

Cladribine Ortho Biotech Inc

Carla Tortorella, Marco Rovaris & Massimo Filippi*

Address

Neuroimaging Research Unit
Department of Neuroscience
Scientific Institute and University Ospedale San Raffaele
Via Olgettina
20132 Milan
Italy
Email: m.filippi@hsr.it

*To whom correspondence should be addressed

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Cladribine, an adenosine deaminase inhibitor, has been developed and launched by Ortho Biotech in collaboration with The Scripps Research Institute 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. It was first launched in the US in February 1993 [224609]. Ortho Biotech and The Scripps Research Institute have since been developing the compound for its potential use in multiple sclerosis (MS) [203216].

In 1997, Ortho filed an NDA in the US for the use of cladribine in the treatment of relapsing-remitting and secondary progressive MS [309586], [351798]. An FDA drug advisory committee was planning to meet in January 1999 to discuss the NDA [309586]. However, Ortho cancelled the meeting [313428]. Following an FDA inspection during December 1998 and January 1999, the Scripps Clinic received a warning letter from the FDA in April 1999 regarding violations in the clinical studies of cladribine for MS, and Ortho withdrew the NDA after concluding that further clinical studies would be necessary [337358].

Cladribine has been known since the 1960s as an intermediate for the synthesis of 2-deoxynucleotides and its potential for the treatment of leukemia was disclosed in 1984 [65313]. The Scripps Research Institute and the Johnson & Johnson group hold several patents claiming preparation methods (US 05208327), and additional indications, such as multiple sclerosis (WO-09316706) and rheumatoid arthritis (US-05310732). The associated patent, WO-09323508, is the only one among those patents that claims the use of unmodified cladribine for the treatment of leukemia, but it focuses particularly on a specific form of the disease, chronic myelogenous leukemia [224609].

Analysts at UBS Warburg predicted in October 2001, that the product would make US sales of \$50 million in 2004 for its MS indication [427553].

Introduction

Multiple sclerosis (MS) is considered to be an organ-specific, T-cell-mediated, autoimmune disorder of the central nervous system (CNS). In MS, CNS myelin components are thought to represent the target of the immunological attack, which leads to the formation of lesions with heterogeneous pathological substrates, ranging from reversible inflammatory changes to irreversible demyelination and axonal loss. In most MS cases, the progressive accumulation of irreversible neurological disability starts after an initial relapsing-remitting (RR) phase.

Originator Ortho Biotech Inc

Licensees IVAX Corp, Scripps Research Institute

Status Phase III Clinical

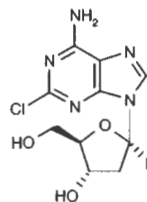
Indication Multiple Sclerosis, Leukemia, Rheumatoid Arthritis

Action Adenosine deaminase inhibitor

Biotechnology Oral formulation

Synonym 2-CdA, Leustat, Leustatin, NSC-105014F, RWJ-26251

CAS Adenosine, 2-chloro-2'-deoxy-
Registry No: 4291-63-8



However, in about 10% of the cases a progressive clinical deterioration occurs following the onset of the disease. Given the pathogenesis of MS, several immunomodulating and immunosuppressive therapies have been used in an attempt to favorably modify the disease course.

Cladribine is a highly specific lymphocytotoxic agent which has become the first-line treatment for hairy-cell leukemia and which is also used to treat lymphoid malignancies. The potent and long-lasting lymphocytotoxic activity of cladribine has also suggested its potential for influencing favorably the autoimmune process underlying the evolution of MS.

Synthesis and SAR

Cladribine (2-chloro-2'-deoxyadenosine) has been known for four decades as an intermediate for the synthesis of 2'-deoxynucleotides. It is a chlorinated purine analog derived from deoxyadenosine by substituting chlorine for hydrogen at the 2'-position of the purine ring. This substitution renders 2-cladribine resistant to the action of adenosine deaminase [65313].

Cladribine was first synthesized chemically and shown to be an inhibitor of L1210 leukemia in mice. Subsequently, Carson *et al* detailed a method utilizing a stereospecific enzymatic transfer of a deoxyribosyl moiety from thymidine to 2-chloroadenine [64003]. This reaction is catalyzed by a partially purified transdeoxyribosylase from *Lactobacillus helveticus* and the drug was isolated using ion exchange chromatography [64003].

Anti-infective

Anti-inflammatory

Cardiovascular

CNS

Oncological

Pharmacology

Cladribine, like other antimetabolite cytotoxic drugs such as pentostatin (Pfizer Inc), fludarabine (Southern Research Institute/Schering AG) and cytarabine, are prodrugs requiring phosphorylation to become biologically active. Deoxypurine nucleosides, such as cladribine, enter cells through an efficient transport system and are phosphorylated by deoxycytidine kinase to the corresponding mononucleotide. Deoxyadenosine concentration is maintained at a low level by adenosine deaminase (ADA), which deaminates the compound to deoxyinosine [17808]. Administration of cladribine, which is resistant to the action of ADA, causes a toxic concentration of deoxynucleotides, which are then incorporated into the DNA. This impairs DNA synthesis and cellular metabolism and causes the death of both dividing and quiescent cells [17808], [64003].

Cladribine activity is very efficient in cells, such as lymphocytes and monocytes, with high levels of deoxycytidine kinase and low deoxynucleotidase activity, since the latter enzyme usually dephosphorylates deoxyadenosine monophosphate nucleotides, and, as a consequence, prevents the action of deoxycytidine kinase and ribonucleotide accumulation. For these reasons, cladribine concentrations, which are not harmful to normal bone marrow cells and other cell types, can selectively damage lymphocytes, particularly of the CD4+ subset [241296], and monocytes [64003], [106552]. Cladribine treatment can induce a 4-fold decrease in CD4+ to CD8+ T-cell ratio which may persist for several months [423894] and which is 2-times higher than those caused by cyclophosphamide [423896] or chlorambucil [423908]. The immunosuppressive efficacy of cladribine is, therefore, at least equal to that of cyclosporine [241277]. To explain the toxicity of cladribine against resting lymphocytes, it has also been suggested that the accumulation of an abnormal concentration of deoxyribonucleotides may act as a triggering factor for cell apoptosis [17808].

Metabolism

The bioavailability of orally administered cladribine ranges from 37 to 51%, while that of subcutaneous (sc) preparations is 100%. [122098], [423910]. As a consequence, a double dose of orally administered cladribine can substitute for a sc injection, which, in turn, results in a high peak concentration of short duration, with an area under the curve identical to that obtained for intravenous (iv) administration [122098]. Following the sc administration of a single dose, the absorption of cladribine is rapid and peak-plasma concentrations (C_{max}) are achieved in most subjects 60 to 70 min after dosing. The disposition kinetics are similar following administration of single or multiple sc doses and only a minimal accumulation has been observed after repeated daily dosing for 5 days. Cladribine is mainly excreted in the urine; the renal clearance is 51% of total clearance, and 21 to 35% of an iv dose is excreted unchanged in the urine. The terminal half-life of cladribine varies from 5.7 to 19.7 h and the apparent volume of distribution ranges from 54 to 357 l/m² [105448], [423910].

In MS patients, cladribine was administered iv in the first trial (MS-Scripps [241294]) and sc in the following studies [422449], [422627]. In two placebo-controlled, double-blind

studies of subjects with chronic progressive [422627] or RRMS [422449], cladribine was administered sc at 0.07 mg/kg for 5 consecutive days for 2 to 6 monthly courses, ie, at a total dose of 0.7 to 2.1 mg/kg. Even though a higher dose (2.8 mg/kg) was found to be effective in a previous study [241294], this regimen was abandoned because of the increased degree of myelosuppression and incidence of infections.

Two different cladribine formulations have been used in MS studies: a 1 mg/ml formulation was used in the double-blind phase of the placebo-controlled studies [241294], [422627] and a 5 mg/ml formulation was used in the retreatment phase of the phase III study [422449]. The pharmacokinetics of the two cladribine formulations were, however, similar.

Oral cladribine has been used in MS patients only in a preliminary study. The dose was of 10 mg once a day for 5 consecutive days in six monthly courses, followed by one or two additional courses at 3 or 6 month intervals. Oral cladribine treatment was well-tolerated and relatively safe [241271].

Toxicity

Although the analogs of deoxyadenosine are more specific for lymphocytes than other cell types, they can potentially harm normal somatic cells. Since their toxicity is correlated with sustained increases in the plasma concentration of endogenously generated deoxyadenosine and adenosine, both toxicity and therapeutic response are dose-related.

The use of cladribine in MS was considered after the drug was used to test lymphoid leukemias and autoimmune hemolytic anemia [181788], [181838]. The primary toxicity caused by the drug is myelosuppression, which is a dose-limiting factor. Long-term hematologic observations of the effect of cladribine on 'normal' bone marrow have been made on 29 patients with MS undergoing experimental therapy with monthly courses of 0.07 to 0.1 mg/kg cladribine/day for 7 days. The typical hematologic response consisted of an acute transient monocytopenia, a prolonged and severe lymphopenia (mainly affecting CD4+ cells), and a modest lowering of granulocytes and hemoglobin, followed by a long-lasting macrocytosis. Two patients developed severe aplastic anemia, which required transfusion. One of these patients, however, had previously received chlorambucil, while the other had previously received carbamazepine and was receiving phenytoin during cladribine therapy [241296].

Clinical Development

Phase I

The recommended cladribine doses for MS treatment (0.7 and 2.1 mg/kg) have similar safety profiles, as regards the incidence of infections. However, 2.1 mg/kg cladribine seems to cause a somewhat greater degree of lymphopenia and myelosuppression. The dose of 2.8 mg/kg used during the first year of the MS-Scripps trial was subsequently lowered because of dose-related myelosuppression [241294]. Cladribine safety and tolerability have also been tested in MS patients by Selby *et al* [423894], who did not report any significant myelosuppression or infections, despite the

presence of a profound lymphocytopenia in treated patients. In this study, which used a 2.1 mg/kg dose, the rate of decline in CD4+ cells was less rapid than that previously reported with a higher dose [241296], although after 6 months CD4+ cell blood levels were comparable in the two studies. However, a partial recovery of CD4+ levels was found one year after treatment in the patients treated with lower doses, whereas CD4+ cell counts remained markedly decreased in patients treated with higher doses [423894]. The concomitant use of corticosteroids and purine analogs has been associated with an increased risk of opportunistic infections [423912]. Further studies are needed to establish whether cladribine is safe when used with or soon after other immunomodulating or immunosuppressive therapies, such as β -interferon, glatiramer acetate (Teva Pharmaceutical Industries Ltd), mitoxantrone (Immunex Corp), azathioprine or cyclophosphamide.

Phase II

Two randomized, double-blind, placebo-controlled, phase II trials have been conducted to evaluate the efficacy and safety of cladribine in MS (MS-Scripps [241294]; Scripps C [422449]). These trials enrolled patients with chronic progressive MS [241294] and RRMS [422449], respectively. In both studies, the primary efficacy measure was the proportion of subjects with contrast-enhancing lesions on magnetic resonance imaging (MRI) scans obtained during the double-blind phase. Secondary outcomes included changes in neurological disability scores, as measured by the Expanded Disability Status Scale (EDSS) [423913] and Scripps Neurological Rating Scale (SNRS) [423914], and changes in the total volume of contrast-enhanced and T2-hyperintense MRI lesions. In addition, the time to disease progression and the annualized exacerbation rate were considered secondary clinical outcomes for chronic progressive MS [241294] and for RRMS [422449], respectively.

The MS-Scripps double-blind trial lasted for two years, during which time 49 patients were studied [241294]. During the first 4 months of the study, each subject received seven daily infusions of 0.1 mg/kg of cladribine each month (total dosage: 2.8 mg/kg) or placebo over a 1 month period, followed by an 8-month interval without treatment. In the second year of the study, subjects initially randomized to placebo received four monthly courses of cladribine at a total dosage of 1.4 mg/kg and subjects who received the drug in the first year received placebo with the same regimen.

Cladribine 2.8 mg/kg was effective in suppressing contrast-enhanced MRI activity and slowing the increase in T2-lesion volume over the double-blind period. In addition, evidence of a reduced neurological deterioration was observed in cladribine-treated patients but not in placebo patients. Such clinical efficacy has not been confirmed by the phase III trial and might be, in part, due to a type I (false positive) error. This is suggested by the following characteristics of the MS-Scripps trial: (i) the replacement of cladribine dropout patients in such a small-sized cross-over study; (ii) the lack of confirmation after 3 to 6 months of the observed clinical deterioration; (iii) the use of means of ordinal scores (EDSS) as an outcome measure; (iv) the rapid worsening of the placebo group.

The Scripps C study was designed to evaluate the efficacy and safety of cladribine 2.1 mg/kg in 52 patients with RRMS. Again, the drug was effective in reducing the proportion of subjects with contrast-enhanced MRI lesions. This effect appeared to be significant 3 months after study initiation and was still present one year after treatment ceased. No significant treatment effect on neurological disability was observed. On the contrary, the treatment effect on exacerbation rate was statistically significant and its dynamics mirrored the delayed effects on contrast-enhanced MRI lesions. A correct interpretation of the clinical data is made difficult by the high dropout rate (25% in the placebo patients) during the second and third semester of the treatment period, and by the fact that there was no significant clinical worsening in the placebo group.

In both phase II trials, the most common treatment emergent adverse events were due to the known pharmacological effects of the drug on bone marrow and lymphocytes. In the MS-Scripps study, only four chronic progressive MS patients in the cladribine 2.8 mg/kg group withdrew from the study during the first year. This was because of injury, aplastic anemia, hepatitis and thrombocytopenia, respectively. The subject with hepatitis died, but the investigator considered it unlikely that the event was drug-related [241294]. The observed changes in liver and renal functions, vital signs and physical examination were not considered clinically significant in any of the study subjects.

Phase III

A multicenter, randomized, double-blind, parallel-group, placebo-controlled phase III trial has also been conducted to evaluate the safety and efficacy of two different doses of cladribine in patients with primary progressive (PP) and secondary progressive (SP) MS [422627]. 159 MS patients (30% with PP and 70% with SPMS) randomly received 2.1 mg/kg or 0.7 mg/kg of cladribine or placebo. The lowest dose was chosen to minimize bone marrow toxicity. After a one-year, double-blind phase, a six-year, open-label extension was planned. MRI evaluation was carried out at baseline and every 6 months for the first two years. The primary outcome measure was the mean change in EDSS score at the final evaluation. Secondary clinical and MRI outcome measures were similar to those used for the phase II cladribine MS studies [241294], [422449]. In addition, two ancillary studies [422447], [422567], assessed the treatment efficacy on MRI-measured brain volume [422447] and T1-hypointense lesion load [422567]. These two MRI-derived parameters are considered markers of MS-related irreversible tissue loss [423916], [423918].

No significant treatment effects on disability were found. However, the mean changes of EDSS and SNRS scores were minor in all three of the treatment groups. Subgroup analysis suggested a stabilization of disability in cladribine-treated patients with SPMS, but not in those with PPMS. Exacerbations, steroid use and hospitalizations did not differ among the treatment subgroups compared to the placebo group. Both of the cladribine treatment groups had a significant reduction of MRI-measured disease activity, as expressed by the number and volume of contrast-enhanced lesions, which were on average 90% lower at months 6 and 12 of the double-blind phase. T2-lesion load modestly improved in treated patients and worsened in placebo

patients. Lesion load percentage changes were significantly lower in patients who received cladribine 2.1 mg/kg compared to patients receiving placebo during the double-blind phase. This was also the case for SPMS patients during the first year of the study extension phase. No significant treatment effect of either dose of cladribine on brain volume or T1-hypointense lesion load changes over time was observed [422447], [422567].

The discrepancy between the lack of effect of cladribine on MS disability and its efficacy on MRI measures of MS activity can be explained by the relatively short duration of this phase III trial, combined with the clinical characteristics of the patients studied. At study entry, the mean level of disability was relatively high in all three arms. This might have prevented the detection of additional disease progression over such a relatively short follow-up period in the placebo patients. Clearly, follow-up is an essential prerequisite to demonstrate any treatment effect. In addition, PPMS patients typically have low degree inflammatory changes [423919]. This might have rendered clinical and MRI measures of disease activity uninformative in these patients. However, the results of the ancillary MRI studies indicate that an alternative explanation might be that cladribine does not affect the progression of severe demyelination and axonal loss, which are likely to be responsible for the increasing irreversible disability in MS.

The phase III study confirmed that cladribine treatment is not related to serious adverse events. Herpes infections occurred rarely and had a similar frequency in the three treatment groups. Furthermore, doses used in this study reduced the hematopoietic effects of the drug, which were previously reported for higher doses [241294].

Side Effects and Contraindications

Treatment-emergent adverse events, apart from myelosuppression, are not treatment-limiting and include

nausea, infections, muscle weakness, hypertonia, purpura, ataxia and skin reactions [422627]. There is no known drug interaction with cladribine. However, given the marked lymphocytotoxicity and the moderate myelosuppressive activity of the drug, particularly at high doses, caution should be exercised when administering cladribine concomitantly with other immunosuppressive agents.

Current Opinion

Phase II and III trials have demonstrated that the effect of cladribine on MRI surrogate markers of MS inflammatory activity is similar, if not more pronounced, to that found for other immunomodulating or immunosuppressive drugs that have been approved for the treatment of RR and SPMS, such as β -interferon, glatiramer acetate and mitoxantrone.

That cladribine was not found to be effective against MS clinical deterioration might be due to the characteristics of the only available phase III trial, which was based on patients in an advanced phase of the disease, and of which a relevant proportion were affected by PPMS. Both these factors might have prevented the investigators from detecting any drug effect, as suggested by the results of the subgroup analysis, which demonstrated a trend toward a positive response for SPMS patients.

Considering that conflicting results have been obtained as regards the efficacy of β -interferon in SPMS [423922], [423925] and that the use of mitoxantrone is limited by its cardiotoxicity [423939], the results of available studies suggest that a further assessment of cladribine efficacy in selected subgroups of patients, such as those with SPMS or rapidly deteriorating RRMS, could prove useful. The known immunosuppressive action of cladribine also makes it a potential rescue therapy for MS patients who are unresponsive to other first-line treatments. Finally, the possibility of combination treatments of cladribine and other immunomodulating drugs also deserves further consideration.

Licensing

IVAX Corp

In December 2000, IVAX entered into an exclusive agreement with The Scripps Research Institute to develop and market cladribine worldwide for the treatment of multiple sclerosis [392111]. The Institute and Ortho Biotech have a separate agreement relating to cladribine [224373].

Development history

Developer	Country	Status	Indication	Date	Reference
Ortho Biotech Inc	US	C3	MS	01-DEC-95	172942
Scripps Research	US	C3	MS	01-APR-99	337358
IVAX Corp	US	C2	MS	01-MAY-01	420751

Literature classifications

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
<i>In vitro</i>	Growth inhibition.	Non-dividing and proliferating human lymphocytes.	Selective toxicity of cladribine on both dividing and resting lymphocytes.	64003
<i>In vivo</i>	Antileukemic and immunosuppressive activity.	Patients with a T-cell leukemia lymphoma and chronic myelogenous leukemia in blast crisis.	Cladribine lowered blast count in leukemic patients and terminated hemolytic process in a patient with severe autoimmune hemolytic anemia.	65313

Biology (continued)

Study Type	Effect Studied	Experimental Model	Result	Reference
<i>In vitro</i>	Effect on clonal growth.	Myeloid progenitors and T-lymphocyte colony-forming cells from normal human bone marrow and peripheral blood.	Marked inhibition of myeloid progenitor and lymphocyte colony forming cells in a dose-dependent manner.	106552
<i>In vivo</i>	Toxicity.	Normal bone marrow from MS patients.	Acute and transient monocytopenia, prolonged, profound lymphopenia especially of CD4+ cells, modest lowering of granulocyte count and hemoglobin.	241296
<i>In vivo</i>	Lymphocyte count.	Lymphocytes from MS patients.	Long-lasting 4-fold reduction in CD4+ to CD8+ T-cell ratio.	423894

Metabolism

Study Type	Effect Studied	Experimental Model	Results	Reference
<i>In vivo</i>	Pharmacokinetics; rates of administration.	High-performance liquid chromatography.	Oral bioavailability 37 to 51%; subcutaneous bioavailability 100%.	122098
<i>In vivo</i>	Pharmacokinetics.	High-performance liquid chromatography.	$t_{1/2} = 5.7$ to 19.7 h. Apparent volume of distribution = 54 to 357 l/m ² .	105448

Clinical

Effect Studied	Experimental Model	Results	Reference
Toxicity.	Cladribine 0.1 mg/kg/day as a 7-day continuous iv infusion every 28 to 35 days in patients with previously untreated chronic lymphocytic leukemia.	Myelosuppression was the primary toxicity, 20% of patients developed grade III/IV thrombocytopenia.	181788
Toxicity.	Cladribine 0.1 mg/kg/day as a 7-day continuous iv infusion for 5 or 7 days every 28 days for a maximum of six cycles trial in patients with either relapsed or refractory chronic lymphocytic leukemia.	31% Of the patients sustained early toxicity and most died before the first re-evaluation of infection; no nausea, vomiting, renal, hepatic or cardiac toxicity observed.	181838
Safety and efficacy in chronic progressive MS patients.	Double-blind, randomized, placebo-controlled, parallel group design.	Cladribine (2.8 mg/kg iv) was effective on MRI (T1-enhancing lesions, T2-lesion load) and clinical endpoints (EDSS and Scripps scale scores). Bone marrow suppression was the main adverse event.	241294
Safety and efficacy in RR MS patients.	Double-blind, randomized, placebo-controlled, parallel-group design.	Cladribine (2.1 mg/kg sc) was effective on MRI (T1-enhancing lesions) but not on clinical endpoints (EDSS and SNRS scores). Mild segmental herpes zoster was the only adverse event.	422449
Safety and efficacy in chronic progressive MS patients.	Double-blind, randomized, multicenter, placebo-controlled, parallel-group design.	Cladribine (0.7 to 2.1 mg/kg sc) was effective on MRI (T1-enhancing lesions, T2-lesion load), but not on clinical endpoints (EDSS and SNRS scores). The effect on T2-lesion load was dose-related as well as the treatment emergent adverse event.	422627
Effects of cladribine on the accumulation of 'black holes'.	Double-blind, randomized, multicenter, placebo-controlled, parallel-group design.	No significant difference between placebo and treated arms, or when PP and SPMS patients were considered separately.	422567
Effects of cladribine on the changes in brain volume.	Double-blind, randomized, multicenter, placebo-controlled, parallel-group design.	No significant difference between placebo and treated arms. No correlation in the placebo group between brain atrophy and other MRI measure at baseline (enhancing lesion number and volume, T2-hyperintense and T1-hypointense lesion volume).	422447

Anti-infective

Anti-inflammatory

Cardiovascular

CPNS

Oncological

Associated patent

Title Use of substituted adenine derivatives for treating multiple sclerosis.

Assignee Scripps Research Institute

Publication WO-09316706 01-SEP-93

Priority US-00838546 19-FEB-92

Inventor Beutler E.

Associated references

17808 **Cladribine (2-chlorodeoxyadenosine)**. Beutler E *LANCET* 1992 **340** 8825 952-956

• Review on drug profile of cladribine.

64003 **Specific toxicity of 2-chlorodeoxyadenosine toward resting and proliferating human lymphocytes**. Carson DA, Wasson DB, Taetle R, Yu A *BLOOD* 1983 **62** 4 737-743

65313 **Antileukemic and immunosuppressive activity of 2-chloro-2'-deoxyadenosine**. Carson DA, Wasson DB, Beutler E *PROC NATL ACAD SCI USA* 1984 **81** 7 2232-2236

105448 **On the pharmacokinetics of 2-chloro-2'-deoxyadenosine in humans**. Liliemark J, Juliusson G *CANCER RES* 1991 **51** 20 5570-5572

106552 **Inhibitory effect of 2-chlorodeoxyadenosine on granulocytic, erythroid, and T-lymphocytic colony growth**. Petzer AL, Bilgeri R, Zilian U, Haun M, Geisen FH, Pragnell I, Braunsteiner H, Konwalinka G *BLOOD* 1991 **78** 10 2583-2587

122098 **On the bioavailability of oral and subcutaneous 2-chloro-2'-deoxyadenosine in humans: Alternative routes of administration**. Liliemark J, Albertoni F, Hassan M, Juliusson G *J CLIN ONCOL* 1992 **10** 10 1514-1518

172942 **Johnson & Johnson**. *PHARMA BUSINESS* 1995 **1** 84-88

181788 **2-Chlorodeoxyadenosine activity in patients with untreated chronic lymphocytic leukemia**. Saven A, Lemon RH, Kosty M, Beutler E, Piro LD *J CLIN ONCOL* 1995 **13** 3 570-574

181838 **Cladribine in the treatment of relapsed or refractory chronic lymphocytic leukemia**. Tallman MS, Hakimian D, Zanzig C, Hogan DK, Rademaker A, Rose E, Variakojis D *J CLIN ONCOL* 1995 **13** 4 983-988

203216 **Investigational agents for rheumatoid arthritis**. Merkel PA, Letourneau EN, Polisson RP *RHEUM DIS CLIN NORTH AM* 1995 **21** 3 779-796

224609 **US FDA Cladribine approved for hairy cell leukemia**. *CANCER WEEKLY* 1993 March 15

241271 **Effect of repeated treatments with cladribine (2-chlorodeoxyadenosine) on blood counts in multiple sclerosis patients**. Grieb P, Stelmasiak Z, Solski J, Nowicki J, Jakubowska B, Ryba M *ARCH IMMUNOL THER EXP* 1995 **43** 5-6 323-327

241277 **Cladribine (2-chloro-2'-deoxyadenosine): new perspectives in clinical immunosuppression**. Gorski A, Grieb P *ARCH IMMUNOL THER EXP* 1994 **42** 1 11-12

241294 **Cladribine in treatment of chronic progressive multiple sclerosis**. Sipe JC, Romine JS, Koziol JA, McMillan R, Zyffoff J, Beutler E *LANCET* 1994 **344** 8914 9-13

• Phase II trial on cladribine in chronic progressive MS.

241296 **Marrow suppression produced by repeated doses of cladribine**. Beutler E, Koziol JA, McMillan R, Sipe JC, Romine JS, Carrera JS *ACTA HAEMATOL* 1994 **91** 1 10-15

309586 **In Brief**. *FDC REPORTS PINK SHEET* 1998 **60** 49

313428 **In Brief**. *FDC REPORTS PINK SHEET* 1999 **61** 3

337358 **ClinCon monitoring of Lotrisine and Floxin Otic studies inadequate, FDA says**. *FDC REPORTS PINK SHEET* 1999 **61** 21 25

351798 **Johnson & Johnson - 1997 mid-year report**. Johnson & Johnson *COMPANY BROCHURE* 1997 July 01

392111 **IVAX to develop new drug for multiple sclerosis IVAX licenses cladribine, in advanced clinical development, from The Scripps Research Institute**. IVAX Corp *PRESS RELEASE* 2000 December 04

420751 **US Specialty Pharmaceuticals: Monthly Dose - May**. *MERRIL LYNCH CAPITAL MARKETS* 2001 May

• This report contains financial analysis and pipeline information for Allergan, Andrx, Forest Laboratories, IVAX, SangStat, Sepracor and Watson.

422447 **Whole brain volume changes in patients with progressive MS treated with cladribine**. Filippi M, Rovaris M, Iannucci G, Mennea S, Sormani MP, Comi G *NEUROLOGY* 2000 **55** 11 1714-1418

• Ancillary phase III study for the evaluation of the effect of cladribine on brain atrophy.

422449 **Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial**. Cladribine MRI Study Group. Rice GP, Filippi M, Comi G *NEUROLOGY* 2000 **54** 5 1145-1155

• Phase II trial of cladribine in RRMS.

422567 **The effect of cladribine on T(1) 'black hole' changes in progressive MS**. Filippi M, Rovaris M, Rice GP, Sormani MP, Iannucci G, Giacomotti L, Comi G *J NEUROL SCI* 2000 **176** 1 42-44

• Ancillary phase III study for the evaluation of the effect of cladribine on the accumulation of T1-hypointense lesion.

422627 **A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis**. Romine JS, Sipe JC, Koziol JA, Zyffoff J, Beutler E *PROC ASSOCIATION AM PHYSICIANS* 1999 **111** 1 35-44

• Phase III trial of cladribine in chronic MS.

423894 **Safety and tolerability of subcutaneous cladribine therapy in progressive multiple sclerosis**. Selby R, Brandwein J, O'Connor P *CAN J NEUROL SCI* 1998 **25** 295-299

423896 **Administration of monthly pulses of cyclophosphamide in multiple sclerosis patients**. Moody DJ, Fahey JL, Grable E, Ellison GW, Myers LW *J NEUROIMMUNOL* 1987 **14** 175-182

423908 **Preferential reductions in lymphocyte subpopulations induced by monthly pulses of chlorambucil: studies in patients with chronic progressive multiple sclerosis**. Chiappelli F, Myers L, Ellison GW, Liao D, Fahey JL *INT J IMMUNOPHARMACOL* 1991 **13** 455-461

423910 **The clinical pharmacokinetics of cladribine**. Liliemark J *CLIN PHARMAKOKINET* 1997 **32** 120-131

423912 **Infectious and immunosuppressive complications of purine analog therapy**. Cheson BD *J CLIN ONCOL* 1995 **13** 2431-2448

423913 **Rating neurological impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS)**. Kurtzke JF *NEUROLOGY* 1983 **33** 1444-1452

423914 **A neurologic rating scale (NRS) for use in multiple sclerosis**. Sipe JC, Knobler RL, Braheney SL, Rice GP, Panitch HS, Oldstone MB *NEUROLOGY* 1984 **34** 1368-1372

423916 **Progressive cerebral atrophy in multiple sclerosis: a serial MRI study**. Losseff NA, Wang L, Lai HM, Yoo DS, Gawne-Cain ML, McDonald WI, Miller DH, Thompson JA *BRAIN* 1996 **119** 2009-2019

423918 **Histopathological correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis**. van Walderveen MMA, Kamphorst W, Scheltens P, van Waesberghe JH, Ravid R, Valk J, Polman CH, Barkhof F *NEUROLOGY* 1998 **50** 1282-1288

423919 **A comparison of the pathology of primary and secondary progressive multiple sclerosis**. Revesz T, Kidd D, Thompson AJ, Barnard RO and McDonald WI *BRAIN* 1994 **117** 759-765

423922 **European Study Group on interferon β -1b in secondary progressive multiple sclerosis**. Placebo-controlled multicentre randomized trial of interferon β -1b in treatment of secondary progressive multiple sclerosis. *LANCET* 1998 **352** 1491-1497

423925 **Effect of interferon beta 1b on magnetic resonance imaging outcomes in secondary progressive multiple sclerosis: results of a European multicenter, randomized, double blind, placebo-controlled study**. Miller DH, Molyneux PD, Barker GJ, McManus DG, Moseley IF, Wagner K *ANN NEUROL* 1999 **46** 850-859

423939 **Multiple Sclerosis: immunotherapy**. Bielekova B, Martin R *CURR TREAT OPTIONS NEUROL* 1999 **1** 201-220