lymphocytes must be within normal limits prior to initiating the first course and at least 800 cells/mm^3 prior to initiating the second course. Modeling simulations suggest that 92% of patients would not require a delay in receiving the second treatment course and < 1% would be ineligible for treatment in year 2 due to a delay in recovery of more than 6 months [70]. No further treatment with cladribine tablets may be required in years 3 and 4; a patient cohort

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