Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Cladribine Tablets

Proprietary Product Name: Movectro

Sponsor: Merck Serono Australia Pty Ltd

July 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of indications, new dose form, new route of administration
Decision:	Approved[1]
Date of Decision:	2 September 2010
Active ingredient(s):	Cladribine
Product Name(s):	Movectro
Sponsor's Name and Address:	Merck Serono Australia Pty Ltd Units 3-4, 25 Frenchs Forest Road East Frenchs Forest NSW 2086
Dose form(s):	Tablet
Strength(s):	10 mg
Container(s):	Blister pack
Pack size(s):	1, 4, 5, 6, 7, 8, 9 and 10
Approved Therapeutic use:	Movectro is indicated for the treatment of relapsing-remitting multiple sclerosis (MS) for a maximum duration of two years.
Route(s) of administration:	Oral
Dosage:	Depending on the patient's body weight, a treatment course consists of a single daily oral administration of one or two 10 mg tablets given for the first 4 or 5 days of a 28-day period. Treatment is initiated with two consecutive courses at a 28-day interval at the beginning of a first 48-week period. Re-treatment consisting of two additional, consecutive courses at a 28-day interval is started at the beginning of a second 48-week period.
ARTG Number:	166483

Product Background

Cladribine (2-chloro-2′-deoxyadenosine [2-CdA]) is a synthetic chlorinated purine analog (PA) of the naturally occurring nucleoside deoxyadenosine. It differs in structure from deoxyadenosine only by the substitution of a chlorine for hydrogen in the 2-position of the purine ring. This change renders cladribine resistant to deamination by adenosine deaminase (ADA). Cells with high levels of deoxycytidine kinase (DCK) and low levels of deoxynucleotidase (5'NTase) activity (for example, lymphocytes) phosphorylate cladribine to the monophosphate form (CdAMP). Subsequently, CdAMP is further phosphorylated to the active CdATP by other kinases. Accumulation of this 5'-triphosphate derivative of cladribine leads to numerous effects on the metabolism of susceptible cells,

[1] The TGA announced on 23 June 2011 that the sponsor had indicated that Movectro would be withdrawn from supply in Australia for commercial reasons.

including: 1) in dividing cells, depletion of the deoxynucleotide triphosphate pool, resulting in inhibition of DNA synthesis; and 2) in resting cells, defective repair of DNA strand breaks and activation of poly (ADP-ribose) polymerase, with depletion of nicotinamide adenine dinucleotide and adenosine triphosphate, leading to cell death. Therefore, cladribine causes a potent and preferential reduction of lymphocyte count due to its mechanism of action.

Two products containing cladribine are registered in Australia. Leustatin, sponsored by Janssen-Cilag was registered in 1994 and Litak, sponsored by Orphan Australia was registered in June 2004. Both are indicated for the treatment of hairy cell leukaemia and second line treatment of patients with B-cell chronic lymphocytic leukaemia in whom treatment with alkylating agents has failed. Leustatin is given intravenously and Litak by subcutaneous injection.

Multiple sclerosis (MS) is a chronic, progressive and debilitating neurological disease for which there is no cure. The immunopathological process leads to a wide range of variable clinical symptomatology including changes in sensation (hypoaesthesia and paraesthesia), muscle weakness, muscle spasms, or difficulty in moving; difficulties with coordination and balance (ataxia); problems in speech (dysarthria) or swallowing (dysphagia), visual problems (nystagmus, optic neuritis or diplopia), fatigue, acute or chronic pain, and bladder and bowel dysfunction. Cognitive impairment and mood disorder are also commonly encountered.

Prior to approval of cladribine tablets, the only treatment options were parenteral therapies administered by intravenous, intramuscular or subcutaneous injection varying in frequency from once a day to once a month depending on the product. Parenterally administered disease modifying drugs (DMDs) approved for treatment of MS include interferon beta preparations, glatiramer acetate and natalizumab. Despite the availability of these DMD treatments, many patients with MS refuse to use or are unable to tolerate these parenterally administered agents. Injection-related concerns are a barrier to initial treatment and a frequent reason for discontinuing therapy. Cladribine tablets are the first effective and well tolerated oral therapy for the treatment of relapsing-remitting MS (RRMS).

Cladribine tablets have the potential to offer an improvement compared to existing treatments for RRMS by providing the first oral therapy. An oral formulation eliminates the adverse effects associated with frequent injections. In addition, unlike the current parenteral treatment regimens, cladribine tablets are administered in short treatment courses allowing the patients significant “treatment-free” periods where they are not required to think about treating their MS. A course consists of daily oral administration of one or two 10 mg tablets given for the first 4 or 5 days of a 28 day period. Treatment is initiated with 2 consecutive courses at the beginning of a first 48-week period. Re-treatment consisting of 2 additional, consecutive courses is started at the beginning of a second 48-week period.

Regulatory Status

A similar application to the current Australian submission has been submitted in the European Union (EU) on 2 July 2009, Canada on 24 July 2009, Switzerland on 17 September 2009 and the US in May 2010. The product was approved in Russia in August 2009. All other applications are under review.

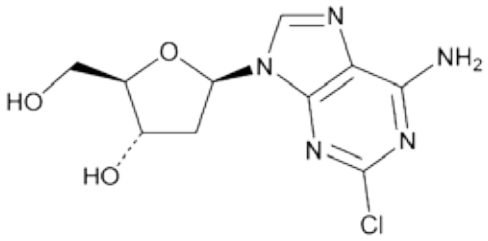
Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Cladribine is the subject of monographs in the European and US Pharmacopoeias. It has the following structure:



A Drug Master File from this manufacturer has been evaluated and found satisfactory.

There are three chiral centres in the drug molecule, but the drug substance is a single stereoisomer. The aqueous solubility of cladribine is about 0.1-0.5%. Its pKa is 1.21 (it is a very weak base).

Drug Product

Cladribine is currently available in Australia as 10 mg/5 mL and 10 mg/10 mL injections.

Cladribine is unstable in acid. A number of strategies were investigated to overcome this instability, including the development of an enteric coated product. However, the oral formulation eventually developed involves the formation of a complex of cladribine with hydroxypropyl beta cyclodextrin. The two ingredients are dissolved in water, the solution is lyophilised, and the resulting solid is milled then combined with sorbitol and magnesium stearate and compressed into tablets.

The tablet specifications include a dissolution limit of 70% in 15 minutes using a paddle apparatus at 50 rpm in 900 mL pH 6.8 phosphate buffer. The assay limits and the limit for water content of the tablets have been tightened at the request of the TGA. The revised specifications are satisfactory.

No significant changes occur in the tablets during storage. A shelf life of 30 months below 25°C has been approved.

Biopharmaceutics

The absolute bioavailability of the tablet proposed for registration has been shown to be 42%. This was similar to the absolute bioavailability of an oral solution of cladribine given with omeprazole.

A high fat meal delayed the time to maximal plasma concentration (T_{max}) by about one hour and reduced the maximal plasma concentration (C_{max}) by 29% but had no significant effect on the area under the plasma concentration time curve (AUC).

The sponsor adequately justified not performing a bioequivalence study of the clinical trial and registration formulations, which differ moderately in the content of sorbitol and magnesium stearate.

Quality Summary and Conclusions

This application was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) on 24 May 2010. The

subcommittee noted that the PI recommends dosing on the basis of body weight, even though population pharmacokinetic analyses indicated that body weight is not an influential covariate. The subcommittee recommended that the PI include instructions for handling the product given that cladribine is cytotoxic. However, the PI already does include this information, together with reference to a more detailed pack insert.

With regard to chemistry, manufacturing and controls, there were no objections to registration of Movectro tablets.

III. Nonclinical Findings

Introduction

Merck Serono Australia Pty Ltd submitted an application to register cladribine as a 10 mg tablet for the treatment of relapsing-remitting multiple sclerosis (MS). Cladribine is currently registered as a parenteral agent for the treatment of lymphoid malignancies. The current application is for a new dosage form (with 2-hydroxypropyl- β-cyclodextrin; HPβCD), a new route of administration (oral) and a new indication (MS) for a currently-registered compound. The maximum approved parenteral dose of cladribine is 7 mg/day subcutaneously (SC) or 6 mg/day intravenously (IV) for 5 or 7 days of a 28 day period (assuming a 50 kg individual). The current application is for a maximum oral dose of 10 mg/day for 5 days of a 28 day period (assuming a 50 kg individual).

The sponsor submitted a comprehensive application with pharmacology, pharmacokinetics, toxicity and carcinogenicity studies to support the current application. The majority of the studies using the oral administration route used a cladribine-HPβCD combination, similar to that used in the clinical formulation, albeit at various ratios.

Submitted studies were performed, where appropriate, under Good Laboratory Practice (GLP) conditions and were adequately conducted. Exposure ratios for findings in a number of studies, in particular reproductive toxicity studies, were re-calculated based on exposure data achieved with an oral dose of 10 mg/day. Adequate toxicity data were submitted to support the new dosage form and administration route.

Pharmacology

Primary pharmacodynamics

Rationale and mechanism of action

The aetiology of MS is not completely understood; however, damage to the central nervous system (CNS) is believed to be mediated by the immune system. T cells specific for the myelin proteins become activated and attack the myelin sheath, inducing the influx of a variety of effector cells into the CNS, leading to disease pathology and neuronal conduction block. Cladribine is a chlorinated adenosine. It enters the cell *via* a purine transporter. Once inside the cell, cladribine is phosphorylated by deoxycytidine kinase to form cladribine monophosphate and eventually the active form, cladribine triphosphate. Cladribine triphosphate is lethal to dividing and non-dividing cells by mechanisms including induction of single and double strand breaks in DNA. The susceptibility of cells to the cytotoxic activity of cladribine depends on the levels of phosphorylating activity, dephosphorylating activity and competition from endogenous deoxycytidine. Lymphocytes have a low intracellular ratio of dephosphorylating activity to phosphorylating activity, making them particularly sensitive to cladribine (Kawasaki *et al.*,

1993).[2] As cladribine specifically targets lymphocytes it was anticipated that it could suppress the immune response leading to the pathophysiology of MS.

Efficacy

The efficacy of cladribine was examined in a mouse model of multiple sclerosis, experimental allergic encephalomyelitis (EAE). Cladribine treatment (1 mg/kg/day intraperitoneally or up to 3 mg/kg/day IV for 10 days) immediately after EAE induction had no positive effects on the development of symptoms or histological analyses of the brain and spinal cords. These doses would be expected to result in exposures approximately 14 times the anticipated clinical exposure[3]. The sponsor stated that the lack of efficacy in mice was likely due to an insufficient plasma level of cladribine for pharmacological activity. Consistent with this was a lack of effect on any of the lymphocyte sets in the spleen or lymph nodes. Based on repeat dose toxicity studies, only doses ≥10 mg/kg/day cladribine (provided subcutaneously for 7 days) had any noticeable effect on white blood cell parameters. An SC dose of 10 mg/kg/day resulted in a systemic exposure (area under the plasma concentration time curve for zero to 7 hours - $AUC_{0\text{-}7h}$) of 3202 ng.h/mL, approximately 44 times the anticipated clinical exposure. As mice have a higher plasma level of deoxycytidine, cladribine has less pharmacological activity in this species. Thus the submitted nonclinical data are inconclusive to support the proposed indication.

Secondary pharmacodynamics and safety pharmacology

Slight inhibition of hERG K^+ tail current was seen at a cladribine concentration of 100 µM but no significant effects were observed on action potential parameters in isolated canine Purkinje fibres at concentrations up to 100 µM (350 µg/mL). These concentrations are greater than 10,000-fold the anticipated clinical plasma C_{max}, and given that the maximum plasma concentrations of cladribine from the 10 mg tablet are less than those from IV and SC dosing, there is unlikely to be a greater concern for adverse cardiovascular effects with the new formulation compared with existing registered formulations.

Pharmacokinetics

Cladribine was rapidly absorbed after oral administration with maximum plasma concentrations seen 0.5-1.8 hours after administration in rats, dogs, monkeys and humans. As stated in previous evaluation reports, the terminal elimination half-life of cladribine was longer in humans than animals ($t_{½}$ values 20 hours compared with 1.2 hours in rats and 3.6 hours in monkeys). The oral bioavailability of cladribine was 26%-45% in rats, dogs and humans, but only 11% in monkeys, most likely due to a higher first pass metabolism to 2-chloroadenine in this species. The plasma AUC of 2-chloroadenine, on a molar basis, was 4-5% that of cladribine following SC or IV administration but 60% that of cladribine after oral dosing in monkeys. This was not the case in clinical studies where the 2-chloroadenine/cladribine AUC ratios appeared to be similar following parenteral or oral dosing (2.5-3.5%). There were no apparent gender differences in exposure in mice or monkeys and no evidence of accumulation with repeat dosing

Cladribine was found to bind minimally (10-20%) to protein in the plasma from animals and humans but is approximately equally distributed between the plasma and blood cells. Radioactivity distributed widely after SC administration of ^{3}H-cladribine to mice and

[2] Kawasaki HF, Carrera CJ, Piro LD, Saven AF, Kipps TJ, Carson DA. Relationship of deoxycytidine kinase and cytoplasmic 5´-nucleotidase to the chemotherapeutic efficacy of 2-chlorodeoxyadenosine. Blood 1993; 81: 597-601.

[3] Linear pharmacokinetics for a 3 mg/kg IV dose and absolute bioavailability for a 1 mg/kg IP dose were assumed.

cleared rapidly, with levels in the excretory organs (bladder, kidney and liver), adrenal glands and heart muscle higher than that in blood. Cladribine readily crossed the blood-brain barrier with exposures in the brain or CSF 8-38% those in the blood of mice, dogs and monkeys.

Cladribine was not extensively metabolised after parenteral administration to mice, monkeys and humans with unchanged parent constituting >85% of drug-related material in the plasma. The only significant metabolite found in the plasma was the oxidative cleavage product, 2-chloroadenine. Ten metabolites were detected at low levels in the urine of one or all of the species examined. These metabolites were formed *via* oxidative cleavage at the adenosine and deoxyribose linkage, oxidation at adenosine or deoxyribose or *via* conjugation. As in plasma, unchanged cladribine constituted the majority of drug-related material in urine (>60% in humans). The level of each individual metabolite was ≤10% in the urine. Although only a low level of cladribine metabolism was seen, multiple human cytochrome P450 (CYP) isoforms (CYP1A1, CYP1A2 and CYP2D6) were found to be involved.

Urinary excretion was the main route of excretion in mice and humans after parenteral administration (65% and 41%, respectively). The excretion profile in monkeys is unclear but urinary excretion does not appear to be a major route with only 1.6% of drug-related material detected in urine. Overall, the absorption, distribution, metabolism and excretion (ADME) profiles in mice and, for the most part, monkeys support the use of these animals in the toxicity studies.

Pharmacokinetic drug interactions

No significant induction of CYP1A2, 2C9, 2C19 or 3A4 in human hepatocytes was observed at cladribine concentrations up to 500 ng/mL (17 times the clinical C_{max}) and no significant inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4 was noted at concentrations up to 2.9 µg/mL (100 times the clinical C_{max}). As cladribine was not extensively metabolised and no significant induction or inhibition of cytochrome P450 activities was observed, there are unlikely to be any pharmacokinetic drug interactions involving P450 enzymes. Cladribine was a weak substrate and poor inhibitor of P-glycoprotein when tested at concentrations up to 15 µM (4.3 µg/mL; approximately 145 times the clinical C_{max}), suggesting drug interactions involving this transporter are unlikely.

Relative exposure

The AUC exposure ratio was calculated based on a 28 day cycle, with animal dosing occurring for 5 or 7 consecutive days and clinical dosing for 5 days in a 28 day cycle (Table 1). Animal AUC exposures have been compared to human AUC exposure by adjusting for the number of treatment days per 28 day cycle, so that comparisons were based on average daily exposure over the cycle. Exposure ratios achieved in oral toxicity studies were several multiples of the clinical AUC and C_{max}; up to 213 and 5 times the clinical AUC and 417 and 4 times the clinical C_{max} in mice and monkeys, respectively. Given the low exposure margins and the absence of toxicological findings in treated monkeys, higher oral doses should have been considered, although this may in part be overcome by toxicity studies using the SC route of administration where exposures achieved were 10 and 7 times the clinical AUC and C_{max}, respectively.

Table 1: Relative exposure of cladribine in repeat dose toxicity studies. All dosing was oral, except where indicated.

Species (Strain)	Study	Treatment duration	Dose (mg/kg /day)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	Exposure ratio based on:	
						AUC[a]	C_{max}
Mouse (CD-1)	25329	7 months	0.2	12	7.4	0.17	0.26
			2	102	97	1.4	3
			20	1623	2085	23	72
	DS94125	3-8 months	1 (SC)	304	291	4	10
			10 (SC)	3130	3174	44	109
			30 (SC)	10770	9739	152	336
Mouse (CByB6F1-Tg(HRAS)-2Jic)	28853	5 weeks	5 (tablet)	645	588	7	20
			20 (tablet)	2428	2434	25	84
			30 (tablet)	4186	4273	42	147
			60 (tablet)	21047	12080	213	417
			30 (DS)	4136	3715	42	128
	29174 [carcinogenicity]	26 weeks	5 (tablet)	527	579	5	20
			15 (tablet)	1812	2125	18	73
			30 (tablet)	4022	4303	41	148
			15 (DS)	1758	1903	18	66
Monkey (Cynomolgus)	26210	28 days	0.6	21	4.3	0.3	0.15
			2	91	22	1.3	0.8
			5	345	83	5	3
	26669/26992	3 months	1.5	82	21	1.2	0.7
			3	205	60	3	2
			6	352	102	5	4
			0.3 (SC)	200	117	3	4
Human	0513	single dose	[10 mg]	99	29	–	–

[a]calculated as animal AUC_{0-24h} × no. of sampling days/28 days :human AUC_{0-24h} × 5/28; data are for the sexes combined, and averages across sampling days; DS, drug substance

Toxicology

General toxicity

Single dose toxicity

Single dose toxicity studies were conducted following parenteral administration to mice, rats and dogs. Consistent with the findings of previously submitted studies with cladribine, the target organs for toxicity were the gastrointestinal (GI) tract, bone marrow, spleen, kidney and testes.

Repeat dose toxicity

A number of the submitted repeat dose toxicity studies have previously been evaluated by the TGA. Cladribine administration in these studies was by SC or IV injection. New repeat dose toxicity studies were conducted in mice for up to 7 months and monkeys for up to 3 months, using a cyclic oral dosing regimen similar to that proposed clinically. Adequate animal numbers were used with administration occurring *via* the proposed clinical route (oral) with the proposed clinical formulation (including HPβCD). All pivotal studies were conducted under GLP conditions. One study in monkeys compared the toxicity of cladribine following oral (PO) and SC dosing, the formulation of the latter did not include HPβCD. An additional non-GLP compliant, not previously evaluated, study following SC dosing to mice was also included. Exposures in this latter study were estimated to be >44 times the clinical AUC.

In oral toxicity studies, no treatment-related toxicity findings were observed in CD-1 mice treated with 20 mg/kg/day (7 days/cycle) for 7 months, transgenic Tg rasH2 mice treated with 20 mg/kg/day for 5 weeks or 15 mg/kg/day for 26 weeks (5 days/cycle), or cynomolgus monkeys treated with 6 mg/kg/day (the highest tested oral dose; 7 days/cycle) for 3 months. The exposures at these doses were, in mice and monkeys, respectively, up to 25 and 5 times the anticipated clinical exposure. At higher exposures (>40 times the clinical AUC) following oral dosing to mice, histopathological changes in the kidneys, testes, thymus and bone marrow were observed. All findings reported following oral dosing with the proposed clinical formulation were similar to those previously seen in SC toxicity studies with cladribine; no new toxicities were identified. All findings were apparently reversible or showed a trend towards recovery during a subsequent treatment-free period.

Mice have a higher plasma level of endogenous deoxycytidine than humans. Deoxycytidine competes with cladribine for transporters and other cell machinery involved in converting cladribine to its active phosphorylated form. Therefore, cladribine is likely to be less pharmacologically active at target tissues in mice than in humans and exposures at the No Observable Adverse Effect Level (NOAEL) for findings in the GI tract, haematopoietic and lymphoid tissues, and male reproductive organs are likely to be over-estimates in mice. Therefore, it is possible that findings in the kidneys may not be related to the pharmacological activity of cladribine and therefore greater confidence can be placed in the exposure ratios for these. There are similar levels of deoxycytidine in monkeys and humans and exposure margins for pharmacologically-mediated findings in monkey studies are likely to be a more accurate reflection of safety margins than those in mouse studies.

Toxicity associated with the pharmacological activity

Testicular findings included seminiferous tubular degeneration and testicular atrophy. These were seen at oral and SC doses in mice resulting in exposures ≥40 times the clinical AUC and SC doses in monkeys at exposures 10 times the clinical AUC. At the highest oral dose in monkeys, resulting in 5 times the clinical AUC, a decrease in spermatozoa with rapid progressive motility was observed but without observable histopathological changes.

Decreased thymic weights were observed in mice at oral doses resulting in >40 times the clinical AUC with lymphocytic depletion in the spleen and/or thymus at SC doses resulting in ≥150 times the clinical AUC. Myeloid hyperplasia in the bone marrow, with accompanying haematological changes (decreased levels of white blood cells, neutrophils, lymphocytes, red blood cells, haemoglobin, haematocrit, platelets and/or reticulocytes) were seen at oral doses resulting in ≥150 times the clinical AUC. Similar bone marrow and

lymphoid tissue findings were seen in monkeys at SC doses resulting in exposures 10 times the clinical AUC.

No GI tract changes were reported in the oral studies, but, consistent with the single dose toxicity studies and previously submitted SC and IV toxicity studies, crypt cell necrosis in the duodenum was seen in mice treated with SC doses resulting in ≥150 times the clinical AUC.

Toxicity not associated with the pharmacological activity

Renal findings included minimal to mild mineralisation, tubular degeneration and cellular infiltration. Similar renal findings were reported in monkeys receiving SC doses of cladribine achieving exposures 10 times the clinical exposure.

Though not reported in oral toxicity studies, the brain and spinal cord appeared to be organs for toxicity in a previous cladribine submission. Cerebral acute, multifocal necrosis and focal/multifocal gliosis were observed in monkeys treated with an SC dose resulting in 10 times the clinical exposure. Serious neurological toxicity has been reported clinically with cladribine in leukaemia patients (Leustatin Product Information document). While cladribine crosses the blood-brain barrier in test species with exposures 8-38% of those in plasma, it is unclear if a compromised human blood-brain barrier, as in the case of MS patients, would increase CNS exposure posing a greater risk of neurotoxicity.

Genotoxicity and carcinogenicity

Based on its pharmacology, cladribine would be expected to interact with DNA, thereby affecting its integrity. Cladribine was not mutagenic in a bacterial mutagenicity test but was clastogenic *in vitro* (CHO cells) and *in vivo* (mouse micronucleus test; ≥10 mg/kg IV). Carcinogenicity studies were conducted in CD-1 mice following intermittent SC dosing for 22 months and in transgenic Tg rasH2 mice following intermittent oral dosing for 26 weeks. It was stated that carcinogenicity studies were not conducted in rats, as cladribine has little or no pharmacological activity in this species, due to high plasma levels of deoxycytidine. Given the different toxicological profiles reported for rats compared with mice and monkeys, it is considered acceptable that rats are not an appropriate species to assess the carcinogenic potential of cladribine. The choice of a long term and a short term carcinogenicity study in a wild-type and a transgenic mouse model, respectively, is considered acceptable according to the TGA-approved EU guideline on carcinogenicity testing[4] (but see discussion below). Group sizes used and the duration of dosing were appropriate for the test species (TGA-approved EU guideline in carcinogenic potential and Morton *et al.*, 2002).[5,6] Dual negative control groups were included in the long term study. Doses used achieved estimated maximum exposure ratios ≥40 times the clinical AUC.

No treatment-related neoplastic findings were seen after oral dosing for 5 days each 28 day cycle in Tg rasH2 mice at doses up to 30 mg/kg/day (41 times the clinical AUC). However, an increase in the incidence of Harderian gland adenomas was seen in CD-1 mice treated with intermittent dosing (7 days/28 day cycle) of 10 mg/kg/day SC cladribine, associated with an estimated exposure ratio of about 44. Harderian gland tumours are generally not thought to be clinically-relevant as humans do not have this anatomical structure. However, these findings may indicate a propensity of cladribine for

[4] EMEA, Committee for Proprietary Medicinal Products (CPMP), March 1998. Note for guidance on carcinogenicity: testing for carcinogenicity of pharmaceuticals. CPMP/ICH/299/95.
[5] EMEA, Committee for Proprietary Medicinal Products (CPMP), 25 July 2002. Note for guidance on carcinogenic potential. CPMP/SWP/2877/00.
[6] Morton, D, Alden CL, Roth AJ, Usui T. The Tg rasH2 mouse in cancer hazard identification. Toxicol Pathol 2002; 30: 139-146.

tumour formation. At the No Observable Effect Level (NOEL) dose for Harderian gland adenomas (1 mg/kg/day) the estimated exposure ratio was about 4.

Though there appeared to be no clinically relevant tumour findings at reasonably high exposures, there are some concerns regarding the submitted studies. In the long term SC study, there were no haematological or histopathological indications that cladribine was pharmacologically active in mice at the high dose. Mice are less susceptible to cladribine with only SC doses ≥10 mg/kg/day being pharmacologically active in this species. Therefore, the lower doses of 0.1 and 1 mg/kg/day used in the long term study were probably not adequate to test the carcinogenic potential of cladribine. However, body weight gain was reduced at 10 mg/kg/day SC and a 10 mg/kg/day IV dose was shown to be clastogenic in CD-1 mice. Assuming 100% bioavailability, an SC dose of this level may have been adequate for carcinogenicity testing. Exposure in mice was estimated from a dose-range finding study and not from treated animals and therefore an assumption of exposure values was made. This, together with the lower activity of cladribine in mice, suggests low reliability for estimated animal/human relative exposures.

In the short term study, where no neoplastic findings were observed, there was some indication of pharmacological activity at the highest dose (30 mg/kg/day PO) with testicular and thymic changes but no haematological changes were identified, suggesting the highest dose may be at the threshold of pharmacological activity. Therefore, in this study also, there are concerns regarding the adequacy of dose levels, with only the highest dose possibly adequate for carcinogenicity testing.

There were minimal indications of toxicity in the submitted studies and, based on data from shorter duration studies, treatment at higher doses (for example, 30-60 mg/kg/day SC) may have been feasible. Long term treatment at these higher doses would have provided more reliable data to address carcinogenic potential. Due to uncertainties as to the adequacy of both carcinogenicity studies, along with the positive *in vivo* genotoxicity test and based on its mode of action, a carcinogenic potential of cladribine cannot be excluded.

Reproductive toxicity

All submitted reproductive toxicity studies have been evaluated previously. The details of relevant findings and their associated exposure margins are provided below.

Male fertility

In male mice treated with up to 30 mg/kg/day SC for 28 days prior to mating, there was no effect on mating index, time to copulation or number of females becoming pregnant. However, at doses ≥10 mg/kg/day, reduced testicular and epididymal weights were observed with lower sperm counts identified. Though the number of motile sperm was similar with controls, there was a 2.8 fold increase in the number of non-motile sperm in mice treated with 30 mg/kg/day. The NOAEL for adverse testicular or sperm findings in mice was 5 mg/kg/day. Based on an AUC of 1.6 µg.h/mL, estimated from a 10 mg/kg/day SC dose and 28 days of dosing, the exposure at the NOAEL is approximately 90 times the clinical AUC, over 28 days.

Repeat dose toxicity studies in monkeys revealed dose- and time-dependent effects on the male reproductive system. Cyclic treatment for 3 months was associated with only reduced sperm motility (6 mg/kg/day PO and 0.3 mg/kg/day SC; NOEL 3 mg/kg/day PO), without histopathological changes. Cyclic SC dosing for 12 months was associated with testicular degeneration, prostatic inflammation, and prostatic and seminal vesicle secretion depletion (1 and 0.3 mg/kg/day; NOEL 0.15 mg/kg/day), and epididymal hypospermia and increased incidence of degenerated cells (1 mg/kg/day; NOEL 0.3

mg/kg/day). Thus, the NOEL for changes in sperm quality was an oral dose of 3 mg/kg/day, with estimated exposure (plasma AUC) 3 fold clinical exposure. Exposure was not measured in the 12 month study. As the pharmacological activity of cladribine in monkeys and humans is similar but lower in mice, and the testicular findings are associated with its pharmacology, exposure margins in monkeys are probably a better representation of risk than those in mice. Therefore, potential risks on male fertility exist with cladribine.

Female fertility

No effect on mating index, time to copulation or number of pregnant dams was observed in female mice treated with up to 8 mg/kg/day SC cladribine for 14 days prior to mating and up to Day 13 of gestation. Also at this dose, there was no effect on the numbers of corpora lutea, implantations or pre-implantation loss. However, at 8 mg/kg/day SC, the number of resorptions was 4-5 fold greater with a subsequent reduction in live fetuses. The NOAEL for female fertility was deemed to be 8 mg/kg/day SC. Extrapolating from 10 mg/kg/day SC data, this dose given daily for 14 days would be estimated to produce an AUC of 2.5 µg.h/mL, approximately 70 times the clinical AUC, over 14 days. The NOEL dose in this study was 4 mg/kg/day SC, associated with an estimated AUC of 1.25 µg.h/mL (35 times the clinical AUC).

Embryofetal toxicity

Previous embryofetal studies with cladribine in mice showed potent embryolethal effects at doses ≥5 mg/kg/day IV, with total fetal resorption at 10 mg/kg/day. IV doses up to 3 mg/kg/day on gestation days 6 to 15 was associated with lower maternal bodyweights, related to an increased resorption rate, reduced fetal bodyweights (at 3 mg/kg/day), and a significant increase in fetal variations at doses ≥1.5 mg/kg/day IV. These variations included increases in cervical ribs, irregularly-shaped exoccipital bones and variations in sternal ossification. At the higher dose of 3 mg/kg/day, exencephaly, thoracogastroschisis, fused ribs and a lower number of tarsal and phalangeal bones were also seen. As these fetal effects occurred at non-maternotoxic doses, they are most likely test item-related. No effect on fetal development was seen at 0.5 mg/kg/day IV. This dose, assuming 100% SC bioavailability and 10 days dosing, would be estimated to produce an exposure 3 times the anticipated clinical exposure.

In the rabbit developmental toxicity study in which animals were treated with up to 3 mg/kg/day IV cladribine on gestation days 7 to 19, there was no evidence of the embryolethal effects seen in mice, but a teratogenic effect was observed at the highest dose. Fetal malformations included cleft palate, abnormal forelimb flexure, ectromelia, malrotated limbs, oligodactyly, adactyly and syndactyly. Skeletal variations seen included incompletely ossified palates; agenesis, shortened, misshapen and/or malpositioned radius/ulna, as well as other changes. The NOEL for fetal development was 1 mg/kg/day. This is estimated to be approximately 5 times the clinical dose on a cumulative mg/m^2 basis[7]. Based on deoxycytidine levels, cladribine would be expected to be as pharmacologically active in rabbits as it is in mice, and therefore lower than in humans. Thus, dose or exposure comparisons in the embryofetal studies in both mice and rabbits are likely to be over-estimates. The observed teratogenic effects are consistent with the pharmacology of cladribine, and cladribine should not be given during pregnancy.

[7] Calculated using mg/kg to mg/m^2 conversions of 12 and 33 for rabbits and humans, respectively. Human dosing was assumed to be 10 mg to a 50 kg individual for 5 days. Rabbit dosing was assumed to be 1 mg/kg/day for 13 days.

Postnatal development

In a pre/postnatal study, an IV dose of 3 mg/kg/day cladribine to pregnant mice from Day 6 of gestation to Day 21 of lactation resulted in a 20% decrease in the number of live offspring (attributed to a higher incidence of resorptions) and an increase in the incidence of skeletal anomalies; the NOEL for these effects was 1.5 mg/kg/day. Consistent with the embryofetal studies, a higher number of offspring with skeletal variations was seen at doses ≥1.5 mg/kg/day. There was no apparent effect of treatment on survival to lactation Day 21, body weight gain, development or reproductive function of pups. The NOEL for effects on any parameter was 0.5 mg/kg/day. The estimated exposures at the 0.5, 1.5 and 3 mg/kg/day doses were 5, 14 and 28 times the anticipated clinical exposure, based on the SC data and 15 days dosing.

Pregnancy classification

The sponsor recommended the same pregnancy category designation as currently-registered cladribine products (Category D). This was considered acceptable.

Use in children

No specific nonclinical studies were conducted to support a paediatric indication.

Local tolerance

Local tolerance studies were performed in Golden Syrian hamsters following buccal administration, in mice following SC administration and in rabbits following administration by IV, intra-arterial (IA) and paravenous (PV) routes. There was no obvious irritation in the oral cavity of treated hamsters (1.57 mg) and no cladribine associated irritation following IV, PV or IA administration (at 1 mg/mL). Cladribine (5 mg/mL) was slightly irritating following SC administration.

Excipients

Cladribine tablets contain 2-hydroxypropyl-β-cyclodextrin (HPβCD). This excipient is included in only a handful of registered oral products, including itraconazole, which is registered for the treatment of buccal/oesophageal candidiasis in HIV-positive and other immunocompromised patients. The sponsor provided a number of toxicity studies and an expert report to toxicologically qualify the daily dose of this excipient from cladribine tablets[8]. The expert report relied largely on the published review article of Gould and Scott (2005).[9] HPβCD was also included in all oral toxicity studies with cladribine, in a ratio similar to or greater than the clinical cladribine: HPβCD ratio.

In the submitted 12 month rat study conducted solely with HPβCD, minimal to moderate diffuse mucosal hyperplasia was seen in the large intestine at intermittent oral doses of ≥500 mg/kg/day and minimal to mild transitional epithelial vacuolation in the urinary bladder at 5000 mg/kg/day (intermittent dosing), with evidence of recovery following a treatment-free period. Consistent with other cyclodextrins, histological changes were seen in the kidneys, with diffuse vacuolation and vacuolar degeneration at 5000 mg/kg/day (daily). The NOAEL was considered to be an oral dose of 100 mg/kg/day (6 times the clinical dose on a mg/m^2 basis).

Exocrine pancreatic hyperplasia was also seen after 12 months daily oral dosing at 5000 mg/kg/day. This neoplastic finding is consistent with published reports of pancreatic tumours in rats following HPβCD treatment (Gould and Scott, 2005). The

[8] The mg/kg to mg/m^2 conversion factors were 3, 6, 12 and 33 for mice, rats, rabbits and humans, respectively. Dose comparisons were made based on the number of days dosed per 28 day cycle period.

[9] Gould S, Scott RC. 2-hydroxypropyl-β-cyclodextrin (HP- β-CD): a toxicology review. Food Chem Toxicol 2005; 43: 1451-1459.

formation of these pancreatic tumours has been attributed to cholecystokinin hypersecretion with rats being particularly sensitive to its mitogenic effects (Irie and Uekama, 1997).[10] The NOEL for tumour formation in rats was an oral dose of 2000 mg/kg/day (reported in Gould and Scott, 2005). This dose is approximately 700 times the clinical dose on a mg/m^2 basis and monthly exposure. In a mouse carcinogenicity study no tumours that could be attributed to HPβCD were seen at the highest tested oral dose of 5000 mg/kg/day (approximately 884 times the clinical dose on a mg/m^2 basis) (reviewed in Gould and Scott, 2005). In the submitted 26 week carcinogenicity study in transgenic Tg rasH2 mice, there was no evidence of exocrine pancreatic hyperplasia or histological changes indicative of neoplastic formations at an oral dose of 431 mg/kg/day (approximately 14 times the clinical dose on a mg/m^2 basis).

HPβCD was apparently not genotoxic in a series of tests for gene mutation, chromosomal damage and DNA damage (Gould and Scott, 2005).

Based on information contained in Gould and Scott (2005), no impairment of reproductive performance in rats was detected at the highest dose of HPβCD given either orally (5000 mg/kg/day) or intravenously (400 mg/kg). Although HPβCD was both maternotoxic and embryotoxic as shown by an increased incidence of skeletal variants and a slightly higher incidence of small fetuses for rabbits at the highest tested oral dose, 1000 mg/kg/day, no evidence for teratogenicity in either rats or rabbits was found. Peri/postnatal studies showed decreased survival of rat pups during lactation following maternal administration of HPβCD at 5000 mg/kg/day orally or 400 mg/kg/day IV; reduced birth weight and postnatal growth retardation were additional findings in the oral study. These doses are considerably higher than the proposed clinical dose. As cladribine itself is teratogenic and embryo/fetotoxic, there are no additional concerns arising from co-administration of HPβCD.

Given the large exposure margins for toxicological findings with HPβCD, the expected oral intake from one 10 mg cladribine tablet is considered acceptable.

Nonclinical Summary and Conclusions

The efficacy of cladribine in a mouse model of multiple sclerosis revealed no positive effects of treatment at doses up to 3 mg/kg/day IV for 10 days resulting in exposures about 14 times the anticipated clinical exposure. However, based on lower pharmacological activity in this species, the data are inconclusive to support the proposed indication.

Slight inhibition of hERG K^+ tail current was seen at 100 μM (350 μg/mL) but no significant effects were observed on action potential parameters in isolated canine Purkinje fibres. As the tested concentrations were 10,000x the anticipated clinical C_{max} there are unlikely to be adverse cardiovascular effects with the new formulation/dose.

The oral bioavailability of cladribine was 26-45% in rats, dogs and humans, but only 11% in monkeys due to a higher first pass metabolism in this species. Tissue distribution studies demonstrated cladribine crossed the blood-brain barrier with exposure in the brain or cerebrospinal fluid (CSF) ranging from 8-38% the blood/plasma exposure in mice, dogs and monkeys. Limited metabolism of cladribine was observed in mice, rats and humans, with minor human metabolites also seen in animals. Urinary excretion was the main route of excretion in mice and humans, but not monkeys.

[10] Irie T, Uekama K. Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation. J Pharm Sci 1997; 86: 147-162.

No significant induction or inhibition of human CYP450 isozymes was observed. Cladribine was a weak substrate and poor inhibitor of the P-glycoprotein transporter. Drug interactions involving this transporter or CYP450 enzymes are unlikely.

Repeat dose toxicity studies were conducted in mice up to 7 months and monkeys up to 3 months, using a cyclic oral dosing regimen similar to that proposed clinically. No treatment-related toxicity findings were observed in treated CD-1 mice or cynomolgus monkeys at oral doses resulting in at least 5 times the anticipated clinical exposure. At higher exposures following oral dosing to mice, histopathological changes in the kidneys, testes, thymus and bone marrow were observed. All findings reported following oral dosing with the proposed clinical formulation were similar to those previously seen in SC toxicity studies with cladribine. No new toxicities were identified. All findings were apparently reversible or showed a trend towards recovery during a treatment-free period.

Cladribine was not mutagenic in a bacterial mutagenicity test but was clastogenic *in vitro* (CHO-WBL cells) and *in vivo* (mouse micronucleus test). Carcinogenicity studies were conducted in CD-1 mice following intermittent SC dosing for 22 months and in transgenic mice following intermittent oral dosing for 26 weeks. No treatment-related neoplastic findings were seen after oral dosing in Tg rasH2 mice; however, an increase in the incidence of Harderian gland tumours, predominantly adenomas, was seen in CD-1 mice.

A fertility study in mice and a toxicity study in monkeys found reduced testicular and epididymal weights, hypospermia, testicular degeneration, secretion depletion, and reduced sperm motility. In monkeys, exposure at the no-effect PO dose for any parameter was 3-fold the clinical AUC. There was no observable effect on female fertility in mice at high exposures. Consistent with its pharmacology, cladribine was embryolethal in mice and teratogenic in mice and rabbits with estimated exposures at NOEL doses ≥ 3 times the clinical exposure.

In local tolerance studies, there was no obvious irritation in the oral cavity of treated hamsters and no cladribine-associated irritation following IV, PV or IA administration. Cladribine was slightly irritating following SC administration.

Based on large exposure margins for toxicological findings with the excipient, HPβCD, the expected oral intake from one 10 mg cladribine tablet is considered acceptable.

Cladribine has been in clinical use for some time and the safety profile of this drug is well known. There was no evidence in the submitted nonclinical dossier that additional toxicity concerns exist with the new formulation and new administration route for cladribine. Clinical exposures following oral dosing are 2-3 times lower than those obtained from currently-registered cladribine products, thereby lessening some concerns regarding toxicity findings.

The toxicity profile of cladribine is not dissimilar from other registered drugs for MS, with the kidney, GI tract, spleen, thymus and/or the CNS all target organs for toxicity. Haematological changes of thrombocytopenia, leucopenia and anaemia have all been reported with other drugs indicated for MS and may be expected with immunomodulatory drugs.

There are a number of particular concerns with the use of cladribine which need to be considered in a risk-benefit analysis for the proposed indication:

- There was no indication of efficacy in submitted nonclinical data.
- While the safety profile of cladribine has been well-established, it is unknown if a greater neurotoxic risk exists for MS patients who have a compromised blood-brain barrier compared with leukaemia patients.

- Unlike currently-registered drugs for MS, cladribine is genotoxic, there are uncertainties regarding the carcinogenicity testing, and a carcinogenic potential cannot be excluded.
- As with most drugs approved for oncology indications, cladribine should not be used in pregnancy. Adverse effects on sperm quality and integrity are also possible.
- There is existing clinical experience with cladribine for other indications, at exposures 2-3 fold greater than that proposed for MS treatment.
- The clinical need for cladribine as a treatment option for MS, despite its known and potential toxicity profile.

There were no objections on nonclinical grounds to the submission.

IV. Clinical Findings

Introduction

The initial clinical program investigating the use of a parenteral formulation of cladribine in MS consisted of three primary double-blind, placebo-controlled studies (Studies 2-CdAMS- SCRIPP ["MS-Scripps"], 2-CdA-MS-001 ["MS-001"] and 2-CdA-MS-SCRIPC ["Scripps-C"], and two supportive studies (2-CdA-MS-SCRIPA ["Scripps-A"], an open label pilot study, and 2-CdA-MS-SCRIPB ["Scripps-B"], a blinded, placebo-controlled study).

In Scripps-C, a Phase II trial in RRMS, cladribine was shown to be effective clinically as well as across multiple magnetic resonance imaging (MRI) indicators of disease activity compared to placebo. In addition, three double-blind, placebo-controlled studies (MS-Scripps, MS-001, and Scripps-B) and one open-label, uncontrolled trial (Scripps-A) showed that cladribine suppressed lesion development and stabilised disease burden based on MRI findings, particularly reduction in T1 gadolinium (Gd)-enhancing lesion activity. However, these latter studies conducted in PPMS or SPMS failed to demonstrate clinical efficacy in these progressive forms of MS. The full data from this early clinical program are not available, but they have been used as fully as possible in the subsequent development of cladribine oral tablets.

Based on the existing data from the Phase II and Phase III trials in MS with parenteral cladribine, an oral tablet formulation of cladribine was developed by the current sponsor employing a short course dosing regimen. The final tablet formulation was selected based on favourable physicochemical and stability parameters as well as comparative non-clinical and clinical evaluation.

The tablet formulation was tested in two randomised, open-label cross-over studies to evaluate the bioavailability of cladribine following oral administration in comparison to the SC and IV administration of cladribine. The oral cladribine treatment regimens for evaluation in Phase III were selected with the goal of attaining the maximal therapeutic effect with minimal dose-related undesirable effects.

The efficacy of oral cladribine as a disease modifying therapy for RRMS has been examined in the pivotal Phase III trial 25643 ("CLARITY"). Supportive efficacy data were provided from the Scripps-C trial. The primary safety information was derived from the CLARITY trial as well as the placebo-controlled phases of the four double-blind trials with parenteral cladribine: the MS Scripps, Scripps-B, and Scripps-C trials and Study MS-001.

The ***CLARITY trial*** was a Phase III, randomised, double-blind, three arm, placebo-controlled, multicentre clinical trial evaluating the efficacy and safety of cladribine tablets over 96 weeks in subjects with RRMS.

The ***Scripps-C trial*** was a single-centre, placebo-controlled Phase II trial that equally randomised 49 subjects to receive SC parenteral cladribine 2.1 mg/kg cumulative dose (equivalent to cladribine tablets 5.25 mg/kg cumulative dose) or placebo.

In addition to the completed studies, the following ongoing studies listed below are part of the Clinical Development Program for cladribine tablets in MS. Aggregated, blinded data from the CLARITY Extension study and from the ONWARD study (see below) were provided as part of the safety database for the submission.

Trial 27820 (CLARITY Extension) is a Phase IIIb, multicentre, double-blind, randomised, placebo-controlled, parallel group 96-week trial to evaluate the safety, tolerability, and efficacy of cladribine tablets for up to 4 years in subjects with RRMS. Two of the main objectives of this trial are to determine the persistence of the initial 2-year treatment effect in terms of clinical benefit and safety, and to provide long-term safety and efficacy data for the extended use of cladribine tablets in the treatment of subjects with RRMS.

***Trial 26593 (ONWARD*)**, a 96-week Phase II trial, is also ongoing to evaluate the safety, tolerability, and efficacy of cladribine tablets 3.5 mg/kg as an add-on to interferon (IFN)-beta treatment in subjects with RRMS who experience a sub-optimal treatment response to IFN-beta monotherapy. Subjects must have received established treatment with IFN-beta for at least one year before trial entry, and must have had at least one relapse during the 12 months before trial entry.

Trial 28821 (ORACLE MS) is a Phase III, randomised, double-blind, placebo-controlled, multicentre, 3-treatment group trial to evaluate the safety and efficacy of oral cladribine in subjects with early disease who have experienced a first clinical demyelinating event and who are at high risk of converting to MS.

The development of cladribine for the "relapsing forms of MS"/relapsing-remitting MS indication followed applicable international guidelines including the TGA-adopted EU guideline on the treatment of MS.[11]

For the filing to regulatory agencies, the core clinical package included the following trials:

(a) supportive Phase I studies;
(b) the completed, pivotal Phase III trial (CLARITY; 25643);
(c) the completed trials with the parenteral cladribine formulation; and
(d) blinded safety data from the ongoing Phase III CLARITY Extension (27820) and Phase II ONWARD (26593) trials that were available as of January 19, 2009.

The Phase I data allowed extrapolation of the parenteral clinical data with the oral tablet clinical data; it was thus deemed appropriate to conduct a single confirmatory Phase III study in multiple sclerosis with the tablet formulation.

Clinical studies were conducted in accordance with Good Clinical Practice (GCP) guidelines.

Pharmacokinetics

Introduction

The commercial formulation of cladribine will be a 10 mg cladribine/cyclodextrin-tablet (HPβCD cladribine). Differences between the commercial formulation of cladribine and the selected clinical formulation consist of only minor increases in sorbitol and magnesium stearate content in the commercial formulation. The final commercial product

[11] EMEA, Committee for Medicinal Products for Human Use (CHMP), 16 November 2006. Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis, CPMP/EWP/561/98- Rev-1.

and the clinical formulation were shown to have similar dissolution profiles in a variety of dissolution media. Based on the FDA and European Medicines Agency (EMA) guidelines, scientific references, and ethical considerations, a bioequivalence study between the clinical and the commercial formulations was not considered necessary to conduct further bioequivalence studies.

The information about the pharmacokinetics of cladribine has been obtained in studies in subjects with MS after oral administration. In addition, the pharmacokinetics of cladribine has earlier been studied in other indications (malignancies or solid tumours), and with other ways of administration (SC or IV).

To date, all pharmacokinetic (PK) evaluations have been performed in subjects with either MS or malignancies.

Absorption

Following oral administration of tablets containing either 3.0 mg or 10.0 mg cladribine, absorption was rapid with a T_{max} in the range of 0.5 - 1.5 hours. The oral bioavailability for the 10 mg cladribine HPβCD formulation was in the range of 39 - 43%.When cladribine was administered together with a high fat meal, the absorption was delayed (T_{max}: 1.5 hours), C_{max} was lower (29% based on geometric mean), while the AUC was unchanged.

The bioavailability of cladribine is most probably multifactorial. Efflux transport proteins most likely play a role of cladribine absorption and bioavailability, while influx transporters may be of less importance. The uptake of cladribine could in principal be dependent on influx by nucleoside transporters Equilibrative Nucleoside Transporter (ENT)1, Concentrative Nucleoside Transporter (CNT)2 and CNT3; however, the fast absorption of cladribine indicates a high capacity in the absorption process not involving rate limiting active transport. The fast absorption is also in accordance with the high solubility and intermediate permeability of cladribine.

The limited bioavailability of cladribine could be partly due to the instability of cladribine at acidic pH. Cladribine is stable at basic and neutral pH and temperatures up to 85°C. However, at acidic pH, decomposition markedly increases with time. Cladribine is a weak base, and the ionisation behaviour of the molecule over the pH range 0 - 12 is characterised by a single pKa of approximately 1.21. However, the HPβCD component of the formulation seems to protect cladribine from degradation in the acid conditions in the stomach.

Distribution

In spiked human plasma, the plasma protein binding of cladribine was low- (20%) and independent on concentration. The same range of plasma protein binding, 21.1% in 5 healthy subjects and 25.0% in 11 subjects with malignancies has been reported in the literature by Albertioni et al. (1994).[12] Further, protein binding of cladribine was independent on the concentrations tested.

In human blood, cladribine was almost equally distributed between plasma and blood cells. The blood to plasma ratio in human blood was 1.30 at 0.1 µM (= 285.69 ng/mL) and 1.34 at 10 µM (= 2856.9 ng/mL), indicating a somewhat higher distribution to the blood cells. However, this blood to plasma ratio of approximately of 1.3 does not give information about the distribution to the different cells in the blood.

[12]Albertioni F, Herbgren L, Juliusson G, Liliemark J. Protein binding of 2-chloro 2′-deoxyadenosine (cladribine) in healthy subjects and in patients with leukaemia. Eur J Clin Pharmacol 1994; 46: 563-564.

The volume of distribution (Vss) of cladribine is large, with mean (standard deviation [SD]) estimates of 487 (180) L derived from study 25803. The corresponding volume per kg in this study was 6.57 (2.52) L/kg. Vss was determined in the same range with 4.90 (1.97) L/kg in studies (6226 and 6414) in patients with haematological malignancies or solid tumours. This high volume is in line with the intracellular distribution of cladribine, which is important for the primary pharmacological effect of cladribine.

Based on presently available data, there is no clear indication if there is a linear relationship between plasma concentrations of cladribine and intracellular concentrations of the phosphorylated forms of cladribine. The transport of cladribine into the lymphocytes has been reported to be dependent on nucleoside transporters, that is, ENT and/or CNT. Intracellular uptake of cladribine could be enhanced by an active or facilitated transport. Of the ENT transporters, it is reported that cladribine is a substrate for ENT1, ENT2 and ENT3. Literature data suggest that cladribine is able to penetrate the blood brain barrier (Liliemark & Juliusson [1992]).[13]

Elimination

Following an IV infusion of cladribine in MS patients (Study 25803), the mean (SD) total clearance was 45.4 (9.9) L/h. The mean (SD) fraction of dose eliminated by the renal route accounted for 57.5 (20)%. After administration of the HPβCD-cladribine 10 mg tablet in the same patients, 28.5 (20)% [mean (SD)] of the dose was eliminated via the renal route, taking into account the absolute bioavailability of approximately 40%, the fraction excreted unchanged in urine after oral administration is consistent with the fraction excreted after IV administration. Thus the renal clearance [mean (SD)] was independent of administration route, 29.9 (24.4) L/h and 29.2 (12.4) L/h for oral and IV administrations, respectively.

In the pooling population PK (PPK) analysis, the renal and the non-renal routes of cladribine elimination were approximately equally important. The typical population parameter estimates from the final model for the two elimination routes were 23.1 L/h for renal clearance (CL_R) and 22.7 L/h for the non-renal or metabolic clearance (CL_{NR}). The CL_{NR} includes both intracellular metabolism and hepatic metabolism, where the hepatic metabolism is considered as a minor contributor to cladribine's overall clearance.

In the urinary excretion study in Japanese patients with malignancies approximately 39% of the dose was excreted unchanged in urine. This is in the same range as observed in Caucasian subjects with haematological malignancies, and also in subjects with MS.

The renal clearance of cladribine exceeds the glomerular filtration rate, indicating the drug undergoes net tubular excretion in addition to glomerular filtration.

From the PPK model, the renal component of clearance (CL) in subjects with renal impairment could be assessed, and the resulting (simulated) drop in the total clearance was predicted as 18%, 30% and 40% for subjects with mild (creatinine clearance [CL_{CR}] = 65 mL/min), moderate (CL_{CR} = 40 mL/min) and severe (CL_{CR} = 20 mL/min) renal impairment, respectively, suggesting a potential need for dose-adjustment in this special population. However, it should be noted that the predictive value for moderate and severe renal impairment is limited by the fact that subjects with moderate and severe renal impairment were not included in the population used for model development.

The clearance of cladribine is approximately equally dependent on renal and non-renal elimination. The non-renal elimination most probably consists of intracellular metabolism

[13] Liliemark J, Juliusson G. On the pharmacokinetics of 2-chloro-2-deoxyadenosine in cerebrospinal fluid. Blood. 1992; 80: 471a (abstract).

and of hepatic metabolism of which the intracellular metabolism probably is the most important.

The minimal importance of hepatic metabolism was estimated by looking into the total percent of dose excreted in urine as cladribine and as metabolites after IV administration in the 25803 study. The total percent of dose excreted in urine as cladribine [57.5 (20%)] and as 2-chloroadenine [3.9 (5.5%)] was 61.4%. The extent of intracellular metabolism was estimated to be up to 39% of total clearance.

The elimination half-life ($t_{1/2}$) varied across studies between 5-8 hours and 18-21 hours, indicating that different elimination phases could have been captured. The longer half-lives were observed in the more recent studies (25803, 26127 and 26486). This could be explained by the times for collection of PK plasma samples. In the PPK analysis, the typical terminal half-life was estimated to be 23 hours. In the earlier studies, the last sample was collected for 24 hours after dose; while in the later studies, the last sample was collected between 48–172 hours after dose.

Dose Proportionality and Time Dependency

In study IXR 102-09-186, C_{max} and AUC after a single 10 mg HPβCD-cladribine dose increased linearly proportional in relation to the 3 mg (labelled) dose of the same formulation. The dose linearity of the cladribine PK after IV administration was investigated at 9 different dose levels in the range 2.5 – 21.5 mg/$m^{2.}$ With the exception of terminal-phase disposition $t_{1/2}$ and volume of distribution based on the terminal disposition phase (V_z), regression analysis (power function) of PK parameters showed evidence of linear PK. Study results indicate that the PK of cladribine are linear over the dose range 2.5 to 21.5 mg/m^2/day. There was no significant accumulation of cladribine plasma concentrations after repeated oral dosing of a cladribine solution during 5 days, that is, bioavailability of cladribine was similar on Days 1 and 5 (~ 37%) in the Scripps study 93-220. From the final PPK model, no clinically relevant accumulation over the 5 days is predicted.

Special Populations

As already described in the introduction, the long lasting cytotoxic and immunosuppressive effects of cladribine did not allow the design and conduct of a "classical" clinical pharmacology "intrinsic factor" study program in special patient populations not affected by the target disease (MS). Therefore, no dedicated pharmacokinetic studies in typical special populations such as children and adolescents, the elderly, and patients with different degrees of hepatic and renal impairment have been conducted with cladribine HPβCD tablets. In addition, patients from different ethnic backgrounds, other than Caucasians, are hardly represented in the pharmacokinetic study program with oral cladribine in MS patients. This is in part due to the distinctly higher incidence of MS in Caucasians (for example, as opposed to Hispanics or African Americans), that also reflected the regional focus of these studies for patient recruitment purposes. For the evaluation of potential gender differences, no specific study was conducted. Instead, MS patients of both sexes were included in all of the PK and biopharmaceutical studies and results of these studies were subjected to a PPK analysis.

Age

The population of subjects who are typically affected by MS consists of young and middle-aged adults. The safety and effectiveness of cladribine in paediatric MS patients are not known. It is recommended that cladribine should not be used in patients below 18 years of age.

A combined analysis of data from the three clinical pharmacology studies 25803, 26127 and 26486 was performed, where dose corrected C_{max} and AUC were correlated to age. There is no obvious correlation between exposure and age.

In the PPK analysis including the clinical pharmacology studies 25803, 26127 and 26486, and a subgroup of patients in the CLARITY study, age was tested as a covariate. In this analysis, age did not have a significant effect on the PK of cladribine. The age range of the subjects included in the pop PK analysis was 19 – 65 years (40 median).

Clinical studies of cladribine did not include elderly subjects above 65 years. Therefore, it cannot be determined whether patients > 65 years may have different PK of cladribine than younger subjects. In general, for an elderly patient caution is advised, given the greater frequency of decreased renal, cardiac or hepatic function, and of concomitant diseases or concomitantly administered drugs.

Gender

A combined analysis of data from the three clinical pharmacology studies 25803, 26127 and 26486 was performed, where dose corrected C_{max} and AUC were correlated to gender.

There was a trend towards a somewhat higher exposure in female subjects. This effect is likely correlated with body weight, since flat dosing was used in the clinical pharmacology studies. However, in the pooling pop PK analysis it was concluded that the PK of cladribine is independent on gender. The patients included in the pooling pop PK analysis consisted of approximately 69% females in CLARITY and 57% in the three clinical pharmacology studies.

Effect on Pregnancy or Lactation

Cladribine has been shown to inhibit DNA synthesis. Other drugs that inhibit DNA synthesis have been reported to be teratogenic in humans. In women of childbearing potential, pregnancy must be excluded before the initiation of cladribine therapy and before initiation of each subsequent treatment course, and prevented by use of reliable contraception for the duration of each treatment course and for at least 6 months (6 menstrual cycles) after the last dose of the most recent course. Women who become pregnant under therapy with cladribine should discontinue treatment.

It is unknown whether cladribine is excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, cladribine is contraindicated during breast-feeding.

Renal Impairment

The impact of renal function on the PK of cladribine has been evaluated in three studies (6226-6414, 25803 and JK-6251-1); however no dedicated study in renal impairment has been performed in subjects with MS.

After IV administration the mean (SD) percentage of the dose excreted in urine as cladribine was 57.5 (20.0) % and as 2-chloroadenine 3.9 (5.5) %. The mean (SD) percentage of the dose excreted in urine after oral administration of the 10 mg HPβCD tablet were 28.5 (20) % and 1.4 (1.7) %. The corresponding oral/IV excretion ratios for cladribine and 2-chloroadenine were 0.47 and 0.43, respectively. The total clearance of cladribine after IV administration to MS patients was determined to be 45.4 (9.9) L/h.

In the PPK analysis it could be concluded that total clearance of cladribine is dependent on the CL_{CR} in the individual patient. The predicted decrease in total clearance for a typical patient with typical creatinine clearance representing the different degrees of renal function was predicted to 18% in mild impairment (CL_{CR} = 65 mL/min), 30% in moderate renal impairment (CL_{CR} = 40 mL/min), and 40% in severe renal impairment (CL_{CR} = 20

mL/min). Experience in patients with moderate to severe renal impairment is limited; therefore, cladribine is not recommended in patients with moderate or severe renal impairment.

Hepatic Impairment

A dedicated hepatic impairment study has not been performed in subjects with MS. The non-renal part of the elimination of cladribine (40-80%) consists of fractional hepatic metabolism and presumably of extensive intracellular distribution and trapping of the active cladribine principle (CdATP) within the targeted intracellular compartment (that is, the lymphocytes) and subsequent elimination of intracellular CdATP according to the life course and elimination pathways of these cells.

The importance of hepatic function for the elimination of cladribine is considered low. In the 25803 study, 3.9 (5.5) % and 1.4 (1.7) % of the dose was excreted in the urine as 2-chloroadenine after IV and oral administrations, respectively. In plasma, the ratio between 2-chloroadenine and cladribine was in the range 0.012 – 0.045 after IV dose and 0.026 – 0.053 after oral dose. Moreover, *in vitro* experiments with human hepatic S9 fractions and microsomes showed that cladribine was metabolised only to a very low extent with unchanged cladribine accounting for at least 90% of the sample radioactivity. Therefore, hepatic impairment should not have any substantial impact on the elimination of cladribine. However, in absence of data, use of cladribine is not recommended in patients with moderate or severe liver impairment.

Drug Interactions

Interferon

A Phase I study looking primarily at the PK interaction between cladribine and Rebif (IFN beta-1a) has been conducted in subjects with MS (26486). The primary objective of this study was to assess the effect of oral cladribine on the PK of IFN-β1a in subjects with MS and vice versa.

For cladribine, no clinically significant difference between the cladribine exposure in combination therapy and in monotherapy could be observed. Due to incomplete serum concentration-time curves for IFN-β1a in some of the patients, IFN-β1a could only be determined in a subset of subjects (9 out of 15 subjects). Therefore the results have to be interpreted with some caution. However, the (descriptive) geometric mean ratio for the area under the plasma concentration time curve truncated at various sampling times ($AUC_{(0\text{-trunc})}$) between cladribine + IFN-β1a combination therapy and IFN-β1a monotherapy was 0.99 (90% CI: 0.71, 1.37), strongly suggesting absence of a clinical relevant effect of cladribine on the disposition of IFN-β1a in patients with MS.

Pantoprazole.

The primary objective with this study was to investigate the influence of pantoprazole on the pharmacokinetics (PK) of cladribine. Repeated oral pantoprazole 40 mg single doses administered 15 hours and 3 hours prior to administration of cladribine had no influence on the PK profile of cladribine.

Food

The objectives with this study (26127) were to assess the effect of food on the PK of cladribine in the fed and the fasted states. One cladribine HPβCD 10 mg tablet was administered in the fasted and in the fed states in a cross-over design. All subjects were fasting for no less than 10 hours prior to dosing in each study period. According to the randomisation list subjects remained in a fasting state or were given a standardised breakfast within 30 minutes prior to drug administration.

A high fat breakfast resulted in a 29% reduction in cladribine C_{max} (geometric mean). This was associated with an increase in the median T_{max} from 0.5 hours in the fasted state to 1.5 hours in the fed state. The effect of the high fat breakfast on the extent of absorption (that is, the area under the plasma concentration time curve from time zero to infinity [AUC_{∞}]) of cladribine did not reach statistical significance. The outcome of the study indicates that cladribine can be administered without regard to food.

Potential Metabolic Interactions

The potential for clinically significant metabolic interactions involving CYP450 enzymes is considered to be low, because cladribine does not significantly inhibit or induce CYP450 enzymes. In addition, cladribine undergoes only fractional metabolism that is subject to a large variety of CYP450 enzymes involved. Further, about 50% of the total clearance of cladribine consists of renal elimination that occurs predominantly in form of the unchanged parent drug. Therefore inhibition of any or several of the CYP450 enzymes is not expected to cause a significant alteration in the overall clearance of cladribine.

It has been reported (Chtioui et al 2009) that lamivudine can inhibit the phosphorylation of cladribine intracellularly and thereby the therapeutic efficacy of cladribine.[14] Therefore, compounds that require intracellular phosphorylation to become active such as lamivudine, zalcitabine, ribaravin, stavudine, and zidovudine should not be administered concomitantly with cladribine. This group of drugs is already contraindicated since cladribine therapy must not be initiated in immunocompromised patients, including patients receiving immunosuppressive therapy.

Determination of the Oral Dose in Subjects with MS

When cladribine was proposed as a potential treatment for MS, the dose ranges, toxicity and PK in human subjects were known from studies in lymphoid neoplasms. Therefore, no traditional multiple ascending dose study was performed in subjects with MS. The selection of the dose regimen and the strength of the oral formulation were based on information obtained in three clinical studies in MS patients where cladribine was administered by the SC and IV routes (MS-Scripps, MS-001, Scripps-C). In these studies the dose range 0.7 – 2.8 mg/kg/year (0.07 – 0.1 mg/kg during 5-7 day courses, repeated monthly 2 – 6 times during the year) were studied. The outcome of these studies showed a favourable balance between positive MRI outcomes and safety in the range of 0.7 to 2.1 mg/kg total dose.

Based on these results, exposure corresponding to SC (100% bioavailability) or IV dose of 1.4 mg/kg/year in the first year and 0.7 mg/kg/year in the second year was targeted for an oral formulation. The absolute bioavailability that could be achieved with oral dosage forms was assumed to be approximately 40%, and this was later confirmed for the 10 mg cladribine HPβCD tablet. Therefore, the estimated corresponding oral dose of cladribine tablets was found to be 0.875 mg/kg/course (equivalent to a parenteral dose of 0.35 mg/kg).

In CLARITY, the pivotal Phase III study (25643) two dosing regimens were used, denoted “low dose” and “high dose” regimens. For the low dose regimen, the maximum oral dose administered in the first 48-week treatment period was 1.75 mg/kg and for the high dose regimen, the maximum oral dose administered in the first 48-week treatment period was 3.5 mg/kg. For both regimens, the dose in the subsequent 48-week period was 1.75 mg/kg. The comparisons between the oral and IV doses are presented in Table 2.

[14] Chtioui H, Millius C, Lammle B et al. Concomitant treatment with lamivudine renders cladribine inactive by inhibition of its phosphorylation. Br J Haematol 2009; 144: 136-7.

Table 2: Comparison between oral and IV doses

Year	1				2		
Course number	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
High dose oral/kg	0.875	0.875	0.875	0.875	0.875	0.875	5.25
Low dose oral/kg	0.875	0.875			0.875	0.875	3.5
Low dose i.v./kg	0.35	0.35	0.35	0.35	0.35	0.35	2.1
High dose i.v./kg	0.35	0.35			0.35	0.35	1.4

It was approximated that a comparable systemic exposure and similar body-weight adjusted treatment algorithms could be achieved with a single tablet strength containing about 10 mg of cladribine. The treatment algorithm used in CLARITY is presented in Table 3.

The recommended dosing regimen in this application is equivalent to the "low dose" regimen in the CLARITY trial, that is, initiating treatment with 2 consecutive courses at the beginning of a first 48-weeks treatment period with re-treatment consisting of 2 additional, consecutive courses is started at the beginning of a second 48-week treatment period.

Based on the risk benefit consideration, the 5.25 mg/kg treatment regimen (equal to 4 courses in the first 48-week period and 2 courses in the second 48-week period) will not be pursued for approval in the treatment of RRMS.

Table 3: The Treatment Algorithm Used in CLARITY

		Number of 10 mg Tablets per Course					
		Courses					
Weight Range		**Initial Treatment 2-4 consecutive 28 day courses**				**Re-treatment 2 consecutive 28 day courses**	
Kg	**Lb**	**1**	**2**	**3***	**4***	**1**	**2**
40* to <50	81 to <110	4	4	4	4	4	4
50 to <60	110 to <132	5	5	5	5	5	5
60 to <70	132 to <154	6	6	6	5	6	6
70 to <80	154 to <176	7	7	7	6	7	7
80 to <90	176 to <198	8	7	8	7	8	7
90 to <100	198 to <220	9	8	9	8	9	8
100 to <110	220 to <242	10	9	9	9	10	9
110 and above	242 and above	10	10	10	10	10	10

* Courses 3 and 4 are only administered to patients assigned to a 6-course (5.25 mg/kg) regimen

Evaluator's Overall Conclusions on Pharmacokinetics

The studies presented for evaluation have characterised the PK of cladribine after administration of the HPβCD cladribine tablet over a 5-day treatment course. The elimination of cladribine was shown to be dependent on renal and non-renal routes, where the non-renal elimination consists predominantly of intracellular metabolism, and only to a minor extent hepatic metabolism.

A number of transporters have been identified to have a potential impact on absorption, distribution, and elimination of cladribine. Among them, ABCG2 (BCRP) plays likely the

most important role; thus, strong inhibitors of that transporter could potentially increase cladribine bioavailability and should not be co-administered with cladribine.

A modest reduction in total clearance for subjects with different degrees of renal impairment was shown. Cladribine tablets should not be recommended in patients with moderate or severe renal impairment.

There is only minor hepatic metabolism of cladribine, however due to the lack of relevant data, the sponsor proposes that cladribine tablets are not recommended for use in patients with moderate or severe hepatic impairment. The evaluator agreed with the sponsor's recommendation.

The PK of cladribine is not dependent on age, gender, or body weight.

Pharmacodynamics

MS is a chronic, inflammatory, demyelinating disease of the central nervous system. The neuropathology of the disease is marked by an aberrant activation of specific T and B cells that recognise self (that is, myelin) antigens expressed in the CNS. This in turn leads to oligodendrocyte loss, demyelination, axonal atrophy, and neuronal loss.

The aberrant activation of self-specific T and B cells observed in MS is affected by immunomodulatory treatments that have demonstrated efficacy in relapsing forms of MS. However, unlike other immunomodulatory treatments, cladribine selectively targets and depletes lymphocytes. Therefore, cladribine's mechanism of action, leading to potent and selective reduction of lymphocytes, provides a strong rationale for possible use of this drug in the treatment of MS.

The effects of cladribine tablets on T and B lymphocyte reduction, pro-inflammatory cytokines and chemokines, and cellular migration into the CNS may have the potential to interrupt the cascade of events that are central to the pathophysiology of MS and the progression of the disease. Intracellular phosphorylation of cladribine is specifically mediated by the enzyme deoxycytidine kinase (DCK), which is highly expressed in lymphocytes. At the same time, the levels of the 5'-nucleotidases (5'NTases) responsible for degradation of cladribine triphosphate (CdATP) are low in lymphocytes and cladribine, a chlorinated purine nucleoside analog, is resistant to the action of adenosine deaminase. CdATP represents the active principle, causing a disruption of cellular metabolism, DNA damage and impairment of DNA synthesis, thereby causing subsequent cell death of both dividing and quiescent cells.

As the mode of action of cladribine was previously elucidated and well established in other therapeutic areas, no dedicated proof of concept/PD studies have been performed. No new pharmacodynamic studies were provided for evaluation.

Efficacy

Introduction

The clinical development program evaluating the efficacy of cladribine in the treatment of MS included the following trials:

- ***Study 25643***, A phase III, randomised, double-blind, three-arm, placebo-controlled, multi-centre study to evaluate the safety and efficacy of oral cladribine in subjects with relapsing- remitting multiple sclerosis (***"CLARITY"***), and
- ***Study 2-CdA-MS-SCRIPC***, Cladribine (2-CdA) treatment of relapsing-remitting multiple sclerosis (***"Scripps-C"***).

The CLARITY trial met the American Academy of Neurology (AAN) criteria for class I evidence and the Scripps-C trial met the AAN criteria for class II evidence. The design of

the CLARITY trial was consistent with the Committee for Medicinal Products for Human Use (CHMP) guidance on confirmatory studies. The CLARITY trial is therefore considered the pivotal study, with Scripps-C providing further efficacy data.

Other placebo controlled clinical trials have been conducted in the treatment of other forms of MS (2-CdA-MS-SCRIPB "Scripps-B", 2-CdA-MS-001 "MS-001", and 2-CdA-MSSCRIPP "MS-Scripps"). Subjects in these trials were diagnosed with progressive forms of MS (chronic progressive MS, that is, primary progressive or secondary progressive MS), whereas subjects enrolled in the CLARITY and Scripps-C trials were diagnosed with relapsing remitting MS (RRMS). Clinical Study Reports for the Scripps-B, MS-001, and MS-Scripps trials were provided; however efficacy results from these studies will not be included in this report as these studies enrolled patients with forms of MS not directly relevant to the proposed indication for registration. However, the relevant safety data from these trials will be discussed in the safety section of this report.

Main Pivotal study - Study 25643 (CLARITY)

This was a multicentre, double-blind, placebo-controlled trial with three parallel treatment groups randomised 1:1:1. The study was conducted from January 2005 to March 2009 at 155 centres in North and South America, Eastern and Western Europe, Russia, the Middle East and North Africa. The primary objective of the trial was to evaluate the efficacy of oral cladribine versus placebo in the reduction of qualifying relapse rate at 96 weeks of treatment in subjects with RRMS. The trial included a pre-trial evaluation period (up to 28 days prior to the start of treatment); an initial treatment period during the first 48 weeks in the trial; and a re-treatment period during the second 48 weeks in the trial. A treatment course was defined as daily administration over 4 to 5 consecutive days of the initial 5 days during a 28-day treatment course.

Eligible subjects were equally randomised by a central randomisation system to receive:

• Cladribine tablets 3.5 mg/kg (high dose [HD])(administered orally (PO) as 0.875 mg/kg/course for two courses plus placebo PO for two courses during the first 48 weeks and 0.875 mg/kg/course for two courses during the second 48 weeks), or

• Cladribine tablets 5.25 mg/kg (low dose [LD])(administered PO as 0.875 mg/kg/course for four courses during the first 48 weeks and 0.875 mg/kg/course for two courses during the second 48 weeks), or

• Matching placebo (administered PO for four courses during the first 48 weeks and two courses during the second 48 weeks). The administered dose was standardised based on weight.

In addition to the usual safety assessments, at the Week 44 visit, all subjects were assessed for their lymphocyte count prior to retreatment at Week 48. For all randomised subjects, a rescue option of treatment with Rebif (44 µg three times a week [tds]) was available if the subject experienced more than one qualifying relapse, and/or experienced a sustained increase in their Expanded Disability Status Scale (EDSS) of ≥one point, or ≥1.5 points if baseline EDSS was 0 (over a period of three months or greater), during a calendar year beginning at Week 24.

Cladribine was administered orally in 10 mg tablets. The number of tablets administered was standardised based on weight, using 10 kg weight ranges (that is, 60-69.9 kg, 70-79.9 kg, etc). A course was defined as daily administration given consecutively over four to five days during a 28-day period. The courses administered for all treatment groups were initiated at Trial Day 1, Week 5, Week 9 and Week 13 (for the first 48-week period), and at Week 48 and Week 52 (for second 48-week period).

Endpoints

The primary endpoint was qualifying relapse rate at 96 weeks. The documentation and follow-up of relapses were conducted throughout the trial period with scheduled and unscheduled neurological assessments. Subjects were instructed to inform the trial site within 24 hours of the onset of a relapse. Qualifying relapses were defined as a two grade increase in one or more Kurtzke Functional Systems (KFS) or a one grade increase in two or more KFS, excluding changes in bowel/bladder or cognition, in the absence of fever, lasting for ≥24 hours, and preceded by ≥30 days of clinical stability or improvement.[15]

Neurological examinations including the KFS exam, ambulation up to 500 meters and EDSS were obtained at the Pre-Study Evaluation, Study Day 1 and at Weeks 13, 24, 36, 48, 60, 72, 84 and 96.

MRI scans were assessed at the pre-trial evaluation and at Weeks 24, 48 and 96. The following MRI parameters were measured and analysed for all subjects for each scan obtained during the trial:

• Combined unique (CU) lesions defined as 1) new T1 gadolinium-enhancing, or 2) new T2 non-enhancing or enlarging lesions, or 3) both, without double-counting (designated "combined unique lesions")

• T1 gadolinium-enhanced lesions

• T1 gadolinium-enhancing lesion volume

• Active T1 gadolinium-enhanced lesions

• Active T2 lesions

• T2 lesion volume

• Number of T1 hypointense lesions

• T1 hypointense lesion volume

• Brain atrophy, as measured by Brain Parenchymal Fraction (BPF) at baseline, Week 48 and Week 96.

Key clinical secondary efficacy endpoints were the proportion of qualifying relapse-free subjects and the time to sustained disability progression, defined as the time to a sustained change (or worsening for ≥3 months) in Expanded Disability Status Scale (EDSS) of ≥ 1 point (or ≥1.5 points if baseline EDSS was 0). Additional clinical efficacy endpoints included the time to first qualifying relapse and the proportion of subjects receiving rescue therapy with interferon-beta-1a.

Secondary MRI endpoints were mean number of lesions per patient per scan over 96 weeks for: T1 gadolinium-enhancing lesions; active T2 lesions; and combined unique (CU) lesions defined as new T1 gadolinium-enhancing lesions and/or new or enlarging T2 lesions (without double counting).

Documentation and follow-up of each relapse was conducted throughout the trial period with scheduled and unscheduled neurological assessments. Subjects were instructed to inform the trial site within 24 hours of the onset of a suspected relapse.

[15] The Kurtzke Functional Systems are the 8 function systems within the EDSS and comprise pyramidal (ability to walk), cerebellar (coordination), brain stem (speech and swallowing), sensory (touch and pain), bowel and bladder functions, visual, mental, other (includes any other neurological findings due to MS).

A qualifying relapse was defined as a two grade increase in one or more KFS or a one grade increase in two or more KFS, excluding changes in bowel/bladder or cognition, in the absence of fever, lasting for ≥24 hours, and preceded by ≥30 days of clinical stability or improvement. It was possible, due to resolution of impairment related to a prior relapse or intra-/inter-observer variability on EDSS assessment that the EDSS may not change or may even improve despite worsening in the relevant KFS.

A non-qualifying relapse was any relapse (as determined by the treating physician) that did not include the requisite neurological change of a protocol defined qualifying relapse.

Statistical and Analytical Plans

Descriptive Methods

Continuous variables were summarised using the following descriptive statistics: mean, standard deviation, median, minimum and maximum. The frequency and percentage of observed levels were reported for categorical measures. The number of subjects specified in each treatment group was the number of subjects in that treatment and population. In general, all data were listed, sorted by region, country, site, treatment, subject and, when appropriate, by trial visit/day within subject.

Inferential Methods

In general, the level for confidence intervals (CI) was set at 95%, and the level of significance (overall Type I error) for tests was set at 5%.

Analyses Populations

The analysis sets consisted of intent-to-treat (ITT), Evaluable, and Safety populations. The ITT population included all subjects who were randomised into the trial. Subjects who completed treatment without a major protocol deviation with 96-week data were included in the Evaluable population. The Safety population included all subjects who received at least one dose of trial medication with follow-up safety data.

The ITT and Safety populations were the primary analysis populations for efficacy and safety analyses, respectively. The Evaluable population was utilised as the supportive analysis population.

A subset of approximately 180 subjects were to take part in a PPK and Standard 12-lead electrocardiogram (ECG) sampling.

Sub-group Analyses

If the treatment by region interaction was statistically and clinically relevant for the key efficacy endpoints, then summaries of treatment by region were performed.

Primary Efficacy Endpoint

The qualifying relapse rate was analysed using a Poisson regression model with fixed effects for treatment group and region with log of time on study as an offset variable in the model. An approximate Chi-square test based on Wald statistics was used to compare treatment groups. In addition, the relative risk of developing a qualifying relapse and its associated 95% CI (97.5% CI) was estimated for each treatment group comparison. Annualised qualifying relapse rate and its associated 95% CI (97.5% CI) was estimated for each treatment group. Summary statistics for the number of qualifying relapses during the 96 weeks of the trial included the mean, standard deviation, minimum and median, and was presented by treatment group.

Secondary Efficacy Endpoints

A hierarchical test was used for the following three MRI parameters: the mean number of active T1 gadolinium-enhanced (Gd+) lesions per subject per scan during 96 weeks, the mean number of active T2 lesions per subject per scan during 96 weeks, and the mean number of combined unique (CU) lesions per subject per scan during 96 weeks. These MRI parameters were tested in hierarchical order following the testing of the primary efficacy parameter, and only for those cladribine doses that were determined to be significantly different from the placebo for the primary efficacy parameter.

Determination of Sample Size

It was determined that a sample size of 1290 subjects (430 subjects in each group) provided 90% power to detect a clinically meaningful 25% relative reduction in the primary efficacy endpoint, qualifying relapse rate during 96 weeks, when comparing each of the two cladribine dose groups to the placebo group. The calculation was performed using a two-sided t-test with the following assumptions: the calculation assumed 2.1 for the mean number of qualifying relapses during 96 weeks in the placebo group, and a relative 25% reduction in mean number of qualifying relapses (that is, the mean number of qualifying relapses during 96 weeks was 1.575 in the cladribine group). Other assumptions were: a common standard deviation of 2.02 (estimated from PRISMS-2 year data in the placebo group) for the number of qualifying relapses, a 10% non-evaluable rate and a Type I error rate for each cladribine group versus the placebo group at 2.5%.

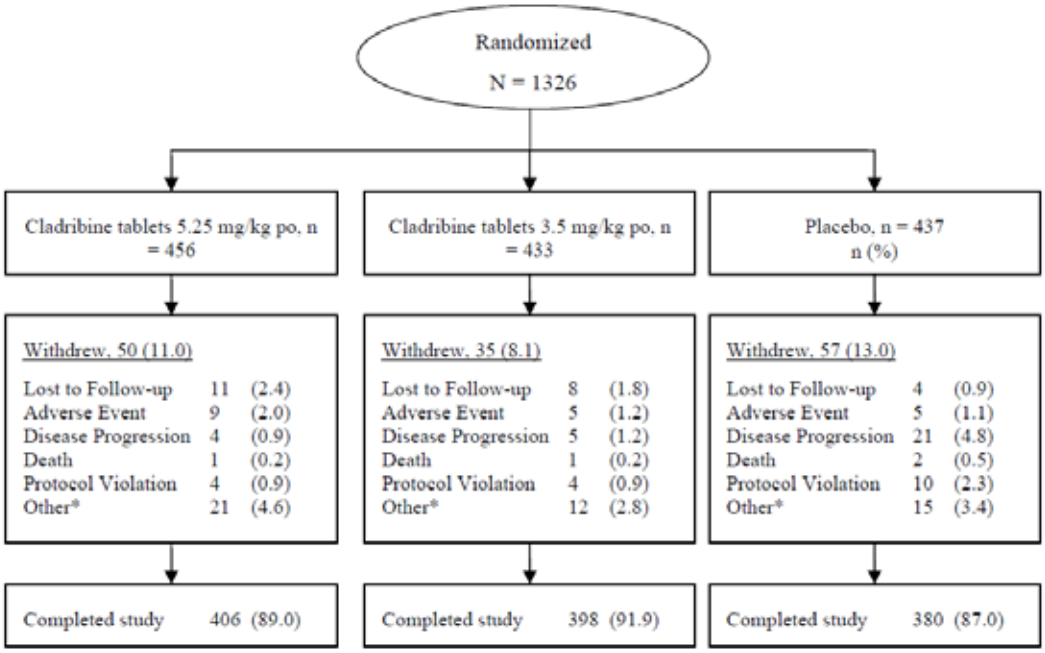
Protocol Amendments

Nine protocol amendments were issued for the CLARITY trial. A discussion of these amendments is beyond the scope of this document.

Subject Disposition and Participant Flow

A total of 1326 subjects were enrolled and randomised in the CLARITY trial and comprised the intent-to-treat population for the primary analyses: 433 subjects were randomised to the cladribine tablets 3.5 mg/kg treatment regimen, 456 subjects were randomised to the cladribine tablets 5.25 mg/kg treatment regimen, and 437 subjects were randomised to receive placebo. The majority of subjects were enrolled from Russia (n=300), Bulgaria (n=190), the United States (n=94), Ukraine (n=80), Czech Republic (n=67), Italy (n=66), Tunisia (n=54), and France (n=47). Disposition of the randomised subjects is described in Figure 1.

Figure 1: Disposition of Subjects in the CLARITY Trial



* The majority of subjects within this category withdrew consent

Approximately one-third of enrolled patients had previously received disease-modifying therapy: 26.1% (3.5 mg/kg group – low dose [LD]), 32.2% (5.25 mg/kg – high dose [HD]) and 32.5% (placebo group). Overall, 1184 (89.3%) patients completed the 96-week trial (87.0%, 91.9% and 89.0% in the placebo, cladribine LD and HD groups) and 1165 completed treatment (86.3%, 91.2% and 86.2%, respectively). For the placebo and the cladribine LD and HD treatment groups, the mean time on study was comparable (87.8, 91.0 and 89.4 weeks, respectively).

The number of subjects in each evaluable group is listed in Table 4.

Table 4: Subject populations and evaluability

Population	Cladribine 5.25 mg/kg n (%)	Cladribine 3.5 mg/kg n (%)	Placebo n (%)	Total n (%)
ITT Population	456	433	437	1326
Evaluable Population	377 (82.7)	381 (88.0)	364 (83.3)	1122 (84.6)
Safety Population	454 (99.6)	430 (99.3)	435 (99.5)	1319 (99.5)
Pop PK Population	61 (13.4)	66 (15.2)	56 (12.8)	183 (13.8)
ECG Population	51 (11.2)	51 (11.8)	48 (11.0)	150 (11.3)
Rescued Population	9 (2.0)	11 (2.5)	27 (6.2)	47 (3.5)

Baseline Data

Consistent with the fact that MS predominantly affects women and people of Caucasian descent, a majority of subjects participating in both the CLARITY and Scripps-C trials were

women, more than two-thirds of subjects in each trial were female, and nearly all subjects in both trials were identified as 'White'. No particular differences were noted in either gender or racial distributions between the cladribine and placebo treatment groups in either trial.

The CLARITY protocol allowed for enrolment of subjects aged 18 to 65 years old and the Scripps-C protocol allowed for enrolment of subjects aged 21 to 55 years old. The mean ages of cladribine and placebo treatment groups in the Scripps-C trial were 43.8 and 39.7 years, respectively, and were slightly older than those in the CLARITY trial, which were 37.8, 39.1 and 38.7 years in the cladribine tablets LD, cladribine tablets HD and placebo groups, respectively. Body weight of subjects eligible to participate in the CLARITY trial was restricted to 40 to 120 kg; however no such limit was placed upon subjects participating in the Scripps-C trial.

Disease duration, EDSS score, and number of T1 Gd+ lesions at baseline tended to be greater among subjects participating in the Scripps-C trial versus subjects participating in the CLARITY trial. These observations reflect not only the older mean age of trial subjects in the Scripps-C trial, but may also reflect differences in diagnostic advances that occurred during the interval of time between the execution of both trials, and the availability of disease modifying drugs (DMD) subsequent to the Scripps-C trial completion.

However, within each trial baseline subject demographics and disease characteristics were generally well-balanced across treatment groups. In the CLARITY trial there were more DMD treatment naïve subjects in the cladribine tablets LD group and this may be linked to the observation that disease duration was shorter in this group compared to the cladribine tablets HD and placebo groups ($p = 0.005$). Also, the cladribine tablets HD group had a greater baseline disease burden on brain MRI as seen on T1 hypointense lesion number and T2 lesion volume.

Efficacy Results

Primary and key secondary efficacy results are summarised in Table 5.

Table 5: Summary of primary and key secondary efficacy results - CLARITY trial

Efficacy Criteria	Cladribine tablets 5.25 mg/kg N = 456	Cladribine tablets 3.5 mg/kg N= 433	placebo N = 437	p-values: a) 5.25 mg/kg vs placebo b) 3.5 mg/kg vs placebo
Relapses				
Annualized qualifying relapse rate at 96 weeks	0.15	0.14	0.33	a) < 0.001 [1] b) < 0.001 [1]
Reduction in annualized qualifying relapse rate at 96 weeks relative to placebo, % [2]	54.5	57.6		
Proportion of subjects qualifying relapse-free over 96 weeks, %	78.9	79.7	60.9	a) < 0.001 [3] b) < 0.001 [3]
Time to first qualifying relapse, weeks, 15th percentile	58.0	58.3	20.1	a) < 0.001 [4] b) < 0.001 [4]
Disability				
Time to 3-month sustained disability progression on EDSS score, 10th percentile, days (weeks) [5]	414 (59.1)	414 (59.1)	330 (47.1)	a) 0.026 [6] b) 0.018 [6]
Hazard ratio vs. placebo, [95% CI]	0.69 [0.49, 0.96]	0.67 [0.48, 0.93]		
Proportion of subjects free of a 3-month sustained disability progression, %	84.9	85.7	79.4	a) 0.032 [3] b) 0.016 [3]
Magnetic Resonance Imaging				
Adjusted Mean (SE) number ofT1 Gd+ lesions per subject per scan over 96 weeks	0.11 (0.05)	0.12 (0.05)	0.91 (0.05)	a) < 0.001 [7] b) < 0.001 [7]
Treatment difference (Cladribine – placebo) Point estimate (SE)	-0.80 (0.07)	-0.78 (0.07)		
Reduction in Adjusted Mean number of T1 Gd+ lesions relative to placebo over 96 weeks (%) [2]	87.9	85.7		
Adjusted Mean (SE) number of active T2 lesions per subject per scan over 96 weeks [3]	0.33 (0.06)	0.38 (0.07)	1.43 (0.06)	a) < 0.001 [7] b) < 0.001 [7]
Treatment difference (Cladribine – placebo) Point estimate (SE)	-1.10 (0.09)	-1.05 (0.09)		
Reduction in Adjusted Mean number of active T2 lesions relative to placebo over 96 weeks (%) [2]	76.9	73.4		

Table 5 (cont): Summary of primary and key secondary efficacy results - CLARITY trial

Efficacy Criteria	Cladribine tablets 5.25 mg/kg N = 456	Cladribine tablets 3.5 mg/kg N= 433	placebo N = 437	p-values: a) 5.25 mg/kg vs placebo b) 3.5 mg/kg vs placebo
Magnetic Resonance Imaging (Cont)				
Adjusted Mean (SE) number. of combined unique (CU) lesions per subject per scan over 96 weeks	0.38 (0.08)	0.43 (0.08)	1.72 (0.08)	a) < 0.001 [7] b) < 0.001 [7]
Treatment difference (Cladribine – placebo) Point estimate (SE)	-1.34 (0.10)	-1.28 (0.10)		
Reduction in Adjusted Mean number of active CU lesions relative to placebo over 96 weeks (%) [2]	77.9	74.4		

1 p-value based on Wald Chi-square test from analysis of number of qualifying relapses using a Poisson regression model with fixed effects for treatment group and region and with log of time on trial as an offset variable.

2 Reduction relative to placebo (%) was calculated as (placebo – active)/placebox100%

3 p-value based on Wald Chi-square test from analysis of endpoint using a logistic regression model with fixed effects for treatment group and region.

4 The 15th percentile of the time to first qualifying relapse was estimated by Kaplan-Meier survival curves: p-value was calculated using Cox proportional hazards model with fixed effects for treatment group and region, and 95% CI was used for the hazard ratio.

5 10th percentile time to 3-month sustained disability progression was based on Kaplan-Meier survival estimates

6 p-values were estimated using Cox proportional hazards model with fixed effects for treatment group and region.

7 p-values calculated based on nonparametric ANCOVA model on ranked data with fixed effects for treatment group and region with covariate of baseline T1 Gd+ lesions.

Primary Efficacy Endpoint

The primary efficacy endpoint of this trial was the qualifying relapse rate at 96 weeks for the ITT population. The annualised qualifying relapse rates were 0.15 for cladribine HD, 0.14 for cladribine LD, and 0.33 for placebo. Treatment with cladribine HD resulted in a 54.5% relative reduction in annualised qualifying relapse rate compared to placebo. Treatment with cladribine LD resulted in a 57.6% relative reduction in annualised qualifying relapse rate compared to placebo. Treatment with cladribine HD and cladribine LD compared to the placebo group resulted in a highly statistically significant difference for the qualifying relapse rate at 96 weeks ($p<0.001$ for both comparisons). As compared to the placebo group, the 95% CI of the relative risk of developing a qualifying relapse during the trial for each cladribine group were: 35% and 54% for the cladribine HD group, and 34% and 54% for the cladribine LD group, respectively. The results of the ITT analysis were supported by results for the Evaluable population, which also demonstrated a highly statistically significant difference in favour of both cladribine HD versus placebo and cladribine LD versus placebo ($p<0.001$ for both comparisons). Treatment with both

cladribine HD and cladribine LD resulted in a 58.1% relative reduction in annualised qualifying relapse rate compared to placebo.

Secondary Efficacy Endpoints

Proportion of Qualifying Relapse-Free Subjects

As shown in Table 5, 78.9% of subjects in the cladribine HD group, 79.7% of subjects in the cladribine LD group, and 60.9% of subjects in the placebo group remained relapse-free at Week 96. Thus, a statistically significantly greater proportion of subjects in both cladribine HD and cladribine LD versus placebo remained relapse-free at Week 96. The odds ratio (OR) was 2.43 ($p<0.001$; 95% CI of the OR=1.81, 3.27) for the cladribine HD group compared to the placebo group, indicating that the odds of subjects treated with cladribine HD remaining relapse-free during the 96 weeks of therapy was 2.43 times of the odds of subjects treated with placebo. The OR was 2.53 ($p<0.001$; 95% CI of the OR=1.87, 3.43) for the cladribine LD group compared to the placebo group, indicating that the odds of subjects treated with cladribine LD remaining relapse-free during the 96 weeks of therapy was 2.53 times of the odds of subjects treated with placebo.

The results of the ITT analysis were confirmed by results of the Evaluable population which also demonstrated highly statistically significant differences in favour of both the cladribine HD group versus the placebo group, and the cladribine LD group versus the placebo group($p<0.001$ for both comparisons). The odds of subjects treated with cladribine HD remaining qualifying relapse-free during the 96 weeks of therapy was 2.78 times of the odds of subjects treated with placebo. The odds of subjects treated with cladribine LD remaining qualifying relapse-free during the 96 weeks of therapy was 2.82 times of the odds of subjects treated with placebo.

Disability Progression at 96 Weeks (time to sustained change in EDSS ≥one point if baseline was 0.5-4.5, or ≥1.5 points if baseline EDSS was 0, or ≥0.5 point if baseline was ≥5, over a period of at least three months)

The hazard ratio (HR) of time sustained change in EDSS score in each of the cladribine groups versus the placebo group and the associated 95% and 97.5% CI was estimated. Treatment with cladribine HD and cladribine LD significantly prolonged the time to sustained change in EDSS score over 96 weeks compared to placebo.

The hazard ratio was 0.69 ($p=0.026$; 95% CI of the hazard ratio=0.49, 0.96) for cladribine HD compared to placebo, indicating that subjects in the cladribine HD group were 31% less likely to experience a 3-month sustained change in their EDSS score compared to placebo.

The hazard ratio was 0.67 ($p=0.018$; 95% CI of the hazard ratio=0.48, 0.93) for cladribine LD compared to placebo, indicating that subjects in the cladribine LD group were 33% less likely to experience a 3-month sustained change in their EDSS score compared to placebo. The results of the ITT analysis were confirmed by results for the Evaluable population.

Mean Number of Active T1 Gadolinium-enhanced Lesions per Subject per Scan at 96 Weeks

The mean number of active T1 gadolinium-enhanced (Gd+) lesions per subject per scan during 96 weeks was analysed using a non-parametric ANCOVA (analysis of covariance) model on ranked data with fixed effects for treatment group and region and baseline T1 Gd+ lesion count as a covariate. Treatment differences and the associated 95% and 97.5% CI were calculated for each treatment group comparison.

The adjusted mean number of active T1 gadolinium-enhancing lesions per subject per scan at Week 96 for the cladribine HD, cladribine LD, and placebo groups were 0.11, 0.12 and 0.91, respectively. Subjects treated with cladribine HD experienced a significantly

lower mean number of active T1 Gd+ lesions per subject per scan when compared to those treated with placebo during the 96-week treatment period (adjusted mean of 0.11 versus 0.91; p<0.001). This represents an 88% relative reduction in mean number of active T1 Gd+ lesions per subject per scan for cladribine HD versus placebo.

Similarly, subjects treated with cladribine LD experienced a significantly lower mean number of active T1 Gd+ lesions per subject per scan when compared to those treated with placebo during the 96-week treatment period (adjusted mean of 0.12 versus 0.91; p<0.001). This represents an 86% relative reduction in mean number of active T1 Gd+ lesions per subject per scan for cladribine LD versus placebo. The results of the ITT analysis were confirmed by results of the Evaluable population which also demonstrated a highly statistically significant difference in favour of both cladribine HD versus placebo and cladribine LD versus placebo (p<0.001 in each case).

Mean Number of Active T2 lesions per Subject per Scan at 96 Weeks

The mean number of active T2 lesions per subject per scan during 96 weeks was analysed using a non-parametric ANCOVA model on ranked data with fixed effects for treatment group and region and baseline T1 Gd+ lesion count as a covariate. Baseline T1 Gd+ lesion count was used as the covariate as there was no available baseline data for this parameter.

The adjusted mean number of active T2 lesions per subject per scan at Week 96 for the cladribine HD, cladribine LD, and placebo groups were 0.33, 0.38 and 1.43, respectively. Subjects treated with cladribine HD experienced significantly lower mean number of active T2 lesions per subject per scan when compared to those treated with placebo during the 96-week treatment period (adjusted mean of 0.33 versus 1.43; p<0.001). This represents a 77% relative reduction in the mean number of active T2 lesions per subject per scan versus placebo. Similarly, subjects treated with cladribine LD experienced significantly lower mean number of active T2 lesions per subject per scan when compared to those treated with placebo during the 96-week treatment period (adjusted mean of 0.38 versus 1.43; p<0.001). This represents a 73% relative reduction in the mean number of active T2 lesions per subject per scan versus placebo. The results of the ITT analysis were confirmed by results for the Evaluable population, which also demonstrated a highly statistically significant difference in favour of the cladribine HD group versus the placebo group, and the cladribine LD group versus the placebo group (p<0.001 for both comparisons).

Mean Number of CU Lesions per Subject per Scan at 96 Weeks

It was stated that this measure provides maximal information on lesion activity in the brains of MS patients by incorporating both T2 weighted and post-gadolinium weighted T1 image information. The mean number of CU lesions per subject per scan during 96 weeks was analysed using a non-parametric ANCOVA model on ranked data with fixed effects for treatment group and region and baseline T1 Gd+ lesion count as a covariate. Baseline T1 Gd+ lesion count was used as the covariate as there was no available baseline data for CU lesions.

The mean number of CU lesions per subject per scan at Week 96 for the cladribine HD, cladribine LD, and placebo groups were 0.38, 0.43 and 1.72, respectively. Subjects treated with cladribine HD experienced significantly lower mean number of CU lesions per subject per scan when compared to those treated with placebo during the 96-week treatment period (adjusted mean of 0.38 versus 1.72; p<0.001). This represents a relative reduction of 78% in the mean number of CU lesions per subject per scan versus placebo. Similarly, subjects treated with cladribine LD experienced significantly lower mean number of CU lesions per subject per scan when compared to those treated with placebo during the 96-week treatment period (adjusted mean of 0.43 versus 1.72; p<0.001). This represents a

relative reduction of 74% in the mean number of CU lesions per subject per scan versus placebo.

The results of the ITT analysis were confirmed by results for the Evaluable population which also demonstrated a highly statistically significant difference in favour of both the cladribine HD group and cladribine LD groups compared to the placebo group ($p<0.001$ for both comparisons).

Tertiary Efficacy Endpoints

Time to First Qualifying Relapse at Week 96

The time to first qualifying relapse during 96 weeks of treatment was analysed using a Cox proportional hazards model with fixed effects for treatment group and region. The hazard ratio (HR) of time to first qualifying relapse in the cladribine HD group versus the placebo group, and the cladribine LD group versus the placebo group, and the associated 95% and 97.5% CI were estimated.

Treatment with cladribine HD and cladribine LD tablets demonstrated treatment benefit by significantly forestalling the time to first qualifying relapse compared to placebo ($p<0.001$, HR=0.46, and $p<0.001$, HR=0.44, respectively. The Kaplan-Meier estimate of the 15th percentile time to first qualifying relapse was 406 days for cladribine HD, 408 days for cladribine LD, and 141 days for placebo, representing a prolongation of 265 days and 267 days, respectively. The Kaplan-Meier estimate of the 25th percentile time to first qualifying relapse was 768 days for cladribine LD and 325 days for placebo, representing a prolongation 443 days. The 25th percentile was not reached for cladribine HD indicating that it would take more than 768 days for 25% of the population in this treatment group to have a qualifying relapse.

The results for the Evaluable population were similar to that of the ITT analysis. Treatment with cladribine HD and cladribine LD significantly prolonged the time to first qualifying relapse compared to placebo ($p<0.001$, HR=0.43, and $p<0.001$, HR=0.42, respectively).

Proportion of Subjects with No Active T1 Gadolinium-Enhanced Lesions at Week 96

This endpoint was analysed using a logistic regression model with fixed effects for treatment group and region. The odds ratio (OR) of remaining active T1 Gd+ lesion-free for the cladribine HD group versus the placebo group, and the cladribine LD group versus the placebo group, and the associated 95% CI and 97.5% CI were estimated.

The proportion of subjects with no active T1 Gd+ lesions at Week 96 was 91.0% for the cladribine HD group, 86.8% for the cladribine LD group, and 48.3% for the placebo group. A statistically significantly greater proportion of subjects in both the cladribine HD and cladribine LD groups versus subjects in the placebo group had no active T1 Gd+ lesions at Week 96. The OR was 11.79 ($p<0.001$; 95% CI of the OR=8.07, 17.24) for cladribine HD compared to placebo, indicating that the odds of subjects in the cladribine HD group experiencing no active T1 Gd+ lesions during the 96 weeks of therapy was 11.79 times of the odds of subjects in the placebo group.

The OR was 7.57 ($p<0.001$; 95% CI of the OR=5.37, 10.67) for the cladribine LD group compared to the placebo group, indicating that the odds of subjects in the cladribine LD group experiencing no active T1 Gd+ lesions during the 96 weeks of therapy was 7.57 times of the odds of subjects in the placebo group. The results of the ITT analysis were confirmed by results for the Evaluable population which also demonstrated a highly statistically significant difference in favour of both the cladribine HD and cladribine LD groups compared to placebo ($p<0.001$ for both comparisons).

Proportion of Subjects with No Active T2 Lesions at Week 96

The proportion of subjects with no active T2 lesions at Week 96 was 62.5% for the cladribine HD group, 61.7% for the cladribine LD group, and 28.4% for the placebo group. A statistically significantly greater proportion of subjects in both the cladribine HD and cladribine LD groups versus the placebo group had no active T2 lesions at Week 96. The OR was 4.35 ($p<0.001$; 95% CI of the OR=3.27, 5.78) for the cladribine HD group compared to the placebo group, indicating that the odds of subjects in the cladribine HD group experiencing no active T2 lesions during the 96 weeks of therapy was 4.35 times of the odds of subjects in the placebo group.

The OR was 4.17 ($p<0.001$; 95% CI of the OR=3.13, 5.55) for the cladribine LD group compared to the placebo group, indicating that the odds of subjects in the cladribine LD group experiencing no active T2 lesions during the 96 weeks of therapy was 4.17 times of the odds of subjects in the placebo group. The results of the ITT analysis were confirmed by results for the Evaluable population, which also demonstrated a highly statistically significant difference in favour of both the cladribine HD and cladribine LD groups compared to placebo ($p<0.001$ in each case).

Mean Change in T2 Lesion Volume (mm^3) from Baseline to Week 96

Subjects in the cladribine HD group experienced a statistically significant decrease in the T2 lesion volume (mm^3) compared to the placebo group during the 96-week treatment period (adjusted mean of -2560.94 versus - 1813.23; $p<0.001$). This represents a 41% relative reduction in T2 lesion volume (mm^3). Similarly, subjects in the cladribine LD group experienced a highly statistically significant decrease in T2 lesion volume (mm^3) compared to the placebo group during the 96-week treatment period (adjusted mean of -2247.94 versus -1813.23 mm^3; $p<0.001$). This represents a 24% relative reduction in T2 lesion volume (mm^3). The results of the ITT analysis were confirmed by results for the Evaluable population, which also demonstrated a highly statistically significant difference in favour of both the cladribine HD and cladribine LD groups compared to placebo ($p<0.001$ in each case).

Mean Number of T1 Hypointense Lesions per Subject per Scan at 96 Weeks

Subjects in the cladribine HD group experienced significantly lower mean number of T1 hypointense lesions per subject per scan when compared to the subjects in the placebo group during the 96-week treatment period (adjusted mean of 6.36 versus 6.93; $p<0.001$). This represents a relative reduction of 8% in the mean number of T1 hypointense lesions per subject per scan. Similarly, subjects in the cladribine LD group experienced significantly lower mean number of T1 hypointense lesions per subject per scan compared to subjects in the placebo group during the 96-week treatment period (adjusted mean of 6.73 versus 6.93; $p<0.001$). This represents a relative reduction of 3% in the mean number of T1 hypointense lesions per subject per scan. The results of the ITT analysis were confirmed by results for the Evaluable population, which also demonstrated a statistically significant difference in favour of both the cladribine HD and cladribine LD groups compared to the placebo group ($p<0.001$ in each case).

Mean Change from Baseline in T1 Hypointense Lesion Volume (mm^3) at Week 96

The mean change from baseline in T1 hypointense lesion volume (mm^3) was similar across the cladribine HD, cladribine LD, and placebo groups (1768.84, 1380.23, and 1311.69 mm^3, respectively). No statistically significant differences were observed for each treatment comparison. Results of the Evaluable population analysis were similar to the results of the ITT analysis.

Proportion of Subjects Rescued at Week 96

A rescue option of treatment with Rebif (44 µg tds) was available for all randomised subjects if a subject experienced more than one qualifying relapse, and/or experienced a sustained increase in their EDSS of ≥one point, or ≥1.5 points if baseline EDSS was 0 (over a period of three months or greater), during a calendar year beginning at Week 24. The portion of subjects rescued was analysed using a logistic regression with fixed effects for treatment group and pseudo-region. The OR in each of the cladribine groups versus the placebo and the associated 95% and 97.5% confidence intervals were estimated.

A greater proportion of subjects in the placebo group (6.2%) were rescued up to Week 96 compared to the cladribine HD and cladribine LD groups (2.0%, and 2.5%, respectively). The odds of being rescued was 0.31 times lower for the cladribine HD group when compared to the placebo group (p=0.003). The odds of being rescued was 0.40 times lower for the cladribine LD group when compared to the placebo group (p=0.011). The results of the Evaluable population analysis were similar to that of the ITT population.

Other Efficacy Analyses

Number of Qualifying Relapses by Assessment Time and Treatment Groups

The annualised qualifying relapse rates for each of the four 24-week time intervals (baseline [Trial Day 1] to Week 24, Week 24 to Week 48, Week 48 to Week 72, and Week 72 to Week 96) was lower for cladribine HD and cladribine LD compared to placebo. The results of the ITT analysis were confirmed by results for the Evaluable population.

Proportion of Qualifying Relapse-Free Subjects by Assessment Time and Treatment Group

The proportion of qualifying relapse-free subjects for the following time intervals: Baseline to Week 24, Baseline to Week 48, Baseline to Week 72, and Baseline to Week 96 was greater for HD and cladribine LD compared to placebo. The results of the ITT analysis were confirmed by results for the Evaluable population.

Proportion of Subjects Without a 3-month Sustained Change in EDSS Score at Week 96

The proportion of subjects without a 3-month sustained change in EDSS score at Week 96 was 84.9% for the cladribine HD group, 85.7% for the cladribine LD group, and 79.4% for the placebo group. The OR of not having a 3-month sustained change in EDSS score was 1.46 (p=0.032; 95% CI=1.03, 2.07) for the cladribine HD group compared to the placebo group, indicating that the odds of subjects treated in the cladribine HD without a 3-month sustained change in EDSS score during the 96 weeks of therapy was 1.46 times of the odds of subjects treated in the placebo group. The OR of not having a 3-month sustained change in EDSS score was 1.55 (p=0.016; 95% CI=1.09, 2.22) for the cladribine LD group compared to the placebo group, indicating that the odds of subjects treated in the cladribine LD group without a 3- month sustained change in EDSS score during the 96 weeks of therapy was 1.55 times of the odds of subjects treated in the placebo group. The results of the ITT analysis were confirmed by results for the Evaluable population.

Notably statistical significance was not reached for the cladribine HD group versus the placebo group.

Number of Active T1 gadolinium-enhancing (Gd+) lesions by Assessment Time and Treatment Group

The number of active T1 Gd+ lesions per subject per scan was displayed for Week 24, Week 48 and Week 96 . Results showed the mean number of active T1 Gd+ lesions was consistently lower for active cladribine treatment compared to placebo for each time point. The mean number of active T1 Gd+ lesions at Week 24 was 0.07 for the cladribine

HD and for the cladribine LD groups, and 0.97 for the placebo group. The mean number of active T1 Gd+ lesions at Week 48 was 0.04 for the cladribine HD group, 0.11 for cladribine LD, and 0.69 for placebo. The mean number of active T1 Gd+ lesions at Week 96 was 0.07 for the cladribine HD group, 0.06 for the cladribine LD, and 0.38 for the placebo group. Results from the Evaluable population were similar to that of the ITT population.

Proportion of Subjects with No Active T1 Gd+ Lesions by Assessment Time and Treatment Group

The proportion of subjects with no active T1 Gd+ lesions was displayed for Week 24, Week 48 and Week 96. Results demonstrated that active cladribine treatment displays a greater proportion of subjects with no active T1 Gd+ lesions compared to placebo for each time point. The proportion of subjects with no active T1 Gd+ lesions at Week 24 was 95.6% for the cladribine HD group, 93.8% for the cladribine LD group, and 66.6% for the placebo group. The proportion of subjects with no active T1 Gd+ lesions at Week 48 was 96.1% for the cladribine HD group, 92.4% for the cladribine LD group, and 69.3% for the placebo group. The proportion of subjects with no active T1 Gd+ lesions at Week 96 was 94.1% for the cladribine HD group, 94.2% for the cladribine LD group, and 77.1% for the placebo group. The results of the ITT analysis were confirmed by results for the Evaluable population.

Number of Active T2 lesions by Assessment Time and Treatment Group

The number of active T2 lesions per subject per scan were analysed for Week 24, Week 48 and Week 96. These results demonstrated that the mean number of active T2 lesions was lower for cladribine treatment compared to the placebo group for each time point. The mean number of active T2 lesions at Week 24 was 0.33 for the cladribine HD group, 0.45 for the cladribine LD group, and 1.59 for the placebo group. The mean number of active T2 lesions at Week 48 was 0.15 for the cladribine HD group, 0.26 for the cladribine LD group, and 0.88 for the placebo group. The mean number of active T2 lesions at Week 96 was 0.27 for the cladribine HD group, 0.22 for the cladribine LD group, and 0.87 for the placebo group. Results from the Evaluable population were similar to that of the ITT population.

Proportion of Subjects with No Active T2 Lesions by Assessment Time and Treatment Group

The proportion of subjects with no active T2 lesions was analysed for Week 24, Week 48 and Week 96. Results demonstrated that cladribine treatment displays a greater proportion of subjects with no active T2 lesions compared to the placebo group for each time point. The proportion of subjects with no active T2 lesions at Week 24 was 78.1% for the cladribine HD group, 76.2% for the cladribine LD group, and 49.7% for the placebo group. The proportion of subjects with no active T2 lesions at Week 48 was 87.9% for the cladribine HD group, 82.4% for the cladribine LD group, and 58.6% for the placebo group. The proportion of subjects with no active T2 lesions at Week 96 was 82.2% for the cladribine HD and cladribine LD groups, and 61.6% for the placebo group. The results of the ITT analysis were similar to that of the Evaluable population.

Change from Baseline in T2 Lesion Volume (mm^3) by Assessment Time and Treatment Group

The results from the observed T2 lesion volume (mm^3) at Baseline, Week 24, Week 48 and Week 96, and the change in T2 lesion volume from Baseline to each of these three time points indicate that active cladribine treatment resulted in a greater T2 lesion volume decrease compared to the placebo group for each time point.

Number of CU lesions by Assessment Time and Treatment Group

The number of CU lesions per subject per scan was analysed for Week 24, Week 48 and Week 96. Results demonstrated that the mean number of CU lesions was consistently

lower for active cladribine treatment compared to the placebo group for each time point. The mean number of CU lesions at Week 24 was 0.38 for the cladribine HD group, 0.49 for the cladribine LD group, and 1.91 for the placebo group. The mean number of CU lesions at Week 48 was 0.16 for the cladribine HD group, 0.30 for the cladribine LD group, and 1.12 for the placebo group. The mean number of CU lesions at Week 96 was 0.29 for the cladribine HD group, 0.23 for the cladribine LD group, and 0.97 for the placebo group. Results from the Evaluable population were similar to that of the ITT population.

Proportion of Subjects with No CU Lesions at Week 96

A greater proportion of subjects in the cladribine HD (60.7%) and cladribine LD (59.6%) groups had no CU lesions at Week 96 compared to the placebo (26.1%) group. The OR of remaining CU lesion-free was 4.51 ($p<0.001$; 95% CI=3.38, 6.00) for the cladribine HD group compared to the placebo group, indicating that the odds of subjects treated with cladribine HD experiencing no CU lesions during the 96 weeks of therapy was 4.51 times of the odds of subjects treated with the placebo group. The OR was 4.27 ($p<0.001$; 95% CI=3.20, 5.71) for the cladribine LD group compared to the placebo group, indicating that the odds of subjects treated with the cladribine LD group experiencing no CU lesions during the 96 weeks of therapy was 4.27 times of the odds of subjects treated with the placebo group. The results of the ITT analysis were confirmed by results for the Evaluable population.

Efficacy Results in Subpopulations

Regional Effects

Subject randomisation in the CLARITY trial occurred within the 155 investigational sites in 32 countries. To address potential variability in patient populations and medical practices across geographic regions, a regional analysis was performed for the primary efficacy endpoint, qualifying relapse rate at 96 weeks. Clinical trial sites were assigned to one of five geographic regions: 1) the Americas (24 clinical trial sites), 2) Eastern Europe (34 clinical trial sites), 3) Western Europe (55 clinical trial sites), 4) Russia (23 clinical trial sites), or 5) the rest of the world (19 clinical trial sites). The analysis taking into account of region into the statistical model did not reveal any notable difference in treatment effect across the regions.

Subpopulation Analyses

Subpopulation analyses were conducted on the CLARITY trial population to assess the effects of gender, age, prior DMD, and baseline disease on the primary endpoint, qualifying relapse rate at 96 weeks.

Gender

MS is a disease with a predilection to affect women disproportionately to men by roughly a 2:1 ratio. Indeed, 898 subjects or 67.7% of the enrolled and randomized trial population in CLARITY were female, and this gender preference was consistent across treatment groups, with 68.8%, 68.4%, and 65.9% female subjects in the cladribine tablets LD and HD treatment groups, and placebo group, respectively.

A subgroup analysis was undertaken to determine if the treatment effect of cladribine tablets on the primary endpoint was comparable across the genders. Female subjects in the cladribine tablets LD treatment group experienced a 54.8% relative reduction in annualised relapse rate (ARR) compared with the female placebo subjects (0.14 versus 0.31, respectively; $p < 0.001$). Female subjects in the cladribine tablets HD treatment group experienced a 48.4% relative reduction in ARR as compared with female placebo subjects (0.16 versus 0.31, respectively; $p < 0.001$).

Cladribine tablets-treated male subgroups also were significantly superior to the male placebo subjects. Male subjects in the cladribine tablets LD treatment group experienced a 60.5% relative reduction in ARR compared with the male placebo subjects (0.15 versus 0.38, respectively; $p < 0.001$). Male subjects in the cladribine tablets HD treatment group experienced a 68.4% relative reduction in ARR as compared with male placebo subjects (0.12 versus 0.38, respectively; $p < 0.001$).

These results indicate that both cladribine tablets treatment regimens are similarly effective compared to placebo in the reduction of ARR in female and male subjects with RRMS.

Age Group

Subjects were stratified according to the following 5 age ranges at trial entry: ≤ (n=33), which identifies a very late adolescent/early adult RRMS cohort, 21 - 34 (n=428), 35 - 44 (n=474), 45 - 54 (n=309), and ≥ 55 (n=82) years of age. Both cladribine LD and HD tablet treatment subgroups were significantly superior to the placebo treatment subgroup for the age ranges 21 – 34 ($p<0.001$ for both groups), 35 - 44 ($p<0.001$ for both groups) and 45 -54 years of age ($p<0.001$ and $p=0.009$, respectively), achieving relative reductions in ARR ranging from 43.3% to 73.3%.

Prior DMD Therapy

Cladribine tablets treatment DMD naïve subgroups were both significantly superior to the placebo DMD treatment-naïve subgroup. DMD treatment-naïve subjects in the cladribine tablets LD treatment group experienced a 61.2% relative reduction in ARR compared with the DMD treatment-naïve placebo subjects (0.12 versus 0.31, respectively; $p < 0.001$). DMD treatment-naïve subjects in the cladribine tablets HD treatment group experienced a 58.1% relative reduction in ARR as compared with DMD treatment-naïve placebo subjects (0.13 versus 0.31, respectively; $p < 0.001$).

DMD treatment-experienced cladribine tablets treatment groups were both significantly superior to the DMD treatment-experienced placebo subjects. DMD treatment experience subjects in the cladribine tablets LD treatment subgroup experienced a 45.0% relative reduction in ARR compared with the DMD treatment experienced placebo subjects (0.22 versus 0.40, respectively; $p = 0.0013$). DMD treatment-experienced subjects in the cladribine tablets HD treatment group experienced a 57.5% relative reduction in ARR as compared with DMD treatment experienced placebo subjects (0.17 versus 0.40, respectively; $p < 0.001$).

Relapse History in 12 Months Prior to Trial Entry

Both cladribine tablet treatment groups were significantly superior to the placebo subjects across all baseline ARR ranges. Subjects in the cladribine tablets LD treatment group and in the cladribine tablets HD treatment group experienced treatment responses on the order of 48.2% and 51.9% relative reductions in ARR compared to placebo treatment for subjects in the baseline ARR ≤ 1 category (0.14 and 0.13 versus 0.27, respectively, both p values < 0.001); 68.9% and 57.8% relative reductions in ARR compared to placebo treatment for subjects in the baseline ARR = 2 category (0.14 and 0.19 versus 0.45, respectively, both p values < 0.001); and 65.7% and 76.1% relative reductions in ARR compared to placebo treatment for subjects in the baseline ARR ≥ 3 category (0.23 versus 0.67, $p = 0.006$ and 0.16 versus 0.67, $p=0.004$, respectively).

Analysis of Clinical Information Relevant to Dosing Recommendations

A single active treatment regimen was evaluated in the Scripps-C trial, the parenteral cladribine 2.1 mg/kg dose that was administered SC. Since, in the Scripps-C trial, a

parenteral cladribine treatment dose that was comparable to the cladribine tablets LD PO dose was not evaluated and since the CLARITY trial represents the most relevant and pivotal efficacy data the sponsor presented an analysis of clinical information relevant to dosing recommendations that focused mainly on comparisons between the cladribine LD and HD treatment regimens in the CLARITY trial.

In the CLARITY trial, both cladribine tablets treatment groups, the LD and HD treatment regimens, were significantly superior compared to placebo in the treatment of RRMS. Both treatment groups met the primary endpoint, were statistically significant and the treatment effect was medically relevant. In addition both cladribine tablets treatment groups were similarly significantly effective with respect to reduction in risk of sustained disability progression on EDSS. Across a spectrum of key secondary brain MRI outcomes that included lesion, relative reductions, and proportions of subjects MRI-activity free for T1 Gd+, active T2, and CU lesions, treatment with both cladribine tablet regimens resulted in similar efficacy results. Thus, with regard to these pre-specified primary and secondary efficacy outcomes, the cladribine tablets LD and HD treatment regimens were similarly effective. The cladribine tablet HD treatment regimen demonstrated a distinct efficacy advantage over the cladribine tablet LD treatment regimen with regard to the pre-specified MRI outcome, change from baseline to last evaluation in T2 lesion volume.

It should be noted that the cladribine tablets treatment regimens differ neither in the daily dosage administered, nor in the dose per treatment course, as each treatment course is designed to deliver a target dose of 0.875 mg/kg oral cladribine. Rather the distinction between treatment regimens is the difference of two versus four treatment courses administered during the first 48-week treatment period for the cladribine tablets LD and HD treatment regimens, respectively. During the second 48-week re-treatment period, treatment regimens are identical and two treatment courses are administered for either treatment regimen. Therefore, the sponsor presented analysis of differences in efficacy outcomes between dosing regimens at the conclusion of the first 48-week period (that is, prior to re-treatment). Table 6 summarises the CLARITY efficacy data at time of assessment.

Table 6: Comparison of efficacy results during the first 48 weeks of the CLARITY trial

Parameter	Time Period / Timepoint	Cladribine tablets 5.25 mg/kg N = 456	Cladribine tablets 3.5 mg/kg N = 433	placebo N = 437
Relapse				
Annualized Qualifying Relapse Rate (95% CI)	Baseline - Week 24	0.21 (0.15, 0.28)	0.18 (0.12, 0.24)	0.44 (0.35, 0.53)
	Week 24 – Week 48	0.12 (0.07, 0.17)	0.17 (0.11, 0.22)	0.32 (0.24, 0.40)
Proportion of Qualifying Relapse Free Subjects	Baseline - Week 24	91.2%	92.1%	82.8%
	Week 24 - Week 48	86.0%	85.9%	74.1%
Magnetic Resonance Imaging				
Mean Number of T1 Gd+ lesions (SD)	Week 24	0.07 (0.42)	0.07 (0.33)	0.97 (2.49)
	Week 48	0.04 (0.26)	0.11 (0.51)	0.69 (1.67)
Mean Number Active T2 lesions (SD)	Week 24	0.33 (0.82)	0.45 (1.14)	1.59 (3.22)
	Week 48	0.15 (0.56)	0.26 (0.74)	0.88 (1.64)
Mean Number Combined Unique Lesions (SD)	Week 24	0.38 (0.91)	0.49 (1.17)	1.91 (3.88)
	Week 48	0.16 (0.60)	0.30 (0.83)	1.12 (2.13)

There was no clear evidence based on 48-week relapse data that suggested a relative advantage in treatment between treatment regimens with regard to mean annualised relapse rate or the proportion of relapse-free subjects.

Post hoc Analyses

A subgroup analysis was performed to distinguish benefit between cladribine treatment groups based on the level of disease activity on MRI at baseline.

Treatment with cladribine tablets LD and HD resulted in a statistically greater proportion of subjects who were disease activity-free over 96 weeks compared to placebo. However, subjects with greater baseline disease activity on brain MRI, defined by the presence of T1 Gd+ lesions, were more likely to be disease activity-free when treated with the HD dose versus the LD dose compared to placebo (39.5% versus 24.6% compared to 3.9% for placebo, both p values < 0.001; odds ratios [95% CI]: 16.03 [6.18, 41.59] versus 8.04 [3.04, 21.31], respectively).

Evaluator's comments

Given the data were presented for evaluation, the cladribine HD (5.25 mg/kg) and cladribine LD (3.5 mg/kg) tablets were both shown to be significantly superior to the placebo group in the treatment of RRMS. Both cladribine tablets treatment groups met their primary endpoint and treatment with cladribine tablets was significantly effective compared to the placebo group across a broad spectrum of clinical and MRI efficacy outcomes. The primary efficacy endpoint of this 96-week, double-blind, placebo-controlled trial was the qualifying relapse rate at 96 weeks for the ITT population. The relative risk of cladribine (5.25 mg/kg or 3.5 mg/kg) to the placebo group was 0.43 ($p < 0.001$ in both cases), indicating that subjects treated with cladribine were 57% less likely to have a qualifying relapse than subjects in the placebo group.

The two clinical secondary endpoints, proportion of qualifying relapse-free subjects and disability progression at 96 weeks, supported the positive primary efficacy endpoint results.

There was no clear evidence based on 48-week relapse data that suggested a relative advantage in treatment between treatment regimens with regard to mean annualised relapse rate or the proportion of relapse-free subjects.

Subjects in the cladribine HD and cladribine LD groups were statistically significantly ($p<0.001$) more likely to remain qualifying relapse-free at Week 96 compared to the placebo group. The odds of subjects treated with cladribine HD and cladribine LD remaining qualifying relapse-free during the 96 weeks of therapy was 2.43 and 2.53 times of the odds of subjects treated with placebo, respectively. In addition, the proportions of qualifying relapse-free subjects from baseline to Week 24, from baseline to Week 48, from baseline to Week 72 and from baseline to Week 96 were consistently higher for the cladribine HD and cladribine LD groups compared to the placebo group.

A clinically relevant endpoint, disability progression, was evaluated as time sustained change in EDSS score over 96 weeks. Treatment with cladribine HD and cladribine LD significantly ($p=0.026$ and $p=0.018$, respectively) prolonged the time to sustained change in EDSS score compared to the placebo group. These results indicate that subjects treated with cladribine HD and cladribine LD were 31% and 33% less likely to experience a 3-month sustained change in their EDSS score during the trial as compared to the placebo group, respectively.

Other relapse related measures showed similar benefit as observed in the primary efficacy endpoint analysis.

MRI-Related Parameters

The 3 pre-specified MRI secondary endpoints were analysed in a pre-specified hierarchical order and included the mean number of active T1 gadolinium-enhancing lesions per subject per scan, mean number of active T2 lesions per subject per scan, and mean number of CU lesions per subject per scan. Results of the analyses for the 3 MRI parameters provide additional support to the positive primary efficacy endpoint results.

Other MRI endpoints analysed displayed similar results in favour of the cladribine HD group and the cladribine LD group compared to the placebo group.

Treatment with cladribine HD and cladribine LD was more effective for each of the three measures of activity (active T1 Gd-enhancing, active T2, and CU lesions) for the proportion of subjects with no lesion activity at Week 96, and the mean change in T2 lesion volume at Week 96.

Study MS Scripps-C

The objective of the study was to evaluate the efficacy and safety of cladribine in subjects with RRMS. The protocol described a randomised, parallel group, double-blind, placebo-controlled design in 50 subjects (planned) with RRMS. Subjects were to be treated with either cladribine 2.1 mg/kg (total cumulative dose) or the corresponding volume of saline vehicle (placebo) administered SC. Subjects were to be treated with up to six 5-day courses of cladribine (0.07 mg/kg/day) for a total dosage of 2.1 mg/kg (one 5-day course per month for six months). The study design included eight monthly courses of treatment with study medication, the last two of which were to be placebo *unless* any of the earlier courses had been replaced with placebo due to the subject not meeting dosing requirements.

Subjects were to be followed in a double-blind manner for a total of 18 months, including the dosing period. After the conclusion of the double-blind period, subjects were eligible to receive a course of treatment with cladribine in an open-label fashion. This included re-treatment (former cladribine 2.1 mg/kg subjects) and new patients. This study was conducted from May 1994 to February 1997.

During Months 1 through 8 of the trial, each subject received a total of six monthly 5-day injections of cladribine 0.07 mg/kg per day plus two months placebo or eight months placebo, followed by a 10-month observation interval during which safety and efficacy evaluations continued. Cladribine-treated subjects received a total dosage of 2.1 mg/kg (that is, six treatments with active drug).

Corticosteroids or other immunosuppressive medications such as cyclophosphamide, azathioprine, or cyclosporine, were to be discontinued at least three months before trial entry. The Scripps-C protocol did not define an accepted use of corticosteroids during the trial. Similarly, there was no provision for rescue therapy specified within the protocol, as treatment options for RRMS were limited at the time the trial was conducted.

Study evaluations were performed in a blinded fashion. Investigators who were not blinded to treatment reviewed clinical laboratory data and delayed or discontinued study treatment if, in their opinion, a subject could not safely be treated with cladribine, for example, because of haematological abnormalities possibly related to the known pharmacologic effects of cladribine.

Efficacy was based on MRI of the brain, clinical relapses (exacerbations) as determined by investigator assessment, the EDSS, and the Scripps Neurology ratings Scale (SNRS). Safety was based on the incidence, severity, and type of treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, and body weight.

This was a prospective, blinded study conducted by the Scripps Research Institute. The study data were collected prospectively, and the resultant data published (Romine at al 1999)[16], although a statistical analysis plan was not available, and as such no study report was written. Data were reanalysed retrospectively by the current sponsor following a third-party audit. For the purposes of the case study report provided for evaluation in the submission, the main focus of the analysis was on the 18-months of double-blind treatment. Data collection for the 18 months of the double-blind trial to be included in the analyses was conducted from March through June 1998.

[16] Romine JS, Sipe JC, Koziol JA, Zyroff J, Beutler E. A double-blind, placebo controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. Proc Assoc Am Phy 1999; 111: 35-44.

Endpoints

The original protocol designated the co-primary endpoints of mean number of active lesions per subject per year as determined by MRI and an index based on the SNRS score and, as a secondary variable, annualised relapse rate. In a meeting with representatives of the FDA on 2 March 1998, the FDA indicated that MRI was an important endpoint and could serve as the basis for the evaluation of efficacy. Therefore, in the final clinical trial report the primary efficacy criterion was the presence or absence of T1 brain lesions at the Final evaluation assessed by gadolinium-enhanced MRI.

Secondary efficacy criteria included annualised exacerbation rates, the change from baseline to Final evaluation in the number and volume of T1 enhanced and volume of T2 lesions, as well as changes from baseline to Final evaluation in the EDSS and SNRS scores. There was no adjustment for multiplicity in the Scripps-C trial.

Study Participants

The CLARITY and Scripps-C trials recruited relatively similar cohorts of subjects with clinically definite RRMS. The Scripps-C trial required all subjects to fulfil criteria of established MS according to the earlier Poser criteria, which is primarily driven by the advent of a second clinical relapse disseminated in space and time. Both trials sought to recruit subjects with clinically-active, relapsing disease.

In the Scripps-C trial, a clinical relapse was defined as follows:

"The appearance of new symptoms or worsening of an existing symptom, attributable to MS and accompanied by progression of objective neurologic findings. To be scored as a relapse, the alterations must have been preceded by disease stability or improvement lasting for at least 30 days, and the worsening of symptoms must have lasted 24 hours and occurred in the absence of fever."

In the Scripps-C trial, neurological status also was recorded using the SNRS. Subjects were eligible to enter the trial with a baseline neurological disability in the range of 0 to 5.5, inclusive, on the EDSS. The Scripps-C trial enrolled subjects ranging in age from 21 to 55 years old.

Of the 52 subjects enrolled, informed consent to retrospectively capture data for the purposes of preparing the clinical study report was obtained from 49 (26 cladribine 2.1 mg/kg, 23 placebo) subjects.

Statistical and Analytical Plans

The original protocol designated an index of clinical disease as calculated from each subject's SNRS scores (an appropriate weighted average over the course of one year) as one primary efficacy variable. The second primary endpoint was the mean number of active lesions per subject per year as determined from the MRI scans. Secondary efficacy variables relating to clinical relapses (exacerbations) were to be a proportion of subjects who experienced exacerbations and characteristics of the severity of exacerbations.

Sample Size Determination

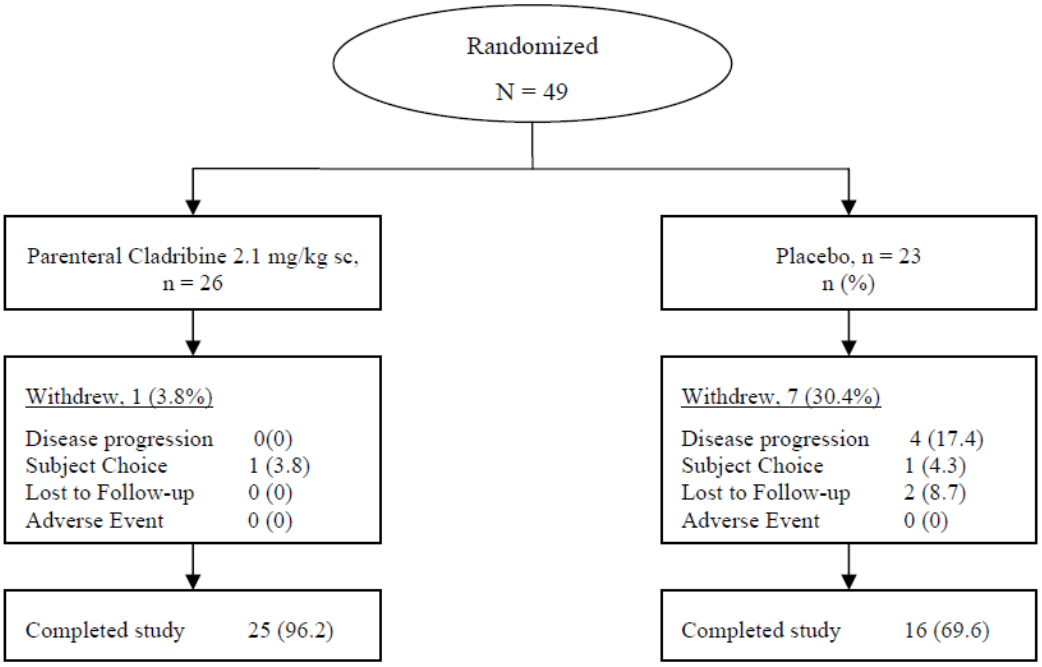
The sample size computation was based on an assumed standard deviation (SD) of 10 units for index of clinical disease in both treatment groups. The planned sample size of 25 subjects per treatment group would provide 85% power based on a one-sided significance level of 0.05 to detect an average decline of 7.5 units in the placebo group relative to the cladribine group. The power calculations for the second primary endpoint were based on the assumption that the number of active lesions observed in any subject follows a Poisson distribution with parameter λ_p or λ_c depending or whether that subject would be in the placebo group or the cladribine group, respectively.

Comparisons between treatment groups (placebo versus cladribine 2.1 mg/kg) of the percents of subjects with T1 enhanced lesions at the Final evaluation (primary efficacy analysis) were made using Fisher's Exact Test. Treatment differences in change and percent change in T2 lesion volume from baseline to Final evaluation as well as in the volume and number of T1 enhanced lesions at the Final evaluation were assessed by the Wilcoxon Rank Sum Test. The Wilcoxon Rank Sum Test was also used to assess treatment differences in mean changes in EDSS and SNRS scores at the Final evaluation. For Months 7-18 and 1-18, treatment effect on the mean annualised exacerbation rates was assessed by an analysis of variance model. For Months 1-18, the probability of being exacerbation-free was assessed using a logistic regression. Time-to-first exacerbation of MS was analysed using survival analysis methods. Kaplan-Meier estimates for probabilities of failure were computed for each group and the statistical significance of a treatment effect was tested using the log rank test. All statistical tests were two-sided. Descriptive statistics were used to evaluate safety data.

Subjects Disposition

Subjects (male or female; aged 21 to 55 years) were eligible if they had clinically definite or laboratory supported RRMS for at least one year with ≥ 2 relapses (exacerbations) in the previous two years and EDSS ≤ 5.5. In the Scripps-C trial 52 subjects were enrolled, however only 49 Scripps' subjects (26 cladribine-treated subjects and 23 placebo-treated subjects) gave written consent to use their data. Data from subjects who denied their permission were not used. Therefore, the efficacy and safety data for subjects randomised in this trial available for analysis comprise 49 subjects. The disposition of subjects participating in the Scripps-C trial is displayed in Figure 2.

Figure 2: Disposition of subjects in the Scripps-C trial



Efficacy Results

The protocol specified that subjects were to be enrolled with EDSS scores ≤5.5. Eleven subjects were enrolled with EDSS scores >5.5, five in the placebo group and six in the cladribine 2.1 mg/kg group.

All 49 subjects randomised to double-blind therapy received at least one dose of study drug, and were included in the efficacy analyses. However, subjects who were otherwise evaluable were not included in analyses of one or more variables at one or more time points due to missed visits or missing data.

Primary and secondary efficacy endpoint results for the Scripps-C trial are summarised in Table 7. Cladribine treatment was significantly more effective in reducing the annualised relapse rate compared to placebo. From Months 1 to 18, the annualised relapse rate was 0.69 versus 1.18 (p=0.011), respectively, corresponding to a relative reduction of 41.5% in cladribine-treated subjects versus placebo. Over Months 7 to 18, the annualised relapse rate was 0.60 versus 1.37 (p=0.005), respectively, corresponding to a relative reduction of 56.2% in cladribine-treated subjects versus placebo. The proportion of relapse-free subjects treated with cladribine was 38.5%, compared to placebo at 17.4% (p=0.034), and patients were 2¼ times more likely to be relapse-free on cladribine treatment. At final evaluation cladribine treatment was statistically significantly superior to placebo with regard to proportion of subjects with T1 Gd+ lesions, mean volume and number of T1 Gd+ lesions, and median change in T2 lesion volume. The response appeared to be persistent. Significant effects were still observed 12 months following cessation of therapy, and at 18 months, 52% of placebo-treated subjects, but only 8% of cladribine-treated subjects had enhancing lesions on MRI (p=0.001).

Table 7: Summary of primary and secondary efficacy results - Scripps-C trial

Efficacy Criteria	Placebo N = 23	Parenteral Cladribine 2.1 mg/kg N = 26	p-value
MRI gadolinium-enhanced T1 lesions at final evaluation			
Proportion of subjects with lesions, % [a]	52	8	0.001
Mean volume of T1 Gd+ lesions, mm^3 [b] (SD)	258 (558)	4 (18)	<0.001
Mean number of T1 Gd+ lesions [b] (SD)	1.7 (2.71)	0.1 (0.27)	<0.001
Change from baseline to final evaluation			
EDSS score [b,c] (SD)	-0.1 (1.66)	-0.3 (0.94)	NS
SNRS score [b,d] (SD)	3.6 (10.74)	3.2 (9.22)	NS
Median change in T2 lesion volume, cm^3 [b]	1.42	-0.12	0.012
Annualized Exacerbation Rate (Covariate Adjusted Means)			
Months 1-18 Reduction in annualized exacerbation rate Months 1-18 relative to placebo, % [g]	1.18 41.5	0.69	0.011[e]
Months 7-18 Reduction in annualized exacerbation rate Months 1-18 relative to placebo, % [g]	1.37 56.2	0.60	0.005[e]
Proportion of Exacerbation-Free Subjects			
Proportion, %	17.4	38.5	0.034[f]
Time to first relapse			
Time to first relapse, 50th percentile, days (weeks)	316 (45.1)	356 (50.9)	NA

Source: Refer to Section 5.3.5.1 Scripps-C Clinical Trial Report: Table 14; Figure 8.

[a] p-value based on Fisher's two-sided Exact Test (active vs. placebo).
[b] p-values based on Wilcoxon Rank Sum Test (active vs. placebo); NS (not significant).
[c] EDSS score can range from 0 to 10; negative change indicates improvement.
[d] SNRS score can range from 0 to 100; positive change indicates improvement.
[e] p-value based on the analysis of variance model.
[f] p-value based on the multiple logistic regression model.
g Reduction relative to placebo (%) was calculated as |placebo – active|/placebo x100%.

MRI Brain Scans: T1 Enhanced Lesions

Presence of T1 Enhanced Lesions

Approximately 50% of subjects in either treatment group had T1 enhanced lesions at baseline. There was no apparent effect on the incidence of T1 enhanced lesions through Month 3. Between Months 4 to 6, the incidence of T1 enhanced lesions in the cladribine 2.1 mg/kg group was lower than the placebo group, but the difference was not statistically significant. At Month 6, the difference was statistically significant ($p<0.001$, Fisher's Exact Test, two-sided) and remained so both for the remaining interval up to 18 months and at the final study visit.

Volume of MRI T1 Enhanced Lesions

The baseline mean (SD) T1 enhanced lesion volume was comparable for the placebo group, 347 (888) mL, and the cladribine 2.1 mg/kg group, 275 (621) mL. The cladribine 2.1 mg/kg group had a substantial decrease (improvement) in mean T1 enhanced lesion volume over time to nearly zero, 4 (18) mL, whereas the placebo group T1 enhanced lesion volume remained essentially equal to baseline, 258 (558) mL. The difference between the groups at the Final evaluation was statistically significant ($p<0.001$, Wilcoxon Rank Sum Test).

Number of MRI T1 Enhanced Lesions

The mean number of MRI T1 enhanced lesions also decreased from baseline for both treatment groups, with a greater decrease observed in the cladribine 2.1 mg/kg group. The difference between the two groups was statistically significant ($p\leq0.002$, Wilcoxon Rank Sum Test) at Months 6 and 18, and at the Final evaluation. Changes in the number and volume of T1 enhanced lesions following treatment with cladribine were consistent with the changes observed for the primary efficacy variable – proportion of subjects with T1 enhanced lesions.

Change from Baseline in EDSS Score at Final Evaluation

During the 18-month period, the mean change from baseline to Final evaluation in EDSS scores was small in both treatment groups. Because there was no change from baseline in mean EDSS score in the placebo group, no significant treatment effects for cladribine on the change in EDSS score were found or could be expected to be found in this study.

Change From Baseline in SNRS Score at Final Evaluation

During the 18-month period, the mean change from baseline to Final evaluation in SNRS scores was small in both treatment groups. Since subjects with RRMS tend to have their neurologic disability scores return to baseline, the absence of a difference between the cladribine and placebo groups would be expected. In addition, the small number of subjects in both groups may explain why no difference was seen.

Extent of Exacerbations of MS

Although the study was randomised, there was an imbalance in the number of pre-study exacerbations occurring in the cladribine group. Five (19%) cladribine-treated subjects and zero (0%) placebo-treated subjects had four exacerbations in the prior 12 months. As time progressed, there was a clear trend toward increased number of exacerbations in the placebo group as compared to the cladribine group. There was a significantly lower annualised exacerbation rate for cladribine 2.1 mg/kg-treated subjects compared to placebo-treated subjects during Months 7 to 18 and for Months 1 to 18, whereas a higher exacerbation rate was noted for Months 1 to 6.

Analysis Performed Across Trials

The efficacy results from the CLARITY and Scripps-C trials were not integrated due to the different route of administration, dosing schedule, trial methodology and number of patients.

Persistence of Efficacy

The CLARITY and Scripps-C trials provide data in relation to the persistence of efficacy and the effects of re-treatment with cladribine. In the CLARITY trial, subjects randomised to cladribine were treated at Study Day 1, Week 5, Week 9 (cladribine tablets 5.25 mg/kg treatment group only), and Week 13 (cladribine tablets 5.25 mg/kg treatment group only)

and again at Week 48 and Week 52. The subjects were then followed until Week 96. In the Scripps-C trial, subjects were given 6 courses of treatment over six to eight months and then followed to Month 18.

The primary endpoints for the CLARITY and Scripps-C trials, annualized relapse rate and the mean number of T1 Gd+ lesions, respectively, are presented by time period in Tables 8 and 9 respectively.

Table 8: Annualised Relapse Rate[1] by time period in the CLARITY trial

Time period	Cladribine tablets 5.25 mg/kg N = 456		Cladribine tablets 3.5 mg/kg N = 433		placebo N = 437	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Baseline to 24 weeks	0.21	(0.15, 0.28)	0.18	(0.12, 0.24)	0.44	(0.35, 0.53)
Week 24 to Week 48	0.12	(0.07, 0.17)	0.17	(0.11, 0.22	0.32	(0.24, 0.40)
Week 48 to Week 72	0.16	(0.10, 0.21)	0.14	(0.09, 0.20)	0.36	(0.27, 0.45)
Week 72 to Week 96	0.10	(0.05, 0.14)	0.08	(0.04, 0.12)	0.21	(0.14, 0.27)

[1] Annualized relapse rate calculated as (the number of relapses x 365.25)/number of days on trial

Table 9: Mean number of T1 Gd+ lesions in the Scripps-C trial

Time period	Parenteral Cladribine 2.1 mg/kg			placebo		
	N	Mean no. of T1 Gd+ lesions	SD	N	Mean no. of T1 Gd+ lesions	SD
Baseline	26	1.6	(2.25)	23	2.8	(6.26)
Month 6	26	0.0	(0.20)	23	2.1	(2.97)
Month 12	25	0.0	(0.20)	22	2.1	(2.21)
Month 18	24	0.1	(0.28)	18	1.4	(2.59)
Final Evaluation	26	0.1	(0.27)	23	1.7	(2.71)

Safety

Introduction

Integrated Safety Summary

The sponsor presented an *Integrated Summary of Safety*. This consisted of a pooled analysis of data from all completed placebo-controlled studies to facilitate an evaluation of the safety of oral cladribine in MS. In addition, this analysis sought to conduct a pooled analysis of available safety data from ongoing, blinded, placebo-controlled studies to complement that from the completed studies. The two ongoing double-blind studies are summarised across all subjects, as these studies are still blinded. The cut-off date for the safety data to be used for the summaries of these ongoing studies was January 19 2009.

The integrated safety database includes data from the 5 placebo-controlled studies, CLARITY, Scripps-C, MS-Scripps, MS-001 and Scripps-B.

In addition to the integrated safety analysis based upon the 5 completed, placebo-controlled studies, safety data were provided by the following 2 double-blind placebo-controlled studies, ONWARD and CLARITY Extension, which are ongoing at the time of this submission:

Ongoing Studies

ONWARD

This is a Phase II, multicentre, randomised, double-blind, placebo-controlled trial (study 26593). The study is designed to evaluate the safety, tolerability, and efficacy of low dose oral cladribine tablets as an add-on therapy to injectable interferon-beta (IFN-beta) treatments (Rebif 44 µg; Avonex 30 µg, or Betaferon 250 µg), in MS subjects with active disease.

CLARITY Extension

This is a multicentre, double-blind, parallel group, extension study to evaluate the safety and tolerability of cladribine in subjects with multiple sclerosis who have completed study 25643 (CLARITY). Additionally, data on cladribine effectiveness is sought. In this ongoing study, treatment allocation depends on the initial treatment randomisation in study 25643 (CLARITY): subjects randomised to placebo during Trial 25643, were randomised to oral cladribine (2 courses; 1.75 mg/kg/yr) throughout the 2-year extension trial; subjects randomised to cladribine tablets 3.5 mg/kg during Trial 25643 were randomised in a 2:1 allocation ratio to receive either oral cladribine (2 courses; 1.75 mg/kg/yr) or placebo throughout the 2-year extension trial; and, subjects randomised to cladribine tablets 5.25 mg/kg during Trial 25643 were randomized in a 2:1 allocation ratio to receive either oral cladribine (2 courses; 1.75 mg/kg/yr) or placebo throughout the 2-year extension trial.

ORACLE MS

Study 28821 ('ORACLE MS') is a Phase III, randomised, double-blind, placebo-controlled, multicentre, 3-treatment group trial to evaluate the safety and efficacy of oral cladribine in subjects with early disease who have experienced a first clinical demyelinating event and who are at high risk of converting to MS. No safety data were available from this study at the time of data cut-off for this analysis

Patient Exposure

Across the 5 completed studies, of the 1587 subjects included in this analysis, 1108 subjects (69.8%) received at least one dose of cladribine and 479 subjects (30.2%) were treated only with placebo. The majority of the subjects (> 93%) were enrolled in the CLARITY and MS-001 studies, with < 7% being enrolled in Scripps-B, Scripps-C and MS-Scripps. Although the CLARITY study contributed the majority of subjects to this integrated analysis approximately 15% of subjects receiving the proposed dosages, cladribine tablets 3.5 mg/kg and 5.25 mg/kg, were treated in one of the parenteral cladribine studies. The explanation for the fact that a substantial number of subjects received cladribine at dose lower than 3.5 mg/kg or higher than 5.25 mg/kg in the CLARITY study was that cladribine was administered in 10 mg tablets and the number of tablets was based on weight, using 10-kg weight ranges, therefore subjects within a weight range received an actual dose which was slightly lower or higher than the 3.5 mg/kg or 5.25 mg/kg doses assigned by randomisation.

Across the 5 completed studies, 1108 subjects have been treated with cladribine with a median cumulative dose of 4.42 mg/kg (range: 0.2, 11.3 mg/kg). Within a median time of treatment of 362.0 days (range: 1, 1704 days), cladribine was actually administered on a median of 30.0 days (range: 1, 70). Cladribine subjects had a median time on study of 1.82

years (range: 0.0, 6.4 years) for a total of 1070.6 subject-years on treatment. The majority of the exposure occurred among subjects who received a cumulative dose of > 3.5 – 5.25 mg/kg (493.7 subject-years) or > 5.25 – 7.0 mg/kg (378.2 subject-years), most of whom were treated in the CLARITY study. The median time on study among the placebo subjects (1.82 years) was the same as that for all cladribine subjects. The time on study was observed to be higher for the > 7-8.75 and >8.75 mg/kg dose ranges.

Subjects participating in the ONWARD and CLARITY Extension trials have median actual dosing days of 15.0 days (range: 1, 33 days) and 10.0 days (range: 1, 15 days), respectively, and time on treatment of 81.5 days (range: 1, 406 days) and 33.0 days (1, 382 days), respectively. Median time on study is 1.08 years (range: 0.0, 1.8 years) and 0.29 years (range: 0.0, 1.1 years) for total subject-years of exposure of 25.0 and 40.9 among the ONWARD and CLARITY Extension subjects, respectively.

Common Adverse Events

Completed Studies

Common adverse events that were reported at an incidence proportion that was at least 2.0% higher among all cladribine-treated subjects versus placebo are summarised by preferred term (PT) in Table 10.

Table 10: Common TEAEs occurring at any time during the studies (at an incidence proportion ≥ 2.0% higher among all cladribine treated subjects versus placebo

	0 mg/kg Subjects (n=479) Events (n=2490)		Cladribine >0 mg/kg Subjects (n=1108) Events (n=8487)	
Preferred Term	Subjects n (%)	Events n (%)	Subjects n (%)	Events n (%)
Headache	93 (19.4)	228 (9.2)	286 (25.8)	710 (8.4)
Lymphopenia	8 (1.7)	11 (0.4)	236 (21.3)	318 (3.7)
Upper respiratory tract infection	54 (11.3)	96 (3.9)	176 (15.9)	315 (3.7)
Nasopharyngitis	55 (11.5)	94 (3.8)	152 (13.7)	235 (2.8)
Nausea	53 (11.1)	72 (2.9)	148 (13.4)	222 (2.6)
Fatigue	38 (7.9)	48 (1.9)	111 (10.0)	187 (2.2)
Back pain	34 (7.1)	52 (2.1)	103 (9.3)	131 (1.5)
Depression	19 (4.0)	21 (0.8)	86 (7.8)	102 (1.2)
Contusion	9 (1.9)	11 (0.4)	69 (6.2)	86 (1.0)
Pyrexia	13 (2.7)	16 (0.6)	63 (5.7)	81 (1.0)
Leukopenia	3 (0.6)	6 (0.2)	65 (5.9)	81 (1.0)
Injection site bruising	8 (1.7)	13 (0.5)	50 (4.5)	82 (1.0)
Rash	7 (1.5)	7 (0.3)	49 (4.4)	65 (0.8)
Multiple sclerosis	5 (1.0)	10 (0.4)	43 (3.9)	65 (0.8)
Alopecia	6 (1.3)	6 (0.2)	37 (3.3)	45 (0.5)
Muscular weakness	5 (1.0)	5 (0.2)	36 (3.2)	50 (0.6)
Lymphocyte count decreased	0 (0.0)	0 (0.0)	39 (3.5)	56 (0.7)
Herpes zoster	1 (0.2)	1 (0.0)	32 (2.9)	33 (0.4)

Among all subjects treated with cladribine, 18 common treatment-emergent adverse effects (TEAEs) were identified as occurring at an incidence proportion at least 2.0% greater than that observed among the subjects receiving only placebo: headache (25.8% vs 19.4%), lymphopenia (21.3% vs 1.7%), upper respiratory tract infection (15.9% vs 11.3%), nasopharyngitis (13.7% vs 11.5%), nausea (13.4% vs 11.1%), fatigue (10.0% vs 7.9%), back pain (9.3% vs 7.1%), depression (7.8% vs 4.0%), contusion (6.2% vs 1.9%), leucopenia (5.9% vs 0.6%), pyrexia (5.7% vs 2.7%), injection site bruising (4.5% vs 1.7%), rash (4.4% vs 1.5%), multiple sclerosis (3.9% vs 1.0%), alopecia (3.3% vs 1.3%), lymphocyte count decreased (3.5% vs 0.0%), muscular weakness (3.2% vs 1.0%) and herpes zoster (2.9% vs 0.2%).

Lymphopenia was reported as a TEAE in 21.3% of all cladribine-treated subjects, as compared to 1.7% of subjects who received only placebo. When examined by cumulative dose range, a dose response was observed with incidences among the cladribine-treated subjects increasing along with the cumulative oral dose: >0-1.75 mg/kg (6.1%), 1.75-3.5 mg/kg (15.2%), >3.5-5.25 mg/kg (20.6%), and >5.25-7.0 mg/kg (28.4%). Leucopenia was also reported at a higher rate among cladribine-treated subjects (5.9%) versus placebo subjects (0.6%) and a dose response was observed when examined by cumulative dose range.

TEAEs coded to the system organ class (SOC) *Neoplasms – Benign, Malignant and Unspecified* were reported for 41 (3.7%) of all cladribine-treated subjects as compared to 8 (1.7%) of placebo subjects. The most common event in this SOC was uterine leiomyoma observed in 10 (0.9%) of cladribine-treated subjects and in 1 (0.2%) placebo-treated subject.

Probably related adverse events reported by ≥ 1% of all cladribine-treated subjects include lymphopenia (12.3%), lymphocyte count decreased (2.3%), nausea (2.3%), injection site bruising (2.3%), leucopenia (2.2%), injection site haemorrhage (2.1%), injection site pain (1.6%), headache (1.2%), injection site irritation (1.1%), and herpes zoster (1.1%).

Ongoing Studies

Due to the relatively small sample size in the ONWARD trial at the time of this analysis (60 subjects), all reported events occurred at an incidence ≥ 1%. However, the most frequently reported events, those occurring in ≥ 10% of subjects, include headache (20.0%), nausea (16.7%), lymphopenia (15.0%), nasopharyngitis (11.7%), urinary tract infection (11.7%), fatigue (11.7%), and white blood cell (WBC) count decreased (10.0%).

Among subjects included in the CLARITY Extension trial at the time of this analysis, no preferred term was reported among ≥ 10% of subjects. Commonly reported events (≥ 1% to < 10% of subjects) include headache (7.3%), lymphopenia (7.1%), nasopharyngitis (4.7%), nausea (3.9%), upper respiratory tract infection (3.4%), urinary tract infection (2.6%), insomnia (2.4%), fatigue (2.2%), back pain (1.9%), diarrhoea (1.9%), pain in extremity (1.9%), lymphocyte count decreased (1.5%), cough (1.7%), influenza (1.7%), rhinitis (1.7%), leucopenia (1.5%), gastroenteritis (1.3%), arthralgia (1.1%), abdominal pain upper (1.1%), toothache (1.1%) and bronchitis (1.1%).

Among the 60 subjects in the ONWARD study at the time of the analysis, probably related events reported by ≥ 3 subjects included lymphopenia (9 subjects, 15.0%), WBC count decreased (5 subjects, 8.3%) and lymphocyte count decreased (4 subjects, 6.7%).

Among the 465 subjects in the CLARITY Extension study at the time of analysis, probably related events reported by ≥ 3 subjects included lymphopenia (23 subjects, 4.9%) and leucopenia (3 subjects, 0.6%).

Serious Adverse Events and Deaths

Completed Studies

Seven subjects died during the placebo-controlled phase of the studies, one subject participating in the MS-Scripps study and six subjects participating in the CLARITY study.

Overall, one or more serious adverse events (SAEs) were reported in 12.9% of all cladribine-treated subjects and 8.1% of all placebo subjects. SAEs were most frequently reported in the SOC of *Infections and Infestations*, occurring in 4.6% of cladribine-treated subjects and 1.9% of placebo subjects. SAEs were also commonly reported (≥ 1% of subjects in either treatment group) in the SOCs of *Nervous System Disorders* (2.3% cladribine-treated vs 1.7% placebo), *General Disorders and Administration Site Conditions* (1.4% vs 0.6%), *Injury, Poisoning and Procedural Complications* (1.3% vs 0.4%), *Gastrointestinal Disorders* (1.2% vs 0.6%), *Hepatobiliary Disorders* (1.1% vs 0.8%), *Neoplasms Benign, Malignant and Unspecified* (1.4% vs 0.0%), and *Psychiatric Disorders* (0.5% vs 1.5%).

SAEs occurring in five SOCs were considered deserving of further attention: *Infections and Infestations*, *Neoplasms Benign, Malignant and Unspecified*, *Hepatobiliary Disorders*, *Skin and Subcutaneous Tissue Disorders* and *Blood and Lymphatic System Disorders*.

Infections and Infestations

One or more serious infections occurred in 4.6% of cladribine-treated subjects and 1.9% of placebo subjects. SAEs (PTs) reported by 2 or more cladribine-treated subjects included pneumonia, urinary tract infection, herpes zoster, pyelonephritis, sepsis, upper respiratory tract infection, urosepsis, adnexitis and cellulitis. The incidence of these events was observed to be higher among the cladribine-treated subjects versus placebo.

Herpes Zoster

Three (0.3%) cases of serious herpes zoster infection occurred among the cladribine-treated subjects and none among the placebo subjects. Two additional subjects reported serious zoster infections including one subject with herpes zoster infection neurological and one subject with herpes zoster oticus.

Unusual Serious Infections

Unusual serious infections observed in the cladribine-treated group included: one subject (MS-Scripps study, parenteral cladribine 2.8 mg/kg (cladribine tablets dose equivalent 7.0 mg/kg)) experienced disseminated pelvic coccidioidomycosis; one subject (CLARITY study, cladribine tablets 5.25 mg/kg) experienced inguinal actinomycosis following bilateral inguinal hidradenitis abscess surgery; one subject (CLARITY study cladribine tablets 5.25 mg/kg) experienced pulmonary tuberculosis.

Sepsis

Three cladribine-treated subjects developed sepsis compared to no placebo subjects. However, it should be noted that one subject developed sepsis while receiving placebo in the MS-Scripps study. Since this subject later received cladribine, the SAE was attributed to cladribine in the integrated analysis. There were reports of two subjects with urosepsis in the parenteral studies.

Neoplasms Benign, Malignant and Unspecified

Serious neoplasia occurred in 15 (1.4%) of cladribine-treated subjects compared to no placebo subjects.

Six cladribine-treated subjects (0.5%) experienced serious uterine leiomyoma. All but one of these events originated from the CLARITY study. One case of serious case of uterine leiomyoma was attributed to cladribine therapy in the analysis as a result of cladribine administration in the long-term extension, although the event occurred during placebo treatment of the double-blind phase the Scripps-C study.

Uterine leiomyomas are very common and many are asymptomatic. The incidence increases with the approach of menopause. Considering the population incidence of uterine leiomyoma of 12.8 per 1000 women-years, these observations do not exceed the published incidence. However, given the limited data available this event would warrant ongoing surveillance.

Five cases of cutaneous malignancy were reported: 3 cases of basal cell carcinoma, 1 case of "nasal skin growth", and 1 case of malignant melanoma. Two cases of cervical carcinoma in situ were reported. There was 1 report of ovarian cancer, and one report of metastatic pancreatic carcinoma.

As neoplasias may take several years to develop, longer term surveillance is required to assess whether there is an increased malignancy risk with cladribine therapy.

Hepatobiliary Disorders

Serious hepatobiliary disorders occurred in 12 (1.1%) of cladribine-treated subjects compared to 4 (0.8%) placebo subjects. There were three SAEs reported as "hepatitis" in the cladribine-treated subjects versus one in the placebo group. Of the three SAEs in cladribine-treated subjects, two occurred in subjects randomised to 5.25 mg/kg of cladribine tablets and one occurred in a subject randomised to cladribine tablets 3.5 mg/kg.

Skin and Subcutaneous Tissue Disorders

Four cladribine-treated subjects (0.4%) experienced 5 SAEs (hydradenitis, lichen sclerosus, purpura, generalised rash, skin reaction) whereas no SAEs were experienced in the placebo group. None of these events were reported as reasons for treatment discontinuation. One of these events was assessed as possibly an allergic skin reaction to cladribine.

Blood and Lymphatic System Disorders

Nine cladribine-treated subjects (0.8%) experienced SAEs compared with no placebo subjects in this SOC. The most common SAEs were lymphopenia in 4 (0.4%), thrombocytopenia in 2 (0.2%), and neutropenia in 2 (0.2%) cladribine-treated subjects. Serious anaemia, bone marrow failure, coagulopathy, leucopenia and pancytopenia were each reported in 1 subject (0.1%). All of the serious lymphopenias occurred in the cladribine >3.5-5.25 mg/kg cumulative dose range.

Ongoing Studies

No deaths had occurred in either of the ongoing studies, ONWARD or CLARITY Extension as of the data cut-off of January 19, 2009.

Events of Special Interest

Myelodysplastic syndrome

Myelodysplastic syndrome (MDS) is a rare disease, mainly presenting in elderly people as otherwise unexplained long-lasting cytopenia that may consist of anything from slight anaemia to severe pancytopenia. MDS may develop *de novo*, but may be a rare potential complication of treatment with cytotoxic chemotherapeutic agents or occupational exposure to environmental solvents and other chemicals.

Two subjects with MS treated with parenteral cladribine, who received 7.0 mg/kg cladribine tablets equivalent, developed probable myelodysplasia several years following treatment. Each subject was exposed to other factors reportedly linked to the development of myelodysplasia. One MS subject treated with cladribine tablets 0.875 mg/kg developed myelodysplastic changes on bone marrow aspirate within six months of treatment, which is not consistent with the known natural history of myelodysplasia. According to the assessment of an independent expert haematologist, what was initially reported as myelodysplasia was likely reactive bone marrow changes caused by tuberculosis infection rather than true myelodysplasia.

While the pathogenesis of MDS remains speculative, the published case reports of myelodysplasia in patients with leukaemic and lymphoproliferative disorders treated with cladribine suggest that cladribine treatment may be associated with the development of myelodysplasia.

Cardiac Safety

The cardiac safety of cladribine tablets was assessed in a sub-population of RRMS patients (N=135) from the pivotal Phase III CLARITY trial. This ECG sub-study in the target population of RRMS subjects was designed to evaluate potential acute and/or accumulative effects of cladribine on the ECG time-intervals (RR, PR, QRS, QT, QT interval corrected using Bazett's correction [QTcB], and QT interval corrected using Fredericia's correction [QTcF]) and T-wave morphology, with a particular emphasis on the heart rate-corrected QT interval (QTcF primary; QTcB supportive). Moreover, subjects included in this sub-study underwent PK sampling in order to allow for concentration/QT analysis.

Standard 12-lead ECGs were recorded at the study sites in patients randomised to the ECG-population. These subjects had ECGs collected at Pre-Study Evaluation, Study Day 1 and at Weeks 5, 9, 13, 48 and 52 at the following time points:

• Three ECGs every 15 minutes pre-dose, and

• Two ECGs taken no longer than five minutes apart between 0.5 and three hours post-dosing.

From the results that were available from the CLARITY trial, the ECG evaluation did not indicate any clear effect of cladribine tablets on heart rate, AV conduction, or cardiac depolarisation as measured by the PR and QRS interval durations.

The comparison to placebo, using the visit baseline, showed the greatest mean increase of 2-3 milliseconds (ms) for the 5.25 mg/kg dose group as compared to that day's baseline when dosed at Day 1, Week 9 and Week 13. These results should be interpreted with caution as these changes were not seen on other dosing days. In addition, at several visits across all treatment groups including placebo, there was a temporal, small post-dose increase versus visit baselines in QTcF ranging between 1 to 4 ms.

The time averaged analysis and the ANOVA analysis indicated that there may be a small dose group related effect on cardiac repolarisation, when group comparisons versus QTcF study baseline values are considered. This potential effect of approximately 6-9 ms appeared at Week 9 in the high dose group and persists through Week 52, but does not increase despite continued cladribine administrations at Weeks 13 (high dose group only), 48 and 52. The 5.25 mg/kg dose group trended higher from the start of the study which would indicate that the conditions in this group might have been different than in the low dose or placebo group, which would be consistent with the finding that patients in this treatment group were on average about 5 and 3 years older than patients of the placebo and cladribine low dose group, respectively, and also had a longer history of MS disease duration. QTcF in the high dose group increased 9 ms by Week 13, but was virtually

unchanged from Week 13 to Week 52. It is difficult to draw conclusions about a causal relationship between cladribine administration and the changes noted.

Overall the data showed no clear evidence of an acute cladribine concentration dependent effect on cardiac repolarisation; however the data cannot rule out a small sub-chronic effect in the high dose group only. This potential effect appears at Week 9 in the high dose group when the study baseline analysis is used and persists through Week 52, but despite additional doses at Weeks 48 and Week 52 the increase in QTcF remains essentially unchanged from Week 13.

Laboratory Findings

Lymphopenia

Cladribine causes a potent and preferential reduction of lymphocyte count due to its mechanism of action. Consequently, lymphopenia is an expected effect of cladribine.

Haematological parameters were closely monitored during the cladribine trials.

Table 11 shows the relationship between the incidence of severe lymphopenia and cladribine dose. Increasing dose clearly increases the risk of severe lymphopenia. It should be noted that the two highest dose ranges were not used in the CLARITY trial, and are above the standard dose recommended for MS treatment.

Table 11: Relationship between Grade 3 or 4 lymphopenia and cladribine dose (Integrated Safety Analysis)

Grade 3 or 4 Lymphocyte count n (%)									
>1.75-3.5 mg/kg (n=125)		>3.5-5.25 mg/kg (n=548)		>5.25-7.0 mg/kg (n=359)		>7.0-8.75 mg/kg (n=19)		>8.75 mg/kg (n=24)	
3	4	3	4	3	4	3	4	3	4
39 (31.2)	3 (2.4)	197 (35.9)	25 (4.6)	170 (47.4)	12 (3.3)	15 (78.9)	5 (26.3)	24 (100.0)	10 (41.7)

There appeared to be no correlation between lymphopenia and gender; however, there was a trend suggesting that older subjects experience lymphopenia more frequently and more severely than younger subjects. In the 96-week CLARITY trial, among the 314 subjects in the cladribine groups who developed Grade 3 or 4 lymphopenia, the absolute lymphocyte counts resolved to Grade 0 or 1 in approximately 50% of subjects; the median duration of severe lymphopenia among these subjects was 23.4 weeks for cladribine tablets 3.5 mg/kg and 24.1 weeks for cladribine tablets 5.25 mg/kg. Grade 3 or 4 lymphopenias in 35 subjects were present as Grade 3 or 4 at the time of final evaluation.

Potential long-term effects of cladribine, particularly those that may be affected by prolonged severe lymphopenia, are being further investigated and monitored in a comprehensive ongoing clinical program and Risk Management/Risk Evaluation measures that have been outlined in the Risk Management Plan submitted in the submission.

T lymphocyte sub-populations ($CD3^+$, $CD4^+$, $CD4^+/CD45RO^+$, $CD4^+/CD45RA^+$, $CD8^+$, $CD8^+/CD45RO^+$, $CD8^+/CD45RA^+$), B lymphocytes ($CD19^+$), and NK cells ($CD16^+/CD56^+$) were assessed in a subset of subjects during the course of the 2-year CLARITY trial. A rapid drop was seen in total lymphocyte counts and in all lymphocyte subset counts early in the treatment course; even if the values returned to normal levels, recovery to baseline values was incomplete at the end of the trial. These findings are consistent with the

frequency and prolonged duration of Grade 3 and 4 lymphopenia seen in both cladribine tablets treatment groups.

White Blood Cells

Consistent with the changes in neutrophil and lymphocyte counts, the median absolute WBC count decreased (-1.30 x 10^9/L) during the first year of cladribine treatment and remained below the baseline level at Week 48 (5.30 x10^9/L, range: 1.8; 14.7). Further decreases were observed following retreatment and at Week 96, the median absolute WBC count remained below baseline at 5.00 x10^9/L. No change in median WBC count was observed over the 96-week period among placebo subjects.

Monocytes

In contrast to the lymphocytes and neutrophils, the monocytes at Week 16 demonstrated a mean increase of 14.89% in cladribine-treated subjects compared to a mean increase of 10.88% in placebo. Similarly, at the last assessments, the mean percent increase from baseline for each was 5.55% versus 8.83%, respectively.

Platelets

At Week 48, a median change of -29.00 x10^9/L was observed among the cladribine-treated subjects. At Week 96, the median platelet count observed among the cladribine-treated subjects was at 224.50 x 10^9/L, for a median change from baseline of - 40.00 x10^9/L. No change in median platelet count was observed over the 96-week period among placebo subjects.

Clinical Chemistry

Overall, in the CLARITY study no apparent differences in blood chemistry parameters were observed in the cladribine groups compared to placebo-treated subjects from baseline to Week 96. The median values fluctuated around baseline values throughout the trial. The results ranges were similar across the groups.

Among the cladribine-treated subjects, most of the Grade 3 and 4 abnormalities of AST, ALT and total bilirubin could be explained by confounding factors or co-morbidities.

Safety in Special Populations

The effects of gender, age, and body weight on safety outcomes were evaluated in the integrated analysis.

Gender

Table 12 summarises by gender the incidence of the most frequently observed AEs (≥ 10% of all cladribine subjects) that were reported in excess versus placebo (≥ 2% higher).

Table 12: Incidence of AEs reported in ≥ 10% of all cladribine subjects and in excess versus placebo subjects (≥ 2% higher) by gender

Preferred Term	Cladribine-Treated Males (N = 364) %	Cladribine-Treated Females (N= 744) %	All Cladribine Treated Subjects (N= 1108) %
Headache	20.9	28.2	25.8
Lymphopenia	20.6	21.6	21.3
Upper respiratory tract infection	13.2	17.2	15.9
Nasopharyngitis	12.6	14.2	13.7
Nausea	6.6	16.7	13.4
Fatigue	11.0	9.5	10.0

The most commonly reported AEs, which were also more frequently observed among cladribine-treated subjects versus placebo subjects, were generally reported among male and female study subjects at rates that were consistent with the overall incidence among all cladribine-treated subjects. Exceptions include nausea and headache, which were more frequently (that is, ≥ 5% difference in incidence proportion) observed among female subjects.

Laboratory Results

Changes in the laboratory parameters over time when examined by gender were similar to the overall population.

Age

The most commonly reported AEs (≥ 10% of all cladribine subjects) that were also reported in excess versus placebo (≥ 2% higher) are summarised by age group in Table 13.

Table 13: Incidence of AEs reported in ≥ 10% of all cladribine subjects and in excess versus all placebo subjects (≥ 2.0% higher) by age

Preferred Term	18 years	19 – 25 years	26 – 35 years	36 – 45 years	46 – 55 years	≥ 56 years	All Cladribine Subjects
	N = 3 %	N = 106 %	N = 259 %	N = 432 %	N = 254 %	N = 54 %	N = 1108 %
Headache	33.3	24.5	22.0	26.6	31.1	14.8	25.8
Lymphopenia	0.0	19.8	18.9	21.5	21.3	35.2	21.3
Upper respiratory tract infection	0.0	11.3	17.8	16.9	15.0	13.0	15.9
Nasopharyngitis	0.0	13.2	13.9	14.6	12.6	13.0	13.7
Nausea	0.0	16.0	12.4	13.9	12.6	13.0	13.4
Fatigue	0.0	9.4	6.6	11.1	13.0	5.6	10.0

Age does not appear to have a major influence in the incidence of AEs within specific SOCs or the occurrence of particular AEs, with the notable exception of lymphopenia, which appears to be more common in older subjects.

Safety Related to Drug-Drug Interactions and Other Interactions

Interferon-beta

A drug-drug interaction study (study 26486) with IFN-beta (Rebif) has been conducted. No clinically relevant interaction between cladribine and INF-beta was observed. The ongoing ONWARD study is assessing the effect of co-administration of cladribine with interferon-beta in MS patients. The results of this study will provide information on potential combined effects of the two treatments.

Glucocorticoid Exposure and Cladribine

High doses of glucocorticoids are often used to treat an acute MS relapse. In addition, glucocorticoids are often administered to treat a number of comorbid conditions and have been associated with an increased risk of infections. The sponsor conducted analyses to ascertain whether systemic glucocorticoid exposure may modify the incidence of infection.

Overall, the incidence of events in the *Infections and Infestations* SOC was higher for both placebo and cladribine-treated subjects receiving corticosteroids, compared to the respective groups not receiving corticosteroids, although the incidence of *Infections and Infestations* among placebo subjects treated concomitantly with corticosteroids (51.2%) was comparable to the incidence observed among cladribine subjects treated concomitantly with corticosteroids (52.3%).

The incidence of upper respiratory tract infection including nasopharyngitis and rhinitis along with bronchitis and sinusitis trended to a higher incidence in cladribine-treated subjects receiving concomitant glucocorticoids compared to both cladribine-treated subjects without systemic glucocorticoids and placebo subjects receiving glucocorticoids. The incidence of urinary tract infection was higher in cladribine-treated subjects with concomitant glucocorticoids, but was similar in incidence to placebo subjects receiving glucocorticoids. Gastroenteritis, viral gastroenteritis and herpes zoster were of higher incidence in cladribine-treated subjects with concomitant glucocorticoids as compared to cladribine-treated subjects without concomitant glucocorticoids and compared to placebo subjects receiving concomitant glucocorticoids.

Discontinuation Due to Adverse Events

Among the 1108 subjects treated with cladribine, 63 (5.7%) prematurely discontinued treatment. Events leading to premature treatment discontinuation occurred primarily within the *Blood and Lymphatic System Disorders* and *Investigations* SOCs. Specific AEs leading to premature treatment discontinuation in 2 or more cladribine-treated subjects included: lymphopenia (11 subjects, 1.0%), lymphocyte count decreased (7 subjects, 0.6%), pregnancy (4 subjects, 0.4%), leucopenia (3 subjects, 0.3%), thrombocytopenia (3 subjects, 0.3%), platelet count decreased (3 subjects, 0.3%), lymphocyte count abnormal (2 subjects, 0.2%), and herpes zoster (2 subjects, 0.2%). All other events among the cladribine-treated subjects that led to premature treatment discontinuation represented isolated reports, occurring in just 1 subject each.

Among the 479 subjects treated with placebo, 10 (2.1%) prematurely discontinued treatment. All events among the placebo-treated subjects that led to premature treatment discontinuation represented isolated reports, occurring in just 1 subject each, except for pregnancy which was the reason for discontinuation in 3 subjects.

Among the 60 subjects in the ONWARD trial for whom data were available at the time of analysis, 12 subjects (20.0%) discontinued treatment prematurely due to adverse events. Events leading to premature treatment discontinuation occurred primarily within the *Blood and Lymphatic System Disorders* and *Investigations* SOCs. AEs leading to premature treatment discontinuation in 2 or more cladribine-treated subjects included lymphopenia (7 subjects, 11.7%) and lymphocyte count decreased (2 subjects, 3.3%). All other events among the ONWARD trial subjects that lead to premature treatment discontinuation represented isolated reports.

Among the 465 subjects in the CLARITY Extension trial for whom data were available at the time of this analysis, 1 subject discontinued treatment prematurely due to an adverse event (lymphopenia).

Clinical Summary and Conclusions

Clinical aspects

Pharmacokinetics

The studies presented for evaluation have characterised the PK of cladribine after administration of the HPβCD cladribine tablet over a 5-day treatment course. The elimination of cladribine was shown to be dependent on renal and non-renal routes, where the non-renal elimination consists predominantly of intracellular metabolism, and only to a minor extent hepatic metabolism.

A number of transporters have been identified to have a potential impact on absorption, distribution, and elimination of cladribine. Among them, ABCG2 (BCRP) plays likely the most important role; thus, strong inhibitors of that transporter could potentially increase cladribine bioavailability and should not be co-administered with cladribine.

A modest reduction in total clearance for subjects with different degrees of renal impairment was shown. It is therefore appropriate that caution is recommended when cladribine is used in patients with mild renal impairment. Cladribine tablets should not be recommended in patients with moderate or severe renal impairment.

There is only minor hepatic metabolism of cladribine, however due to the lack of relevant data the sponsor proposes that cladribine tablets are not recommended for use in patients with moderate or severe hepatic impairment. This evaluator agreed with the sponsor's recommendation.

The PK of cladribine is not dependent on age, gender, or body weight.

Pharmacodynamics

The aberrant activation of self-specific T and B cells observed in MS is affected by immunomodulatory treatments that have demonstrated efficacy in relapsing forms of MS. However, unlike other immunomodulatory treatments, cladribine selectively targets and depletes lymphocytes. Therefore, cladribine's mechanism of action, leading to potent and selective reduction of lymphocytes, provides a strong rationale for possible use of this drug in the treatment of MS. The effects of cladribine tablets on T and B lymphocyte reduction, pro-inflammatory cytokines and chemokines, and cellular migration into the CNS may have the potential to interrupt the cascade of events that are central to the pathophysiology of MS and the progression of the disease.

As the mode of action of cladribine has been previously elucidated and well established in other therapeutic areas, no dedicated proof of concept/PD studies have been performed. No new pharmacodynamic studies were provided for evaluation.

Efficacy

Study 25643 (CLARITY)

Given the data were presented for evaluation, the 5.25 mg/kg and 3.5 mg/kg treatment regimens were both shown to be significantly superior to the placebo group in the treatment of RRMS. Both cladribine tablets treatment groups met their primary endpoint and treatment with cladribine tablets was significantly effective compared to the placebo group across a broad spectrum of clinical and MRI efficacy outcomes. The primary efficacy endpoint of this 96-week, double-blind, placebo-controlled trial was the qualifying relapse rate at 96 weeks for the ITT population. The relative risk of cladribine (5.25 mg/kg or 3.5 mg/kg) to the placebo group was 0.43 ($p < 0.001$ in both cases), indicating that subjects treated with cladribine were 57% less likely to have a qualifying relapse than subjects in the placebo group.

The two clinical secondary endpoints, proportion of qualifying relapse-free subjects and disability progression at 96 weeks, supported the positive primary efficacy endpoint results.

There was no clear evidence based on 48-week relapse data that suggested a relative advantage in treatment between treatment regimens with regard to mean annualised relapse rate or the proportion of relapse-free subjects.

Subjects in the cladribine 5.25 mg/kg and cladribine 3.5 mg/kg groups were statistically significantly ($p<0.001$) more likely to remain qualifying relapse-free at Week 96 compared to the placebo group. The odds of subjects treated with cladribine 5.25 mg/kg and cladribine 3.5 mg/kg remaining qualifying relapse-free during the 96 weeks of therapy was 2.43 and 2.53 times of the odds of subjects treated with placebo, respectively. In addition, the proportions of qualifying relapse-free subjects from baseline to Week 24, from baseline to Week 48, from baseline to Week 72 and from baseline to Week 96 were consistently higher for the cladribine 5.25 mg/kg and cladribine 3.5 mg/kg groups compared to the placebo group.

A clinically relevant endpoint, disability progression, was evaluated as time sustained change in EDSS score over 96 weeks. Treatment with cladribine 5.25 mg/kg and cladribine 3.5 mg/kg significantly ($p=0.026$ and $p=0.018$, respectively) prolonged the time to sustained change in EDSS score compared to the placebo group. These results indicate that subjects treated with cladribine 5.25 mg/kg and cladribine 3.5 mg/kg were 31% and 33% less likely to experience a 3-month sustained change in their EDSS score during the trial as compared to the placebo group, respectively.

Other relapse related measures showed similar benefit as observed in the primary efficacy endpoint analysis.

MRI-Related Parameters

The 3 pre-specified MRI secondary endpoints were analysed in a pre-specified hierarchical order and included the mean number of active T1 gadolinium-enhancing lesions per subject per scan, mean number of active T2 lesions per subject per scan, and mean number of CU lesions per subject per scan. Results of the analyses for the 3 MRI parameters provide additional support to the positive primary efficacy endpoint results.

Other MRI endpoints analysed displayed similar results in favour of the cladribine 5.25 mg/kg group and the cladribine 3.5 mg/kg group compared to the placebo group.

Treatment with cladribine 5.25 mg/kg and cladribine 3.5 mg/kg were more effective for each of the three measures of activity (active T1 Gd-enhancing, active T2, and CU lesions)

for the proportion of subjects with no lesion activity at Week 96, and the mean change in T2 lesion volume at Week 96.

Evaluator's comments

The clinical evaluator agreed that data presented for analyses suggest that cladribine may be efficacious in treating RRMS but expressed concern that several key analyses were not presented, making it difficult to draw clear conclusions about the clinical relevance of the findings.

The evaluator's specific concerns in relation to the data presented from Study 25643 (CLARITY) included the following:

1) The number of subjects screened in the study was not presented. The number of subjects who failed screening, and the reasons for screen failure were not presented.

2) There were no dataset analyses describing the time to subjects taking rescue medication. The proportion of subjects taking rescue medication at 96 weeks was presented; however we do not have information about the time points at which rescue was required. This is important given that there was no clear evidence at the 48-week time point that suggested a relative advantage in treatment between treatment regimens with regard to mean annualised relapse rate or the proportion of relapse-free subjects.

3) There were no data presented on the number of relapses in the 96-week study period.

4) There were no datasets outlining the number of relapses that occurred after taking rescue medication while on study.

5) There are a number of variables described to evaluate relapse; however there are no datasets describing the time to relapse. It is therefore difficult to know exactly how many subjects were relapse free at each of the time points analysed.

MS Scripps-C Study

Evaluator's comment

The sponsor has nominated this study as being one of two pivotal studies. The fact that the data were collected prospectively and analysed retrospectively raises concerns about validity, and the ability to draw firm conclusions from results in relation to efficacy.

Efficacy Results

In the MS Scripps-C study the data analysed were derived from the 18- months of double blind treatment. Data collection for the 18 months of the double-blind trial that was included in the analyses was conducted from March through June 1998. This was a small study with only 49 subjects enrolled.

The data showed that cladribine treatment was significantly more effective in reducing the annualised relapse rate compared to placebo. From Months 1 to 18, the annualised relapse rate was 0.69 versus 1.18 ($p=0.011$), respectively, corresponding to a relative reduction of 41.5% in cladribine-treated subjects versus placebo. At final evaluation cladribine treatment was statistically significantly superior to placebo with regard to proportion of subjects with T1 Gd+ lesions, mean volume and number of T1 Gd+ lesions, and median change in T2 lesion volume. The response appeared to be persistent.

Approximately 50% of subjects in either treatment group had T1 enhanced lesions at baseline. There was no apparent effect on the incidence of T1 enhanced lesions through Month 3. At Month 6, the difference was statistically significant ($p<0.001$, Fisher's Exact Test, two-sided) and remained so both for the remaining interval up to 18 months and at the final study visit.

The cladribine 2.1 mg/kg group had a substantial decrease (improvement) in mean T1 enhanced lesion volume over time to nearly zero, 4 (18) mL, whereas the placebo group T1 enhanced lesion volume remained essentially equal to baseline, 258 (558) mL. The difference between the groups at the Final evaluation was statistically significant ($p<0.001$).

The mean number of MRI T1 enhanced lesions also decreased from baseline for both treatment groups, with a greater decrease observed in the cladribine 2.1 mg/kg group. The difference between the two groups was statistically significant ($p \leq 0.002$) at Months 6 and 18, and at the Final evaluation.

Evaluator's comments

The evaluator's specific concerns in relation to the data presented from the MS Scripps-C study included the following:

1) The number of subjects screened in the study was not presented. The number of subjects who failed screening, and the reasons for screen failure were not presented.

2) The sample size is small; only 49 subjects enrolled.

3) The fact that the data were collected retrospectively and then analysed raises concerns about validity and the ability to draw firm conclusions from results.

4) Although the study was randomised, there was an imbalance in the number of pre-study exacerbations occurring in the cladribine group. Five (19%) cladribine-treated subjects and zero (0%) placebo-treated subjects had four exacerbations in the prior 12 months.

The baseline imbalances in terms of number of exacerbations in the 12 months prior to study have the potential to significantly influence results.

5) The protocol specified that subjects were to be enrolled with EDSS scores ≤5.5. Eleven subjects were enrolled with EDSS scores >5.5, five in the placebo group and six in the cladribine 2.1 mg/kg group. This is a major deviation from the protocol in almost a quarter of the subjects enrolled, which brings the validity of results into question.

6) All 49 subjects randomised to double-blind therapy received at least one dose of study drug, and were included in the efficacy analyses. However, subjects who were otherwise evaluable were not included in analyses of one or more variables at one or more time points due to missed visits or missing data. The number of missed visits and missing data brings the validity of results into question.

In response, the sponsor submitted a new Scripps-C clinical study report addressing many of the concerns raised by the clinical evaluator. The new study report was based on source data verification conducted by an independent auditor and included information from an open-label, long-term extension phase in which subjects, either continuing on treatment or without receiving additional treatment, were followed for a further three and a half years. The sponsor also clarified that Scripps-C was a prospective, blinded study. Data were collected prospectively (in source documents) but transcribed to CRFs retrospectively in order to produce a clinical study report for regulatory purposes.

Safety

The most frequently observed events (those occurring in ≥ 10% of cladribine-treated subjects) were headache (25.8% vs 19.4% in placebo), lymphopenia (21.3% vs 1.7%), upper respiratory tract infection (15.9% vs 11.3%), nasopharyngitis (13.7% vs 11.5%), nausea (13.4% vs 11.1%) and fatigue (10.0% vs 7.9%).

Among the 1108 subjects treated with cladribine, 63 (5.7%) prematurely discontinued treatment due to adverse events. Events leading to premature treatment discontinuation occurred primarily within the *Blood and Lymphatic System Disorders* and *Investigations* SOCs. AEs leading to premature treatment discontinuation in two or more cladribine-treated subjects included lymphopenia, lymphocyte count decreased, lymphocyte count abnormal, leucopenia, thrombocytopenia, platelet count decreased, herpes zoster, and pregnancy. Four subjects discontinued treatment due to different types of skin disorders (dermatitis, facial rash, allergic dermatitis, and erythematosus rash); most were mild and responded to drug discontinuation and topical treatment. All other events that led to premature treatment discontinuation among the cladribine-treated subjects were isolated reports, each occurring in only one subject.

Seven subjects died during the controlled phase of the studies: one subject participating in the MS-Scripps trial and 6 subjects participating in the CLARITY trial. The most relevant events were an exacerbation of latent tuberculosis and hepatitis B, both of which led to fatal outcomes. In addition, one subject died from pancreatic cancer. This indicates that treatment with cladribine has the potential for reactivation of chronic and latent infections and possibly the potential for causing malignancies. The remaining four fatalities were not considered as safety concerns.

Overall, at least one SAE was reported in 12.9% of all cladribine-treated subjects and 8.1% of all placebo subjects. Among the cladribine-treated subjects, 3.3% of all events were serious, and among the placebo subjects, 2.8% of all events were serious.

SAEs were most frequently reported in the MedDRA SOC of *Infections and Infestations*, affecting 4.6% of cladribine-treated subjects and 1.9% of placebo subjects.[17] Some serious events, although rare, appear to be of particular interest and occurred only in cladribine-treated subjects: coccidioidomycosis (1 subject; 0.1%), sepsis (3 subjects; 0.3%), urosepsis (2 subjects; 0.2%), and serious upper respiratory tract infections (3 subjects; 0.3%).

The overall frequency of SAEs in the SOC of *Hepatobiliary System Disorders* was similar between the cladribine and placebo-treated groups (0.8% for placebo and 1.1% for cladribine).

Cladribine causes a potent and preferential reduction of lymphocyte count due to its mechanism of action. Consequently, lymphopenia is an expected effect of cladribine. From the safety data obtained in the clinical trials, lymphopenia emerged as the main identified risk; however the other cytopenias remain potential risks.

From the data submitted for evaluation, no firm conclusions can be drawn about a causal relationship between cladribine and the development of malignancies. Further long-term studies are required to understand this risk more fully.

The evaluator's specific concerns in relation to the safety data presented for evaluation include the following:

1) The *Integrated Summary of Safety* did not include safety data from the pharmacokinetic and bioavailability studies.

This was addressed in the sponsor's response to the Clinical Evaluation Report

2) It is a limitation of the CLARITY study design that ECG data were acquired at only one time point on the visit days per individual patient. The study was designed so that ECGs could be captured in one time window of interest only, that is, the expected C_{max} between 0.5 and 3.0 hours after drug administration. Importantly therefore, there are no ECG data available at cladribine T_{max} and steady state time points.

[17] MedDRA = Medical Dictionary for Regulatory Activities

In response, the sponsor provided an Addendum to the CLARITY ECG report documenting that ECGs in the CLARITY trial were indeed collected during the planned time period, and that a considerable amount of ECG data have been captured around the expected maximum exposure times (T_{max}) of cladribine. The great majority of patients (76 out of 97 in the active dose groups) have at least one ECG between 0.5 and 1.0 hour after cladribine administration, which is the expected T_{max} of cladribine in most subjects. In addition, the sampling strategy of capturing ECGs at random times within a pre-specified time window enabled the capture of ECGs, in individual subjects, at different post-dose times at each of their six different study visits. Hence, this approach provided a set of 6 "serial" post-dose ECGs in each individual patient (from each visit) over the total study duration of 52 weeks.

3) Overall the data showed no clear evidence of an acute cladribine concentration dependent effect on cardiac repolarisation; however the data cannot rule out a small sub-chronic effect in the high dose group only.

The sponsor responded noting that approval was not sought for the "high dose" regimen studied in CLARITY. ANOVA results for the point-estimates of the differences to placebo of post-dose QTcF changes from study baseline ranged between -0.79 ms (Week 52) and 5.99 ms (Week 48) in the cladribine "low dose" group with all other values below 5 ms. In the high dose group the point estimates using this analysis tended to be slightly higher and ranged between 2.65 ms (Day 1) and 8.74 ms (Week 48), with values above 5 ms from Week 9 onwards. This apparent elevation did not increase further despite continued cladribine administrations at Weeks 13 (high dose group only), 48 and 52. This would raise doubt as to the causal relationship of the changes noted, especially since there was no drug accumulation at these time points and there was no further increase in QTcF with continued exposure. The lack of effect is further supported by PK/PD analysis and by the outlier analysis.

4) While lymphopenia appears to be the main identified safety risk, the other cytopenias remain potential risks.

In response, the sponsor agreed that mild decreases of RBC parameters, neutrophil and platelet counts occurred during treatment with oral cladribine, but these parameters generally remained within the normal limits. Severe cytopenias other than lymphopenia will be monitored during the post-authorisation safety study, which has a specific endpoint related to the frequency of these events.

5) Given the data available from MS subjects to date it is not possible to draw firm conclusions in relation to a causal association between cladribine treatment and development of MDS. Long-term monitoring is ongoing, and these data will be important in assessing this safety risk further.

The sponsor agreed that long-term safety monitoring will be important to clarify whether or not the development of myelodysplasia (MDS) represents a safety risk for patients with MS who are treated with cladribine tablets. This monitoring will be accomplished through routine pharmacovigilance activities, as well as by the prospective clinical trial registry which will follow patients who have participated in the sponsor's clinical trials for the long-term, and a post-authorisation safety registry - a prospective cohort study.[18]

6) Concomitant systemic glucocorticoids may increase the risk of the development of certain infections when combined with cladribine.

In response, the sponsor noted that the incidence of Infections and Infestations between cladribine- and placebo-treated subjects who received concomitant corticosteroids was comparable (52.3% versus 51.2%). As corticosteroids exert immunosuppressive activity, it is not unexpected to observe an increased risk of infections in both cladribine and placebo-treated subjects. An additive effect on the immune system is not excluded when corticosteroids and cladribine are used concomitantly. This is addressed in the product labeling which states that chronic use of corticosteroids in combination with cladribine is contraindicated.

Benefit risk assessment

Overall the evaluator believed that, in patients with relapsing-remitting MS, the risks associated with cladribine treatment outweigh the benefits. Given the deficiencies in the safety and efficacy data that have been described in this evaluation report, it was not possible to confirm a positive benefit/risk profile for cladribine treatment.

It was therefore recommended that the application for registration of cladribine for the treatment of patients with relapsing-remitting multiple sclerosis should be rejected.

The sponsor subsequently addressed all the concerns raised by the clinical evaluator and it was the sponsor's understanding that these concerns were then considered as resolved.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). The sponsor identified the following areas of risk:

Important identified risks include: lymphopenia, lymphocyte count decreased, herpes infection, and vertigo/tinnitus.

Important potential risks include: myelodysplastic syndrome, severe cytopenias excluding lymphopenia, aplastic anaemia, anaemia haemolytic autoimmune, serious infections, malignancies, exacerbations of TB or exacerbation of chronic infections, teratogenicity/adverse pregnancy outcomes, neurological toxicity (convulsion, muscular weakness, quadriplegia, encephalopathy, demyelination, coma, blindness, vision blurred, loss of consciousness), nephrotoxicity and hepatotoxicity.

[18] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Areas of missing information include developmental defects in offspring, long term studies to evaluate the myelosuppressive effects of cladribine, use in paediatrics, use in patients with compromised immunocompetence and use in patients at risk of malignancies.

The sponsor proposed routine pharmacovigilance for all identified and potential risks. In addition to routine activities, the following additional pharmacovigilance measures were proposed:

- A long term follow-up registry in patients who participated in five sponsor clinical trials,
- a prospective cohort study of patients exposed to cladribine in the post authorisation setting and
- a pregnancy registry to measure the incidence of diverse pregnancy outcomes.

The sponsor also proposed additional risk minimisation activities in addition to product labelling to address the identified risk of severe lymphopenia, herpes infection and the potential risks of serious infections, activation of latent TB or exacerbation of chronic infections and teratogenicity/adverse pregnancy outcomes.[19] These included requiring prescribers to assess haematological status prior to prescribing, providing educational guides to prescribers and patients and organising specific training for prescribers.

The OMSM reviewer considered that the RMP was acceptable after consideration of issues concerning the draft PI which are not within the scope of this AusPAR.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no quality objections to registration. This submission was considered by the PSC on 24 May 2010. While that subcommittee did not object to registration it was noted that the PI recommends dosing based on body weight despite population pharmacokinetic modelling showing that weight is not an influential covariate.

Nonclinical

There were no nonclinical objections to registration. The nonclinical evaluator noted that cladribine has been in clinical use for some time and its safety profile is well known. There was no evidence in the nonclinical dossier that additional toxicity concerns exist with the new formulation and route of administration. Clinical exposures following oral dosing are 2-3 times lower than those obtained from currently registered cladribine products.

The toxicity profile of cladribine is not dissimilar from other registered products for treatment of MS, with kidney, GI tract, spleen, thymus and/or the CNS all target organs for toxicity. Haematological changes of thrombocytopenia, leucopenia and anaemia have been reported with other medicines indicated for MS and these may also be expects with cladribine.

The nonclinical evaluated noted that unlike current treatments for MS cladribine is genotoxic and a carcinogenic potential cannot be excluded.

[19] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Clinical

Pharmacology

Ten studies contributed information on the pharmacology of cladribine. Six of these studies were conducted in patients with MS, other studies enrolled patients with malignancies. Following oral administration $t_{½}$ ranged from 0.5 to 1.5 hours and oral bioavailability was 39 – 43%. A high fat meal led to an increase in T_{max} and reduction in C_{max} of 29% while the AUC was unchanged. Plasma protein binding is low (~ 20%) and independent of concentration. Vd was estimated as from 6.57 to 4.9 L/ kg in patients with haematological malignancies or solid tumours. Cladribine has a high intracellular distribution. It is not known if there is a linear relationship between plasma and intracellular concentration of cladribine.

Mean CL was 45.4 L/h with ~ 60% eliminated renally, including by active excretion. Intracellular metabolism is considered to account for up to 39% of total clearance. Wide variability in the $t_{½}$ was reported with lower half-lives reported in older studies compared with more recent studies. In the PPK analysis the $t_{½}$ was estimated at 23 hours, though studies have reported the $t_{½}$ as low as 5 hours. PK are linear over the dose range 2.5 to 21.5 mg/m^2/day.

The clinical studies included only adults aged from 18 to 65 years. Patients with significant renal impairment were excluded from the MS studies and no PK study specifically studied patients with MS and renal impairment. Due to the low contribution of hepatic metabolism to elimination of cladribine, it is not anticipated that hepatic impairment would significantly alter the PK of cladribine.

Interaction studies with Rebif (interferon-b-1) and pantoprazole were conducted. Neither of these products had a significant effect on the pharmacokinetics of cladribine. The effect of cladribine on the pharmacokinetics of interferon-b-1 was not fully examined but results from 9/15 patients who had data available suggest no interaction.

Cladribine acts as a prodrug, which is phosphorylated intracellularly to the active nucleotide 2-chlorodeoxyadenosine-5'-triphosphate (CdATP). Lamivudine can inhibit phosphorylation of cladribine, thereby reducing its efficacy. Compounds that require intracellular phosphorylation to become active such as lamivudine, zalcitabine, ribarivin, stavudine and zidovudine should not be given concomitantly with cladribine.

Efficacy

Dose-finding studies with an oral formulation of cladribine in MS were not performed. The selection of dose regimen was based on information from studies in MS patients where cladribine was given subcutaneously or intravenously: MS-Scripps; MS-001; Scripps-C. In these studies annual doses between 0.7 and 2.8 mg/kg were given during 5–7 day courses which were repeated from 2-6 times during the year. Exposure corresponding to a subcutaneous or intravenous dose (both 100% bioavailable) of 1.4 mg/kg/year in the first year and 0.7 mg/kg/year in the second year was targeted for an oral formulation.

The pivotal Phase III study (CLARITY study 25643) compared two dosing regimens: 1.75 mg/kg and 3.5 mg/kg in the first 48-week treatment period. Both groups received a total annual dose of 1.75 mg/kg in the second 48-week treatment period. The proposed treatment algorithm based on body weight was designed to approximate doses given in this study. Table 3 shows the proposed dose regimen which is the same as was given in the "low dose" group in the CLARITY study.

The CLARITY study was a multicentre, double-blind, randomised, placebo-controlled trial with three parallel treatment groups randomised 1:1:1. The trial included a pre-trial evaluation period (up to 28 days prior to the start of treatment); an initial treatment period during the first 48 weeks in the trial; and a re-treatment period during the second 48 weeks in the trial. A treatment course was defined as daily administration over 4 to 5 consecutive days of the initial 5 days during a 28-day treatment course.

The primary objective of the trial was to evaluate the efficacy of oral cladribine versus placebo in the reduction of Qualifying Relapse rate at 96 weeks of treatment in subjects with RRMS. A Qualifying Relapse was defined as a 2 grade increase in one or more Kurtzke Functional Systems (KFS) or a one grade increase in two or more KFS, excluding changes in bowel/bladder or cognition, in the absence of fever lasting 24 hours or more and preceded by at least 30 days of clinical stability or improvement. Neurological examination and MRI were performed periodically throughout the 96-week study period. The proportion of qualifying relapse-free subjects and the time to sustained disability progression (using EDSS) were key secondary endpoints. MRI secondary endpoints included the mean number of lesions per patient per scan over 96 weeks for: T1 gadolinium-enhancing lesions; active T2 lesions; and combined unique (CU) lesions defined as new T1 gadolinium-enhancing lesions and/or new or enlarging T2 lesions (without double counting).

Efficacy results are summarised in Table 5. The annualised qualifying relapse rates were 0.15 for cladribine high dose, 0.14 for cladribine low dose, and 0.33 for placebo. Treatment with cladribine high dose resulted in a 54.5% relative reduction in annualised qualifying relapse rate compared to placebo. Treatment with cladribine low dose resulted in a 57.6% relative reduction in annualised qualifying relapse rate compared to placebo. These differences were highly statistically significant for both dose groups compared to placebo. 79.7% of the cladribine low dose group, 78.9% of the high dose group and 60.9% in the placebo group did not have a qualifying relapse during the 96-week study period.

At the end of study 84.9 %, 85.7% and 79.4% of subjects given cladribine high dose, low dose and placebo respectively had not had a 3-month sustained progression in disability as measured using the EDSS. The mean (SD) change in EDSS was 0.02 (1.06) for cladribine high dose, 0.02 (0.84) for cladribine low dose and 0.30 (1.03) for placebo. The Kaplan-Meier survival estimates for time to 3 months of sustained disability progression on EDSS score (10th percentile) were 414 days for both doses of cladribine and 330 days for placebo. The HR for cladribine versus placebo was 0.69 (p= 0.026) for the high dose group and 0.67 (p= 0.018) for the low dose group. At 96 weeks 84.9%, 85.7% and 79.4% of patients in the high dose, low dose and placebo groups respectively did not have a 3-month sustained change in EDSS score. The OR of not having a 3-month sustained change in EDSS score was 1.46 (p= 0.032; 95% CI: 1.03, 2.07) for the high dose versus placebo comparison and 1.55 (p= 0.016; 95% CI: 1.09, 2.22) for the low dose versus placebo comparison.

With respect to the secondary endpoint results, differences in the number of MRI lesions, favouring cladribine were also statistically significantly fewer with cladribine treatment. The results of the ITT analysis were supported by results for the evaluable population, which also demonstrated a highly statistically significant difference in favour of both cladribine high dose versus placebo and cladribine low dose versus placebo ($p<0.001$ for both comparisons). Subgroup analyses of region, gender, prior disease modifying therapy, age and relapse history all showed positive treatment effects from both doses of cladribine with no large differences between subgroups. Of particular note, subjects who had received prior disease modifying therapy given cladribine low dose experienced a 45% relative reduction in acute relapse rate compared with subjects given placebo (0.22 versus

0.40, respectively; p = 0.0013). Disease modifying treatment-experienced subjects given cladribine high dose experienced a 57.5% relative reduction in acute relapse rate (0.17 versus 0.4 respectively; p < 0.001).

The clinical evaluator raised a number of concerns regarding reliability and completeness of the efficacy data which were considered sufficient to preclude registration. The sponsor was advised of these concerns and responded. The concerns and sponsor responses are summarised below:

A) Concern: The number of subjects screened in the study was not presented. The number of subjects who failed screening, and the reasons for screen failure were not presented.

In response, the sponsor provided details of screening and screening failures. 1641 subjects were screened for enrolment into the trial. Of these subjects, 1326 were randomized into the trial and 315 (19.2%) were screening failures. Satisfactory reasons for screening failure were provided.

B) Concern: There were no dataset analyses describing the time to subjects taking rescue medication. The proportion of subjects taking rescue medication at 96 weeks was presented; however we do not have information about the time points at which rescue was required. This is important given that there was no clear evidence at the 48-week time point that suggested a relative advantage in treatment between treatment regimens with regard to mean annualised relapse rate or the proportion of relapse-free subjects.

The sponsor responded by providing details of the subjects taking rescue medication. The results within the first and second 48-week time periods were consistent with the benefit of cladribine tablets 5.25 mg/kg and 3.5 mg/kg in reducing the need for rescue treatment compared to placebo during the full 96 weeks beginning at Week 24.

A rescue option of Rebif 44 µg 3 times a week was available for all randomised subjects if more than one qualifying relapse was experienced and/or there was a sustained increased in their EDSS of at least 1 point or at least 1.5 points if baseline EDSS was 0 (over a period of 3 months or more) during a calendar year beginning at Week 24 of study. A total of 6.2% of subjects taking placebo received rescue medication to Week 96 compared to 2.0% and 2.5% taking cladribine high dose and low dose respectively. The odds ratio for these differences were statistically significant for the comparisons cladribine high dose versus placebo (p = 0.003) and cladribine low dose versus placebo (p = 0.011).

C) Concern: There were no data presented on the number of relapses in the 96-week study period.

The sponsor responded that there were 114 relapses during the 96-week study in the 5.25 mg/kg group, 109 relapses in the cladribine 3.5 mg/kg group, and 252 relapses in the placebo group. Treatment with cladribine high dose results in a 54.4% relative reduction in annualised qualifying relapse rate compared to placebo and treatment with cladribine low dose resulted in a 57.6% relative reduction in annualised qualifying relapse compared to placebo (p < 0.001 for both comparisons).

D) There were no datasets outlining the number of relapses that occurred after taking rescue medication while in the study.

The sponsor advised that, as noted above, 6.2% (n=27) of subjects given placebo were rescued up to Week 96 compared to 2.0% (n=9) and 2.5% (n= 11) given cladribine high and low dose respectively. Before taking rescue medication there were 15 qualifying relapses in 9 subjects given cladribine high dose, 22 in 11 subjects given cladribine low dose and 51 in 27 subjects given placebo. After rescue medication there were no qualifying relapses in subjects

given cladribine high dose, 1 in a subject given cladribine low dose and 6 in the 4 subjects given placebo.

E) There are a number of variables described to evaluate relapse; however there are no datasets describing the time to relapse. It is therefore difficult to know exactly how many subjects were relapse free at each of the time points analysed.

The sponsor provided Kaplan-Meier estimates of time to first qualifying relapse by treatment group for the ITT population.

The MS Scripps-C study was a small study of 50 patients with RRMS given either subcutaneous cladribine or placebo. The dose form and regimen are not those proposed for registration. This study was however identified as a pivotal study by the sponsor. Given it is supportive only it will not be further described here. The sponsor also provided additional information about this study however, given its limited relevance this will not be discussed further.

Safety

An *Integrated Safety Analysis* was presented for 5 completed studies which included 1587 subjects. Of these, 1108 subjects (69.8%) received at least one dose of cladribine and 479 subjects (30.2%) received placebo. The majority of the subjects (> 93%) were enrolled in the CLARITY and MS-001 studies, with < 7% being enrolled in Scripps-B, Scripps-C and MS-Scripps. The sponsor subsequently provided additional safety analyses for the pivotal efficacy study and additional safety analyses of larger data sets, including the pharmacology studies.

A 2 year extension to the CLARITY study is underway but safety data from that study remain blinded.

Across the 5 completed studies 1108 subjects were given cladribine with a median cumulative dose of 4.42 mg/kg (range: 0.2, 11.3 mg/kg). With the median duration of treatment of 362.0 days (range: 1, 1704 days) cladribine was given on a median of 30.0 days (range: 1, 70). Subjects given cladribine had a median time in the study of 1.82 years (range: 0.0, 6.4 years) for a total of 1070.6 subject-years on treatment. The majority of the exposure occurred among subjects who received a cumulative dose of > 3.5 – 5.25 mg/kg (493.7 subject-years) or > 5.25 – 7.0 mg/kg (378.2 subject-years), most of whom were treated in the CLARITY study.

Among all subjects treated with cladribine, 18 common TEAEs were identified as occurring at an incidence proportion at least 2.0% greater than that observed among subjects given placebo: headache (25.8% vs 19.4%); lymphopenia (21.3% vs1.7%); upper respiratory tract infection (15.9% vs 11.3%); nasopharyngitis (13.7% vs 11.5%); nausea (13.4% vs 11.1%); fatigue (10.0% vs 7.9%); back pain (9.3% vs 7.1%); depression (7.8% vs 4.0%); contusion (6.2% vs 1.9%); leucopenia (5.9% vs 0.6%); pyrexia (5.7% vs 2.7%); injection site bruising (4.5% vs 1.7%); rash (4.4% vs 1.5%); multiple sclerosis (3.9% vs 1.0%); alopecia (3.3% vs 1.3%); lymphocyte count decreased (3.5% vs 0.0%); muscular weakness (3.2% vs 1.0%) and herpes zoster (2.9% vs 0.2%).

Lymphopenia was reported as a TEAE in 21.3% of all cladribine-treated subjects and in 1.7% of subjects given only placebo. A dose response was observed with lymphopenia occurring at the following incidence with increasing cumulative oral doses: 6.1% for doses >0-1.75 mg/kg; 15.2% for doses from 1.75-3.5 mg/kg; 20.6% for doses >3.5-5.25 mg/kg and 28.4% for doses >5.25-7.0 mg/kg. Leucopenia was also reported at a higher rate among cladribine-treated subjects (5.9%) vs. placebo subjects (0.6%) and a dose response was observed when examined by cumulative dose range.

TEAEs coded to the SOC *Neoplasms – Benign, Malignant and Unspecified* were reported for 41 (3.7%) of all cladribine-treated subjects as compared to 8 (1.7%) of placebo subjects. The most common event in this SOC was uterine leiomyoma observed in 10 (0.9%) of cladribine-treated subjects and in 1 (0.2%) placebo-treated subject.

Probably-related adverse events reported by ≥ 1% of all cladribine-treated subjects include lymphopenia (12.3%), lymphocyte count decreased (2.3%), nausea (2.3%), injection site bruising (2.3%), leucopenia (2.2%), injection site haemorrhage (2.1%), injection site pain (1.6%), headache (1.2%), injection site irritation (1.1%) and herpes zoster (1.1%).

Seven deaths occurred in the study but only one (due to tuberculosis) was attributed to the study treatment. However, a patient given cladribine 7 mg/kg in the MS-Scripps study who had an apparently new infection with hepatitis B also died but this was considered not to be related to study treatment. That patient who died of tuberculosis was receiving cladribine high dose in the CLARITY study. Other serious infections of particularly interest occurring in subjects given cladribine include: coccidioidomycosis (1), sepsis (3), urosepsis (2) and serious upper respiratory tract infections (3). Serious pneumonia occurred in 1% (n = 11) subjects given cladribine vs 0.6% (n = 3) given placebo.

Overall, one or more serious adverse events (SAEs) were reported in 12.9% of all cladribine-treated subjects and 8.1% of all placebo subjects. SAEs were most frequently reported in the MedDRA SOC of *Infections and Infestations*, occurring in 4.6% of cladribine-treated subjects and 1.9% of placebo subjects. Serious neoplasia occurred in 15 (1.4%) of subjects given cladribine compared to none in subjects given placebo. Five cases of cutaneous malignancy were reported: 3 cases of basal cell carcinoma, 1 case of "nasal skin growth", and 1 case of malignant melanoma. Two cases of cervical carcinoma in situ were reported. There was one report of ovarian cancer, and one report of metastatic pancreatic carcinoma.

Nine (0.8%) subjects given cladribine experienced SAEs in the *Blood and Lymphatic System Disorders* compared with none given placebo. The most common SAEs were lymphopenia in 4 (0.4%), thrombocytopenia in 2 (0.2%), and neutropenia in 2 (0.2%) subjects given cladribine. Serious anaemia, bone marrow failure, coagulopathy, leucopenia and pancytopenia were each reported in 1 subject (0.1%). All of the serious lymphopenias occurred in the cladribine >3.5-5.25 mg/kg cumulative dose range.

During the evaluation process the sponsor proposed to remove the option for initial treatment to consist of 4 treatment courses, instead of the standard 2 treatment courses in patients with more active disease, that is, to remove the cladribine high dose treatment option. This was consistent with advice given in a pre-submission meeting. More stringent haematological criteria for starting subsequent treatment courses after initial treatment and changes to the Contraindications and Precautions section of the Product Information have also been proposed by the sponsor.

Risk Management Plan

The Risk Management Plan (RMP) reviewer has identified areas of missing information in the evaluation of cladribine for use in patients with MS. The most important omission was information on the long term effects from myelosuppression due to cladribine. Other missing information includes severity of teratogenicity, use in children, patients with compromised immunocompetence, and patients at risk of malignancies. The sponsor's R MP was considered to be acceptable.

The sponsor had proposed routine pharmacovigilance and a long term follow-up registry of patients who participated in 5 sponsored clinical trials, a prospective cohort study of

patients exposed to cladribine in the post-authorisation setting and a pregnancy registry to measure the incidence of adverse pregnancy outcomes. Additional risk minimisation activities involve advice to prescribers and the provision of education and training to prescribers. Following receipt of the RMP evaluation the sponsor revised the RMP, the PI and the CMI. Examples of the proposed educational material were also supplied.

Risk-Benefit Analysis

During the course of evaluation the sponsor amended the proposed dose recommendations to remove the high dose treatment option from the initial treatment course. This action would have been required because that dose regimen showed no increase in efficacy compared to the lower dose and this drug is a cytotoxic agent with known dose-related toxicity. The initial dose-finding studies were performed with subcutaneous cladribine. From those studies an oral dose with systemic exposure similar to the minimum dose examined in the dose finding studies was given in the pivotal study.

It is not known if lower doses would have had similar efficacy. It is also not known if further courses (beyond the 2 years studied) could be considered in patients with MS. The sponsor should clarify if repeat exposures to cladribine beyond the initial 2 years are being considered. In the absence of any data on the safety and efficacy of repeated treatment cycles beyond 2 years there should be a strong statement in the PI advising against no more than 4 treatment cycles should be given and that this should be over 2 consecutive years.

There are also no data on combination treatment with other therapies used in the prevention of relapses in MS. Cladribine should therefore only be given as a sole therapy for prevention of relapses during the 2 years of treatment.

Cytotoxic agents have been used in the treatment of MS after failure of other therapies. Cladribine has been investigated for the treatment of MS primarily in patients who had not previously received disease modifying therapy.

Cladribine was clearly more effective than placebo in reducing relapse rates and lesions on MRI in a general MS population composed primarily of disease modifying treatment-naïve subjects. As noted in the guidelines the most relevant parameter for assessing efficacy in MS is the accumulation of disability. The time to 3-month sustained disability progression based on the EDSS was a secondary endpoint in the CLARITY study. Most patients in all treatment groups had not had a disability progression by the end of 96 weeks on study. It was reported that the tenth percentile of subjects given either the high or low dose of cladribine had a statistically significant prolongation in time to sustained disability progression of approximately 12 weeks compared with placebo.

No statistics based on the entire treated population for disability progression by the end of the study were available and, particularly, no data on disability progression in the subgroup that was disease modifying treatment-experienced were presented. The sponsor was requested to include this information in the Pre-ACPM response.

> *The sponsor responded that in the CLARITY study, the overall mean change in EDSS score from baseline to last visit (Week 96) is in favour of cladribine groups as compared to placebo. This result was statistically significant in the analysis using a two-sided Wilcoxon rank-sum test (p<0.0001). Mean ± SD was 0.02 ± 0.84 for the low dose group, 0.02 ± 1.06 for the high dose group and 0.30 ± 1.03 for placebo.*
>
> *In the CLARITY study, the majority of the overall study population (69.7%) had not been previously treated with a DMD. With respect to the primary endpoint and considering only the dosage regimen proposed for market (3.5 mg/kg treatment group):*

- *DMD-naïve subjects in the cladribine group had a 61.2% relative reduction in ARR compared with the DMD-naïve placebo subjects (0.12 vs. 0.31, respectively; p<0.001).*
- *DMD-experienced subjects in the cladribine group had a 45.0% relative reduction in ARR compared with DMD-experienced placebo subjects (0.22 vs. 0.40, respectively; p=0.0013).*

In the DMD-naïve patients, cladribine tablets were effective in delaying time to 3-month sustained disability progression as measured by EDSS (HR 0.64 for both cladribine groups), while in DMD-experienced there was no statistically significant outcome on this parameter. In the latter subgroup, the Hazard Ratio of the time to 3-month progression (that is, sustained EDSS change) was 0.79 in the cladribine 5.25 mg/kg group versus the placebo group and 0.77 in the cladribine 3.5 mg/kg group versus the placebo group, which points to a clinically meaningful trend. Lack of statistical significance is probably due to the small sample size as assessing disability, due to its slow accumulation and nonlinear nature, may require a larger sample size to demonstrate the statistically significant effect.

For the DMD-naïve patients, the proportion of subjects with 3-month progression was 13.9% in the cladribine 5.25 mg/kg group, 13.4% in the cladribine 3.5 mg/kg group and 19.3% in the placebo group. For the patients who took any prior DMD therapies, the proportion of subjects with 3-month progression were 17.7% in the cladribine 5.25 mg/kg group, 16.8% in the cladribine 3.5 mg/kg group and 23.2% in the placebo group, respectively. The majority of patients in either of the groups did not have 3-month sustained progression. This result was statistically significant for the DMD-naïve subgroup for the lower dose group, with a strong trend for the higher dose group. The outcome was not significant for the DMD-experienced group probably due to the small sample size and the relative lack of disability progression in the placebo group.

Both 3.5 mg per kg and 5.25 mg per kg doses were very effective in the reduction of newly appearing T1 gadolinium enhancing and new or enlarging T2 brain lesions in both treatment-experienced and treatment-naïve patients (with p<0.001 for the effect of both doses in both subgroups).

In conclusion, the subgroup analysis demonstrated a statistically significant effect on the disability progression outcomes in the DMD-naïve patients who received the dose of 3.5 mg per kg, the same for which the sponsor is seeking approval to market in Australia. In the DMD-experienced patients, this effect appears not to be statistically significant probably due to the nature of the endpoint and a small sample size. Given the efficacy results, the sponsor believed that the use of Movectro should be considered for both patients who are DMD-naïve and patients who have previously been previously treated with disease modifying therapies.

The side effects of cladribine were as anticipated given its known safety profile. The relative toxicities of cladribine and alternative treatments for MS can only be indirectly compared. There is a high risk of Grade 3/4 lymphopenia (21.3%) which was serious in four subjects given cladribine. Patients will require careful monitoring of leukocytes during treatment cycles. Assessment for infection and neoplasms will also be required. It is unclear if cladribine exposure will have long term effects on the incidence of neoplasms. The long term effect on human fertility is also not known.

Cladribine is the first oral treatment for MS. The majority of patients in the pivotal study given cladribine or placebo had no sustained increase in disability during the 96-week period of study. Statistically significant but clinically modest reductions in time to

disability that were sustained for at least 3 months were demonstrated in the tenth percentile of patients given cladribine compared with placebo over a 96-week period. Substantial and statistically significant reductions in relapse rates and MRI lesions were seen in subjects given cladribine relative to placebo.

Efficacy has been demonstrated primarily in subjects who were naïve to previous disease-modifying treatment for MS but data were presented to show that for the primary efficacy endpoint of acute relapse rate, cladribine demonstrated statistically significant superiority over placebo in subjects who had previously received disease-modifying treatment. Data on the secondary efficacy endpoints for this subgroup of subjects, including disability progression were not separately presented for treatment-experienced subjects. The sponsor was requested to include this information in the Pre-ACPM response (see *response* above).

The primary concerns with cladribine are that it is cytotoxic, the minimum effective dose for treatment of MS has not been clearly identified and it is not clear if treatment benefits will be sustained once treatment has ceased. Increased incidences of serious, including fatal, infections and malignancies were seen in clinical trials which extended for only 96 weeks. Cladribine is nephrotoxic and toxic to bone marrow.

> *The sponsor responded that because of the inflammatory nature of MS, many current and potential therapies target leucocytes and other mediators of inflammation. Cladribine is not necessarily more unsafe than, for example, agents that affect leucocyte trafficking. Conversely, the fact that the lymphopenia is dose-related, measurable and reversible makes it amenable to risk minimisation strategies. The sponsor believed that restricting the haematological criteria is a more appropriate approach than limiting the number of treatment courses, as patients at risk of severe lymphopenia, that is, those with Grade 2 lymphopenia, will not be eligible for re-treatment. The occurrence of lymphopenia, and the fact that many of the known safety concerns are associated with lymphopenia, provides a visible parameter on which to base treatment decisions. The known safety profile of cladribine provides options, via appropriate patient selection and monitoring, for effective risk mitigation as described in the proposed PI and Risk Management Plan (RMP).*

There are no data on the safety or efficacy of use in patients with MS beyond 6 cycles over 2 years. Treatment with cladribine should not be repeated for more than 4 cycles. Subjects with MS who received 6 cycles of cladribine over 2 years had similar benefits to those who received 4 cycles but had more dose-related toxicity. Patients given cladribine will require long term follow up after their maximum of 4 treatment cycles. It may be that the incidence of neoplasia continues to increase beyond the usual level in MS patients given alternative treatments.

Given the lack of longer term safety data for cladribine in the MS patient group, particularly concerning the relative incidence of malignancy compared with alternative treatments and the fatal infections occurring in subjects given cladribine under clinical trial conditions, the Delegate proposed to approve Movectro (cladribine) for the treatment of relapsing-remitting multiple sclerosis but restrict use to patients who have previously received disease-modifying treatment. Patients should receive no more than 4 treatment cycles.

> *The sponsor argued that limiting the indication is one possible approach to minimising risk with a new medicine but other approaches also need to be considered, particularly in the context of existing medical practice for managing RRMS. It suggested the following indication:*

Movectro is indicated for the treatment of RRMS. The safety and efficacy of Movectro beyond two years are unknown.

The sponsor should be required to submit the results of the 2 year follow-up study to pivotal (CLARITY) study as a condition of registration. Reporting on the RMP activities will also be required. Cladribine should not be administered concomitantly with other disease-modifying therapy for MS.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) was specifically requested to advise on:

- whether cladribine should be permitted for treatment of RRMS in disease-modifying treatment naïve patients?
- whether approval should be deferred until the results of 4 years treatment from the CLARITY extension study are known? and
- whether the proposed haematology monitoring is adequate?

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

For the treatment of relapsing-remitting multiple sclerosis for a maximum duration of two years.

In making this recommendation, the ACPM considered the risk benefit profile for this new dose form and route to be positive overall. Members were concerned, however, that in the absence of long term safety data there was insufficient evidence to support use for a period greater than two years.

The specific conditions of registration should include increased focus on infection risk in the Risk Management Plan.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Movectro containing cladribine 10 mg tablets indicated for:

The treatment of relapsing-remitting multiple sclerosis (MS) for a maximum duration of two years.

Specific conditions of registration included the implementation in Australia of the Movectro (cladribine) Risk Management Plan (RMP), Version 2.0, included with this submission and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

The TGA announced on 23 June 2011 that the sponsor had indicated that Movectro would be withdrawn from supply in Australia for commercial reasons.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

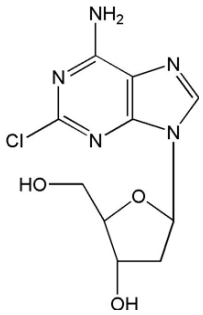
PRODUCT INFORMATION

MOVECTRO® Tablets

NAME OF THE MEDICINE

Non-Proprietary Name: Cladribine

Chemical Structure:



CAS Number: 4291-63-8 **MW:** 285.69

DESCRIPTION

Cladribine differs in structure from the naturally occurring nucleoside, deoxyadenosine, only by the substitution of a chlorine for hydrogen in the 2-position of the purine ring. According to the Biopharmaceutical Classification Scheme, cladribine is highly soluble in water. It is stable at basic and neutral pH and at temperatures up to 85°C. Decomposition increases over time at acidic pH. The ionisation behaviour of the molecule over the pH range 0 to 12 is characterised by a single pKa of approximately 1.21.

MOVECTRO tablets are uncoated, white, round and biconvex, and engraved with 'C' on one side and '10' on the other side. Each tablet of MOVECTRO contains 10 mg cladribine. The tablets also contain hydroxypropyl beta cyclodextrin, sorbitol and magnesium stearate.

PHARMACOLOGY

Mechanism of Action

Cladribine, or 2-chlorodeoxyadenosine, is a chlorinated purine analogue resistant to the action of adenosine deaminase. Cladribine has been shown to exert a sustained anti-inflammatory effect and to suppress lymphocytes, the immune cells implicated in the autoimmune processes involved in the pathophysiology of multiple sclerosis (MS).

In cells with high levels of deoxycytidine kinase (DCK) and low levels of deoxynucleotidase activity, such as T and B lymphocytes, cladribine is preferentially phosphorylated to the triphosphate form (Cd-ATP) and impairs DNA synthesis, disrupts cellular metabolism, and leads to cell death. In a study with a panel of established human cell lines derived from solid tumours, cells with low DCK activity were generally resistant to the drug (ID50: > 500 nM

cladribine), whereas lymphoblastoid cell lines (high DCK activity) were generally very sensitive (ID50: 2 to 50 nM cladribine).

Cladribine affects both resting and proliferating human lymphocytes.

The relationship between the plasma concentration of cladribine and efficacy in MS is currently not known. The clinical studies of cladribine in subjects with cancer and in subjects with MS suggest that treatment effect, including reduction in lymphocyte count, depends on the total (cumulative) dose administered.

Pharmacokinetics

Cladribine has to be phosphorylated intracellularly to be efficacious. The pharmacokinetics of cladribine were studied following oral and intravenous administration in MS patients, in patients with malignancies and in *in vitro* systems.

Absorption and Distribution

Following oral administration of MOVECTRO tablets, cladribine is absorbed rapidly. Administration of 10 mg tablets resulted in a mean C_{max} in the range of 22 to 29 ng/mL and corresponding mean AUC in the range of 80 to 101 ng·h/mL (arithmetic means from various studies). Median T_{max} was 0.5 h (range 0.5 to 1.5 h). When administered with a high-fat meal, absorption of cladribine was delayed (median T_{max} 1.5 h, range 1 to 3 h) and C_{max} was reduced by 29% (based on geometric mean), while AUC was unchanged.

The oral bioavailability of cladribine 10 mg tablets was approximately 40%.

The volume of distribution is large. The mean volume of distribution of cladribine was estimated as 487 L (SD ± 180). The plasma protein binding is 20%, and independent of plasma concentration. Intracellular concentrations of phosphorylated cladribine were found to be several hundred-folds higher than corresponding plasma concentrations.

Cladribine is able to penetrate the blood brain barrier as shown by a cerebrospinal fluid/plasma concentration ratio of approximately 0.25.

Biotransformation and Elimination

The renal and the non-renal routes of cladribine elimination are approximately equally important. Based on pooled population pharmacokinetic data from various studies, the median values for the two elimination routes were 23.1 L/h for renal clearance and 22.7 L/h for metabolic (i.e. non-renal) clearance. Renal clearance exceeded the glomerular filtration rate, indicating active renal secretion of cladribine. The non-renal part of the elimination of cladribine (40-80%) consists of metabolism and intracellular elimination.

The pharmacokinetics of cladribine are best described by a three-compartment model where the estimated terminal half-life for a typical patient from the population pharmacokinetic analysis is 23 hours.

The metabolism of cladribine was studied in MS patients following the administration of a single 10 mg oral tablet and a single 3 mg intravenous dose. Following both oral and

intravenous administration, the parent compound cladribine was the main component present in plasma and urine. The primary metabolite 2-chloroadenine proved to be a minor metabolite both in plasma and in urine. Only traces of other metabolites could be found in plasma and urine.

In *in vitro* systems, minor metabolism of cladribine was observed (92% to 99% was unchanged cladribine). The CYP450 enzymes identified to have any influence on the minor turnover to the 2-chloroadenine metabolite were CYP1A1, CYP1A2, and CYP2D6.

After entering the cell, cladribine is phosphorylated to cladribine monophosphate (Cd-AMP) by deoxycytidine kinase (and also by deoxyguanosine kinase in the mitochondria). Cd-AMP is further phosphorylated to cladribine diphosphate (Cd-ADP) and cladribine triphosphate (Cd-ATP). The dephosphorylation and deactivation of Cd-AMP is catalysed by cytoplasmic 5´-nucleotidase.

In a study of the intracellular pharmacokinetics of Cd-AMP and Cd-ATP in patients with chronic myelogenous leukaemia, the levels of Cd-ATP were approximately half of the Cd-AMP levels. Intracellular $t_{1/2}$ of Cd-AMP was 15 h. Intracellular $t_{1/2}$ of Cd-ATP was 10 h and the plasma $t_{1/2}$ was 21 h.

Dose and Time Dependence

The dose linearity of cladribine pharmacokinetics after intravenous administration was investigated at dose levels in the range of 2.5 mg/m^2 to 21.5 mg/m^2. The AUC showed an approximately linear increase with dose.

After oral administration of cladribine tablets across a dose range from 3 mg to 20 mg, C_{max} and AUC increase in a linear dose-proportional fashion, suggesting that absorption is not affected by rate- or capacity-limited processes up to a 20 mg oral dose.

As predicted from a population pharmacokinetic analysis, no accumulation of cladribine plasma concentrations is expected during the recommended 4 to 5 day treatment course.

In these studies there was no indication of a change in primary pharmacokinetic parameters over time.

Special populations

No studies have been conducted to evaluate the pharmacokinetics of MOVECTRO in elderly or paediatric MS patients, or in subjects with renal or hepatic impairment.

Renal and non-renal routes are equally important for the elimination of MOVECTRO. Total clearance was shown to be dependent on creatinine clearance. Based on a population pharmacokinetic analysis including patients with normal renal function and with mild renal impairment, total clearance in patients with mild renal impairment (CL_{CR} = 65 mL/min) is estimated to decrease by 18%. The predicted decrease in cladribine clearance is 30% in patients with moderate renal impairment (CL_{CR} = 40 mL/min) and 40% in patients with severe renal impairment (CL_{CR} = 20 mL/min).

The non-renal part of the elimination of MOVECTRO (approximately 50%) consists of fractional hepatic metabolism and presumably of extensive intracellular distribution and trapping of the active cladribine principle (Cd-ATP) within the targeted intracellular compartment (i.e. the lymphocytes) and subsequent elimination of intracellular Cd-ATP according to the life-cycle and elimination pathways of these cells. The importance of hepatic function for the elimination of cladribine is considered low.

A population pharmacokinetic analysis did not show any effect of age (range 18 to 65 years) or gender on cladribine pharmacokinetics.

The results of the clinical trials did not show any evidence of cardiotoxicity, however patients with significant cardiac pathology, such as angina, congestive heart failure or arrhythmias, were not eligible to be enrolled in the clinical trials.

CLINICAL TRIALS

Efficacy and safety of MOVECTRO tablets for oral use were evaluated in relapsing-remitting MS in the Cladribine Tablets Treating MS Orally (CLARITY) trial, a randomised, multicentre, double-blind, placebo-controlled clinical study in which 1326 patients were enrolled and randomly assigned to receive either placebo (n = 437), or a cumulative dose of MOVECTRO of either 3.5 mg/kg (n = 433) in a 4-course treatment regimen, or 5.25 mg/kg (n = 456) in a 6-course treatment regimen, over the 96-week trial period.

MOVECTRO was administered orally as 10 mg tablets, with the number of tablets taken daily based on the patient's body weight using 10 kg weight ranges. A 4 course treatment regimen consisted of 2 consecutive courses at a 28 day interval at the beginning of a first 48 week period, followed by 2 additional courses at a 28 day interval at the beginning of a second 48 week period. By comparison, the 6 course treatment regimen consisted of 4 consecutive courses at the beginning of the first 48 week period, followed by 2 additional courses at the beginning of the second 48 week period. Thus, the difference between the treatment regimens was the 2 additional consecutive courses administered at the beginning of the first 48 week period in the 6 course treatment regimen. Pre-defined haematological criteria had to be met prior to treatment initiation and before each subsequent treatment course.

The majority of patients in the placebo (86.3%) and the MOVECTRO 3.5 mg/kg (91.2%) and 5.25 mg/kg (86.2%) treatment groups completed all treatment courses through 52 weeks. A correspondingly high proportion of patients in the placebo and the MOVECTRO 3.5 mg/kg and 5.25 mg/kg treatment groups (87.0%, 91.9%, and 89.0%, respectively) completed the full 96 weeks of the trial.

In the overall trial population, the median age was 39 years (range 18 to 65), and the female to male ratio was approximately 2:1. The median duration of MS prior to trial enrolment was 6.7 years, and the median baseline neurological disability based on Expanded Disability Status Scale (EDSS) score across all treatment groups was 3.0 (range 0 to 6.0). The mean number of T1 gadolinium-enhancing (Gd+) lesions, T1 hypointense lesions, and mean T2 lesion volumes were 0.93, 7.7, and 15,467 mm^3, respectively. Over two thirds of the trial patients were treatment-naive for MS disease-modifying medications.

Both MOVECTRO treatment groups, 5.25 mg/kg and 3.5 mg/kg, were significantly superior to placebo in the treatment of relapsing-remitting MS. Clinical outcomes are shown in Table 1.

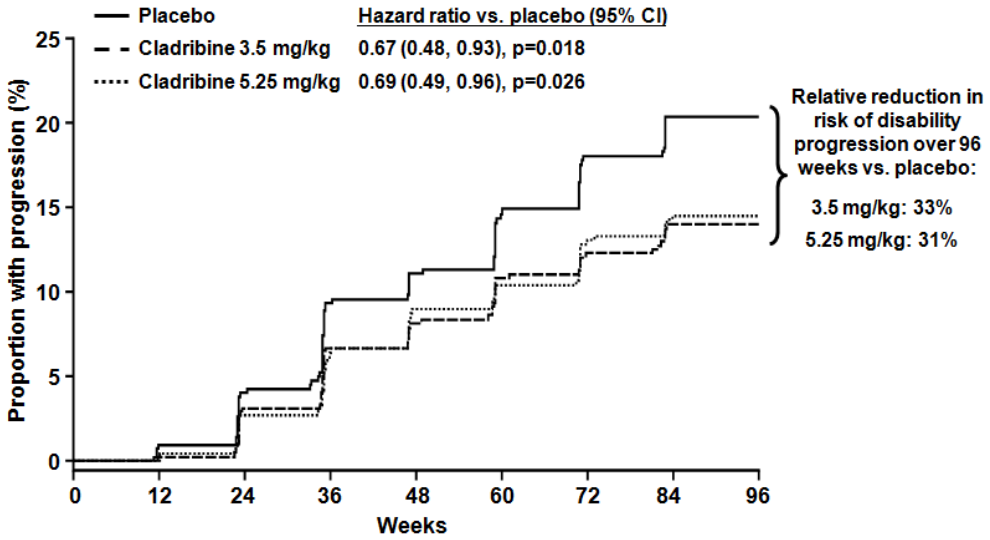
Table 1: Clinical Outcomes in the CLARITY Trial

Parameter	Placebo	MOVECTRO Cumulative Dose	
		3.5 mg/kg	5.25 mg/kg
Annualised relapse rate	0.33 95% CI (0.29, 0.38)	0.14 * 95% CI (0.12, 0.17)	0.15 * 95% CI (0.12, 0.17)
Relative reduction in annualised relapse rate (%)	--	57.6% *	54.5% *
Proportion of patients relapse-free over 96 weeks	60.9%	79.7% * 95% CI (1.87, 3.43)	78.9% * 95% CI (1.81, 3.27)
Time to first relapse (weeks)	20.1	58.3 * 95% CI (0.34, 0.58)	58.0 * 95% CI (0.36, 0.60)

* $p < 0.001$ compared to placebo

Time to sustained disability progression was defined as the time to worsening in EDSS score of ≥ 1 unit if baseline EDSS was 0.5 to 4.5, or ≥ 1.5 units if baseline EDSS was 0, or ≥ 0.5 unit if EDSS was ≥ 5, and persistent for at least 12 weeks. Treatment with MOVECTRO 3.5 mg/kg and 5.25 mg/kg resulted in a prolongation in time to sustained disability progression of 12 weeks (10^{th} percentile, both treatment groups) compared with placebo (Figure 1). The 3.5 mg/kg and 5.25 mg/kg treatment groups had a 33% and a 31% relative reduction in risk of developing disability progression over the 96-week trial period, respectively, compared with the placebo group (hazard ratio = 0.67, 95% CI [0.48, 0.93], p = 0.018; hazard ratio 0.69, 95% CI [0.49, 0.96], p = 0.026, respectively). The proportion of patients progressing to sustained disability was 20.6% in the placebo group, 14.3% in the 3.5 mg/kg treatment group and 15.1% in the 5.25 mg/kg treatment group.

Figure 1: Proportion of Patients with Sustained Disability Progression*



* The hazard ratio, 95% CI and p-values were estimated using Cox proportional hazards model with fixed effects for treatment group and region.

Both MOVECTRO treatment groups were statistically significantly superior to placebo with regard to number and relative reduction of T1 Gd+ enhancing lesions, active T2 lesions and combined unique lesions as demonstrated on brain magnetic resonance imaging (MRI) over the entire 96 weeks of the trial. Patients in the MOVECTRO 3.5 mg/kg and the 5.25 mg/kg treatment groups compared to the placebo treatment group had 86% and 88% relative reductions in the mean number of T1 GD+ lesions, 73% and 77% relative reductions in the mean number of active T2 lesions, and 74% and 78% relative reductions, in the mean number of combined unique lesions per patient per scan ($p < 0.001$ for both groups across all 3 MRI outcomes).

Subgroup analyses of region, gender, age and relapse history all showed positive treatment effects from both doses of MOVECTRO with no large differences between subgroups.

The lowest effective dose of MOVECTRO for the treatment of relapsing-remitting MS has not been determined in clinical trials.

INDICATIONS

MOVECTRO is indicated for the treatment of relapsing-remitting multiple sclerosis (MS) for a maximum duration of two years.

CONTRAINDICATIONS

MOVECTRO is contraindicated in patients with hypersensitivity to cladribine or to any of the tablet excipients (refer to DESCRIPTION).

MOVECTRO therapy and individual treatment courses must not be initiated in patients with acute or chronic infections, including active or latent tuberculosis, or viral hepatitis. Screening is recommended.

MOVECTRO therapy must not be initiated in immunocompromised patients, including patients receiving immunosuppressive or myelosuppressive therapy with agents such as cyclosporin, methotrexate, mitozantrone, azathioprine, natalizumab, or chronic use of corticosteroids. Acute short-term therapy with corticosteroids can be administered.

MOVECTRO therapy and individual treatment courses must not be initiated within 3 months after vaccination with live or attenuated live vaccines (refer to Interactions).

MOVECTRO must not be used in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min) or moderate or severe hepatic impairment (Child-Pugh score > 6).

MOVECTRO is contraindicated during pregnancy and breastfeeding (refer to Use in Pregnancy and Use in Lactation).

PRECAUTIONS

The safety and efficacy of more than two years treatment with MOVECTRO are under investigation. Patients should not receive treatment beyond two years pending further information.

Therapy is to be initiated and supervised by neurologists. Neurologists must discuss the risks and benefits of therapy with the patient and explain the importance of following the recommendations in the Consumer Medicine Information, in particular with respect to infections and haematological monitoring. The long term safety of MOVECTRO has not been assessed. Prior to receiving treatment with MOVECTRO, patients should be counselled that possible long term effects may include an increase in the incidence of malignancies and an unknown impact on fertility.

Haematological Monitoring

The mode of action of MOVECTRO is closely linked to a reduction in lymphocyte count. The effect on lymphocyte count is dose-dependent. Older patients may experience severe lymphopenia more frequently. Decreases in neutrophil count, red blood cell count, haematocrit, haemoglobin or platelet count compared to baseline values have also been observed in clinical studies, although these parameters usually remain within the limits of normal.

A complete blood count and differential must be performed to determine the haematological status of the patient:

- before initiating MOVECTRO therapy
- before each subsequent course of MOVECTRO
- 1 month after the last course of MOVECTRO in the initial treatment
- every 3 months between the initial treatment period and the re-treatment period
- 1 month after the last course of MOVECTRO in the re-treatment period and periodically thereafter, as appropriate.

For treatment decisions based on the patient's haematological status, refer to DOSAGE AND ADMINISTRATION.

Infections

Because of the cladribine-induced reduction in lymphocyte count and potential for myelosuppression, MOVECTRO can reduce the body's immune defence and increase the likelihood and severity of infections. Latent infections may be activated, including tuberculosis, viral hepatitis or herpes zoster infections. Therefore, screening is recommended prior to initiation of therapy and prior to re-treatment.

The majority of serious infections in clinical trials with MOVECTRO were pneumonia, urinary tract infections and herpes viral infections mainly due to herpes zoster. None of the latter resulted in systemic involvement. A fatal case of hepatitis B and a fatality due to reactivation of latent tuberculosis were observed. Other serious infections included pyelonephritis, sepsis, urosepsis and coccidiomycosis.

Patients must be monitored carefully for signs and symptoms suggestive of any infection. If signs and symptoms suggestive of an infection occur, treatment for the infection must be initiated as clinically indicated and MOVECTRO therapy must be interrupted or delayed until full resolution.

Blood Transfusions

In patients who require blood transfusion, irradiation of cellular blood components is recommended prior to administration to prevent transfusion-related graft-versus host disease. Consultation with a haematologist is advised.

Myelodysplastic Syndrome

A limited number of cases of myelodysplastic syndrome have been reported with parenteral cladribine in MS and in other indications as well as with other purine analogues. The risk for development of myelodysplastic syndrome in patients treated with MOVECTRO is not known.

Malignancies

MOVECTRO has not been studied in MS patients with prior or current malignancies (with the exception of *in situ* basal or squamous cell skin cancer surgically removed without recurrence for at least five years). Therefore, in MS patients with current malignancy, the use of MOVECTRO is not recommended. The risk of recurrence of malignancy after MOVECTRO therapy in MS patients with prior malignancy is not known and the benefits and risks of the use of MOVECTRO must be evaluated on an individual patient basis.

In clinical studies, non-haematological malignancies (e.g. choriocarcinoma, melanoma, ovarian carcinoma, pancreatic carcinoma) were observed. Due to the prolonged immunosuppression and the genotoxic potential of MOVECTRO, the risk for development of malignancy cannot be excluded.

Renal Impairment

No dedicated studies have been conducted in patients with renal impairment (refer to CONTRAINDICATIONS).

The safety profile in patients with mild renal impairment (creatinine clearance 50-80 mL/min) was shown to be similar to that in patients with normal renal function.

Hepatic Impairment

No dedicated studies have been conducted in patients with hepatic impairment (refer to CONTRAINDICATIONS).

Fructose Intolerance

MOVECTRO contains sorbitol. Its use is not recommended in patients with fructose intolerance.

Effects on Fertility

The effect of cladribine on human fertility is unknown.

In male mice, cladribine did not affect fertility at subcutaneous doses up to 30 mg/kg per day, but reduced testes weights and increased numbers of non-motile sperm were seen, indicating the presence of testicular effects. For these effects, 5 mg/kg per day was the no-observed-adverse-effect level (NOAEL). In female mice, cladribine did not affect fertility up to a subcutaneous dose of 8 mg/kg per day (higher doses were not tested). The extrapolated daily exposure data (based on plasma AUC) associated with these dose levels in mice exceeded the daily exposure with the oral human dose in MS by at least an order of magnitude.

A 1-year subcutaneous study in monkeys reported testicular degeneration, prostatic inflammation, prostatic and seminal vesicle secretion depletion, epididymal hypospermia and increased incidence of degenerated cells, while a 3-month oral and subcutaneous study noted only reduced sperm motility. The estimated exposure (plasma AUC) at the no-effect oral dose (3 mg/kg/day) was 3-fold clinical MS exposure.

Male Patients

Taking into account the potential genotoxic effect of cladribine on spermatozoa, male-mediated effects on the embryo cannot be ruled out. Therefore, male patients must take precautions to prevent pregnancy of their partner while they are on a treatment course and for at least 3 months after the last dose of the most recent course of MOVECTRO. This will allow time for completion of new male reproductive cycles to clear intracellular phosphorylated cladribine from the body.

If the partner of a male patient becomes pregnant during a course of his MOVECTRO therapy, it is recommended that the partner be informed about the potential hazard to the fetus.

Use in Pregnancy (Category D)

While there were no effects on female fertility, reproductive function or general performance of offspring, cladribine was shown to be embryolethal in pregnant mice, and the compound was teratogenic in mice and rabbits. A significant increase in fetal variations was observed in mice receiving 1.5 mg/kg/day or greater intravenously during the period of organogenesis, or from early gestation to weaning, and increased resorptions, reduced litter size and increased fetal malformations were observed in mice receiving 3 mg/kg/day. Fetal malformations were observed in rabbits that received 3 mg/kg/day intravenously during the period of organogenesis. The observed embryolethal and teratogenic effects are consistent with the pharmacological mechanisms of cladribine.

There are no adequate or well-controlled studies in human pregnancies. A limited amount of data is available from pregnant women exposed to MOVECTRO prior to conception. Estimated conception date varied from less than one week to 16 months after the last dose of MOVECTRO. Miscarriages as well as normal births occurred.

Although clinical data from MOVECTRO did not reveal evidence of teratogenicity in humans, MOVECTRO has been shown to inhibit DNA synthesis. Other agents that inhibit DNA synthesis (e.g. methotrexate) have been reported to be teratogenic in humans.

MOVECTRO is contraindicated in pregnant women (refer to CONTRAINDICATIONS). In women of childbearing potential, pregnancy must be excluded before the initiation of MOVECTRO therapy and before initiation of each subsequent treatment course, and prevented by use of reliable contraception for the duration of each treatment course and for at least 6 months (6 menstrual cycles) after the last dose of the most recent course of MOVECTRO. This will allow for the removal of any follicle that may have been exposed to cladribine during or immediately after a course of treatment. Women who become pregnant during therapy with MOVECTRO tablets should discontinue treatment.

In case of exposure to MOVECTRO during pregnancy, it is recommended that the patient be informed about the potential hazard to the fetus.

Choriocarcinoma, a very rare type of carcinoma, was diagnosed in one patient 19 months following treatment with MOVECTRO. Causal relationship to MOVECTRO treatment cannot be excluded.

Use in Lactation

It is not known whether cladribine is excreted in human milk. Because many medicines are excreted in human milk and the potential for serious adverse reactions in breast-fed infants from MOVECTRO, a decision should be made either to discontinue breast-feeding or to discontinue MOVECTRO, taking into account the importance of MOVECTRO to the mother (refer to CONTRAINDICATIONS).

Paediatric Use

Safety and effectiveness of MOVECTRO in paediatric MS patients are not known. The immune, haematopoietic and nervous system are not fully mature in this patient population and continue to develop in the later years of adolescence. MOVECTRO is not recommended in patients below the age of 18 years.

Use in the Elderly

Clinical studies with MOVECTRO did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients.

Caution is recommended when MOVECTRO is used in elderly patients, taking into account the potential greater frequency of decreased hepatic or renal function, concomitant diseases, and other medicinal therapy.

Carcinogenicity

While no treatment-related tumours were seen in a 26-week carcinogenicity study in transgenic mice by oral administration, an increased incidence of harderian gland adenomas was seen in a 22-month carcinogenicity study in mice by subcutaneous administration. The clinical relevance of this is unclear as humans do not have this anatomical structure. However, based on its mode of action and positive findings in mammalian genotoxicity tests (*in vitro* and *in vivo*), a carcinogenic potential of cladribine cannot be excluded.

Genotoxicity

Cladribine was shown to be genotoxic, causing chromosomal damage in the bone marrow of mice *in vivo* and in CHO-WBL cells *in vitro*. These findings are expected since cladribine is known to cause inhibition of DNA synthesis by an imbalance of deoxynucleotide triphosphate pools, DNA strand breaks, inhibition of DNA repair, and depletion of intracellular nicotinamide adenine dinucleotide (NAD). Cladribine was not mutagenic *in vitro* (bacterial and mammalian cell mutation assays) and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures.

Interactions

If any other oral medicines are taken concomitantly, administration must be separated from that of MOVECTRO by at least 3 hours during the limited number of days of cladribine administration. This is because hydroxypropyl beta cyclodextrin released from MOVECTRO may lead to complex formation with other agents (especially medicines with low solubility), which could cause an increase in bioavailability of such a product.

Haematotoxic, Immunosuppressive and Immunomodulating Agents

Use of MOVECTRO in immunocompromised patients, including patients receiving immunosuppressive or myelosuppressive therapy with, e.g. cyclosporin, methotrexate, mitozantrone, azathioprine, natalizumab, or chronic use of corticosteroids is contraindicated because of a risk of additive effects on immune status (refer to CONTRAINDICATIONS). Acute short-term therapy with corticosteroids can be administered if clearly necessary.

Safety and efficacy of MOVECTRO in combination with other disease-modifying treatments for MS has not been assessed. Concomitant treatment is not recommended.

Use of MOVECTRO in patients who have previously been treated with immunomodulating agents or subsequent use of immunomodulating agents after treatment with MOVECTRO must only be performed under close clinical and haematological monitoring.

Because of the cladribine-induced reduction in lymphocyte count, additive haematological adverse effects may be expected if MOVECTRO is administered concomitantly with other agents that affect the haematological profile (e.g. carbamazepine, non-steroidal anti-inflammatory drugs). Careful monitoring of haematological parameters is recommended in such cases.

Live or Live Attenuated Vaccines

MOVECTRO therapy and individual treatment courses must not be initiated within 3 months after vaccination with live or attenuated live vaccines because of a risk of active vaccine infection (refer to CONTRAINDICATIONS). Also patients must not be vaccinated with live or attenuated live vaccines during a MOVECTRO treatment course and until 3 months have elapsed after the last dose of MOVECTRO.

Potent ENT, CNT and ABCG2 transporter inhibitors

Based on *in vitro* data suggesting inhibition of ENT, CNT or ABCG2 transport proteins, the bioavailability, intracellular distribution and renal elimination of cladribine may theoretically be altered by medicinal products containing potent ENT, CNT and ABCG2 transporter inhibitors, such as dipyridamole, dilazep, nifedipine, nimodipine, cilostazol, sulindac, or reserpine. The net effects in terms of potential cladribine exposure alterations are difficult to predict and hence, the clinical relevance of these findings is unknown.

It is recommended that co-administration of these products be avoided during the 4 to 5 day MOVECTRO treatment courses. If this is not possible, selection of alternative concomitant medicinal products with no, or minimal ENT, CNT or ABCG2 transporter inhibiting properties should be considered. If this is not possible, dose reduction to the minimum mandatory dose of medicinal products containing these compounds, separation in the timing of administration by several hours, and careful patient monitoring is recommended.

Other

In vitro studies suggest that cladribine efflux is not or only minimally P-glycoprotein (P-gp) related. Clinically relevant interactions with inhibitors and inducers of P-gp are not expected.

In vitro data indicated that cladribine could be degraded at acidic pH. However, drug interaction studies *in vivo* showed that the bioavailability of MOVECTRO 10 mg tablet was not changed when co-administered with pantoprazole and the bioavailability of cladribine oral solution was not enhanced when co-administered with omeprazole.

Cladribine showed no significant potential to act as inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Inhibition of one of these enzymes, or polymorphism in CYP2D6, is not expected to result in clinically significant effects on MOVECTRO pharmacokinetics. Cladribine has no inductive effect on CYP1A and CYP3A enzymes.

Effects on the ability to drive and use machines

No studies concerning the ability to drive or use machines have been performed. Caution when driving or operating machines is recommended in patients who experience vertigo under treatment with MOVECTRO.

ADVERSE EFFECTS

The most common adverse reactions (> 20%) are lymphopenia, upper respiratory tract infections and headache (refer to PRECAUTIONS, Haematological Monitoring, Infections). Lymphopenia led to treatment discontinuation in a phase 3 trial (CLARITY trial) in approximately 2.2% of patients.

Clinical Trials

The safety data described below reflect exposure of 884 patients with MS to MOVECTRO in a placebo-controlled study (CLARITY trial). The population was 18 to 65 years of age, and

gender distribution was approximately 2:1 female to male. 91.2% in the MOVECTRO 3.5 mg/kg group and 86.2% in the 5.25 mg/kg group completed all treatment courses (refer to CLINICAL TRIALS).

Table 2 shows all treatment emergent adverse events occurring at any time during the CLARITY trial with an incidence ≥ 5% in any treatment group.

Table 2: Treatment emergent adverse events occurring at any time during the CLARITY trial with an incidence ≥ 5% in any treatment group

System organ class Preferred term [1]	Number of Patients (percent)		
	MOVECTRO 3.5 mg/kg [n = 430]	**MOVECTRO 5.25 mg/kg** [n = 454]	**Placebo** [n = 435] [2]
Infections and infestations			
Nasopharyngitis	62 (14.4)	58 (12.8)	56 (12.9)
Upper respiratory tract infection	54 (12.6)	52 (11.5)	42 (9.7)
Urinary tract infection	23 (5.3)	33 (7.3)	39 (9.0)
Influenza	28 (6.5)	34 (7.5)	27 (6.2)
Gastrointestinal disorders			
Nausea	43 (10.0)	50 (11.0)	39 (9.0)
Diarrhoea	30 (7.0)	31 (6.8)	29 (6.7)
Nervous system disorders			
Headache	104 (24.2)	94 (20.7)	75 (17.2)
Blood and lymphatic system disorders			
Lymphopenia	93 (21.6)	143 (31.5)	8 (1.8)
Leucopenia	24 (5.6)	39 (8.6)	3 (0.7)
Musculoskeletal and connective tissue disorders			
Back pain	34 (7.9)	39 (8.6)	28 (6.4)
Arthralgia	27 (6.3)	23 (5.1)	21 (4.8)
Pain in extremity	16 (3.7)	25 (5.5)	21 (4.8)
General disorders and administration site conditions			
Influenza like illness	34 (7.9)	27 (5.9)	31 (7.1)
Fatigue	20 (4.7)	27 (5.9)	26 (6.0)
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain	19 (4.4)	24 (5.3)	25 (5.7)
Psychiatric disorders			
Depression	18 (4.2)	25 (5.5)	13 (3.0)
Insomnia	25 (5.8)	14 (3.1)	17 (3.9)
Investigations			
Lymphocyte count decreased	13 (3.0)	26 (5.7)	0
Ear and labyrinth disorders			
Vertigo	14 (3.3)	23 (5.1)	11 (2.5)

[1] MedDRA dictionary

[2] two patients in the placebo group had actually received a small amount of cladribine

Listed below are adverse reactions (i.e. causal association with the treatment is considered at least possible) derived from clinical studies with MOVECTRO in MS, including those with lower incidence than 5%. The following definitions apply to the frequency terminology:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000
Frequency not known: cannot be estimated from the available data

Infections and infestations

Common: Dermatomal herpes zoster, upper respiratory tract infections (e.g. nasopharyngitis), female reproductive tract infections (e.g. vaginal infections)
Rare: Reactivation of latent tuberculosis

Blood and lymphatic system disorders

Very common: Lymphopenia, which may be severe (grade 3 or 4)

Nervous system disorders

Common: Headache

Ear and labyrinth disorders

Common: Vertigo, tinnitus

Skin and subcutaneous tissue disorders

Common: Rash (e.g. pustular, papular, macular, pruritic, erythematous rash), allergic dermatitis (which may involve mucous membranes and can resemble an erythema multiforme), alopecia

Reproductive system and breast disorders

Common: Menorrhagia, metrorrhagia

Lymphopenia

Lymphopenia, which is associated with the mechanism of action of cladribine, was observed frequently and showed a difference in rates based on cumulative dose administered. Lymphopenia can also be severe, with lymphopenia classified as Grade 3 or 4 (by CTCAE criteria for assessing haematological toxicity) observed in 26% of patients in the MOVECTRO 3.5 mg/kg treatment group and in 45% of patients in the 5.25 mg/kg group.

Infections

Because of cladribine-induced reduction in lymphocyte count and the potential for myelosuppression, MOVECTRO can reduce the body's immune defence and increase the likelihood and severity of infections, particularly viral infections. Infections for which the percentage in the MOVECTRO group was higher than in the placebo group are presented in the list of adverse reactions above.

Reactivation of latent tuberculosis

Reactivation of latent tuberculosis after treatment with MOVECTRO tablets has been observed and can lead to the development of constitutional complaints, worsening of haematological toxicities, and exacerbation and dissemination of the underlying tuberculosis, which can be fatal.

DOSAGE AND ADMINISTRATION

General Treatment Schedule

MOVECTRO therapy is administered in treatment courses. A course consists of daily oral administration of one or two 10 mg tablets given for the first 4 or 5 days of a 28-day period (see below).

Treatment is initiated with 2 consecutive courses at a 28-day interval at the beginning of a first 48-week period. Re-treatment consisting of 2 additional, consecutive courses at a 28-day interval is started at the beginning of a second 48-week period. Haematological criteria for starting and continuing therapy have to be met before initiating MOVECTRO therapy or administering any subsequent treatment course (see below).

The efficacy and safety of additional treatment courses of MOVECTRO beyond 96 weeks after treatment initiation have not yet been evaluated and are not recommended. Patients should receive no more than 4 treatment courses over two consecutive years. The recommended dose should not be exceeded.

Criteria for Starting and Continuing Therapy

A complete blood count and differential must be performed:

- before initiating MOVECTRO therapy
- before each subsequent course of MOVECTRO

Initiating therapy

It is strongly recommended that haematological parameters be within normal limits before initiating MOVECTRO therapy.

Starting Subsequent Treatment Courses

Prior to administration of subsequent treatment courses, patients have to meet the haematological criteria listed in Table 3. Patients must not receive a subsequent treatment course when one or more haematological parameters are below these values.

Table 3: Haematological criteria for starting subsequent treatment courses		
Lymphocytes	more than	0.8×10^9/L
Leucocytes (Total WBC)	more than	3.0×10^9/L
Neutrophils	more than	1.5×10^9/L
Haemoglobin	more than	10.0 g/dL
Platelets	more than	75.0×10^9/L

Haematological Monitoring between Treatment Periods

A complete blood count and differential must also be performed 1 month after the last course of MOVECTRO in the initial treatment period, every 3 months between the initial treatment period and the re-treatment period, 1 month after the last course of MOVECTRO in the re-treatment period and periodically thereafter, as appropriate.

Dosage

Depending on the patient's body weight, a treatment course consists of a single daily administration of one or two 10 mg tablets of MOVECTRO for 4 or 5 consecutive days. The total number of tablets to be taken per treatment course by patient weight range is provided in Table 4. Note that for some weight ranges the number of tablets may vary from one course to the next.

Table 4: Number of MOVECTRO tablets by patient weight over 96 weeks				
Weight range	Number of 10 mg tablets per course			
	Initial treatment		Re-treatment	
Kg	Course 1	Course 2	Course 1	Course 2
40* to < 50	4	4	4	4
50 to < 60	5	5	5	5
60 to < 70	6	6	6	6
70 to < 80	7	7	7	7
80 to < 90	8	7	8	7
90 to < 100	9	8	9	8
100 to < 110	10	9	10	9
110 and above	10	10	10	10

* Use of MOVECTRO in patients weighing less than 40 kg has not been investigated.

MOVECTRO is supplied in pre-packaged units (blisters in tablet holders) that provide the exact number of tablets required for a treatment course.

A label on the tablet holder shows which tablets are to be taken on which day of the course. Table 5 shows how the total number of tablets per course is distributed over the individual days of a course.

Table 5: MOVECTRO 10 mg tablets per course day as directed by the label on the tablet holder

Total number of tablets per course	Pack size	Day 1	Day 2	Day 3	Day 4	Day 5
4	Tablet holder with 4 tablets	1	1	1	1	0
5	Tablet holder with 5 tablets	1	1	1	1	1
6	Tablet holder with 6 tablets	2	1	1	1	1
7	Tablet holder with 7 tablets	2	2	1	1	1
8	Tablet holder with 8 tablets	2	2	2	1	1
9	Tablet holder with 9 tablets	2	2	2	2	1
10	Tablet holder with 10 tablets	2	2	2	2	2

It is recommended that the daily MOVECTRO doses of a course be taken at intervals of 24 hours at approximately the same time each day. If a daily dose consists of two tablets, both tablets are taken together as a single dose.

Dosing Errors

A missed dose can be taken as soon as remembered, if remembered on the same calendar day.

A missed dose must not be taken if it is not remembered until the following day. In this case, the patient must take the next dose as scheduled, and extend the number of days in that treatment course. For example, if a patient forgets to take the Day 3 dose and does not remember until Day 4, the Day 3 dose is taken on Day 4, and the total number of days in the treatment course is extended by one day. If two consecutive doses are missed, the same rule applies, and the treatment course is extended by two days.

In case of an accidental dose higher than prescribed, the clinical status of the patient must be reviewed and a decision made as to whether and how to continue treatment.

Administration

MOVECTRO tablets must be taken orally, with water, and swallowed without chewing. It is unlikely that food intake will have a clinically significant effect on absorption of cladribine. Therefore, MOVECTRO can be taken before or after a meal.

As tablets are uncoated, they must be swallowed immediately once removed from the tablet holder and not left exposed on surfaces or handled for any period of time greater than that

required for dosing. If a tablet is left on a surface, or if a broken or fragmented tablet is released from the blister, the area must be thoroughly washed afterwards.

The patient's hands must be dry when handling the tablets and washed thoroughly afterwards.

Directions for handling MOVECTRO are included in the pack.

OVERDOSAGE

There is no experience with overdose of MOVECTRO. Some of the adverse reactions of MOVECTRO, such as lymphopenia, may be dose-dependent (refer to PRECAUTIONS and ADVERSE REACTIONS).

There is no known specific antidote to an overdose of MOVECTRO. Treatment consists of immediate discontinuation of MOVECTRO, careful observation and initiation of appropriate supportive measures. Haemodialysis has not been proven effective for elimination of cladribine.

Particularly close monitoring of haematological parameters is recommended in patients who have been exposed to an overdose of MOVECTRO.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Tablets 10 mg (white, uncoated, engraved with 'C' on one side and '10' on the other) in aluminium-aluminium blister with child-resistant plastic tablet holder: packs of 1, 4, 5, 6, 7, 8, 9 or 10 tablets.

Protect from moisture. Store below 25°C in the original container.

POISON SCHEDULE

S4 (Prescription Only Medicine)

NAME AND ADDRESS OF SPONSOR

Merck Serono Australia Pty Ltd
Units 3-4, 25 Frenchs Forest Road East
Frenchs Forest NSW 2086

Date of TGA Approval: 2 September 2010

Therapeutic Goods Administration

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Reference/Publication #