22 June 2017
EMA/435731/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

MAVENCLAD

International non-proprietary name: cladribine

Procedure No. EMEA/H/C/004230/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

2-CdA	2-chlorodeoxyadenosine triphosphate
ADP	Adenosine diphosphate
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ANOVA	Analysis Of Variance
ARR	Annualised Relapse Rate
AUC	Area under the curve
BCRP	Breast cancer resistant protein, ATP-binding cassette transporter ABCG2
CDMS	Clinically Definite Multiple Sclerosis
CI	Confindence Interval
CIS	Clinically Isolated Syndrome
CL	clearance
CNS	Central Nervous System
c_{max}	maximum plasma concentration
CYP	Cytochrome
DB	Double-Blind
DCK	Deoxycytidine kinase
DMD	Disease Modifying Drug
EAE	Experimental Autoimmune Encephalomyelitis
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
Emax	inhibitory maximum exposure
ERA	Environmental risk assessment
FDA	Food and Drug Administration
F_{pen}	refined market penetration factor
GCP	Good Clinical Practice
Gd+	Gadolinium-enhancing
HDA	High Disease Activity
HPβCD	Hydroxypropyl betadex (2-hydroxypropyl-β-cyclodextrin)
HLLL	Cladribine high/low dose
HLPP	Cladribine high dose/placebo
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IFN-β	Interferon beta
i.m.	Intramuscular
i.p.	Intraperitoneal
i.v./IV	Intravenous
IMP	Investigational Medicinal Product
ITT	Intent-to-treat
IVIG	Intravenous Immunoglobulin G
K_{ow}	n-octanol-water partition coefficient
LLLL	Cladribine low/low dose

LLPP	Cladribine low/placebo
LTBI	latent tuberculosis infection
LTFU	Long-Term Follow-Up
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NE	Non Estimable
NEDA	Non Evidence of Disease Activity
NMSC	Non-melanoma skin cancer
NOAEL	no-observed-adverse-effect-level
HPßCD	hydroxypropylbetadex
OR	Odds Ratio
PBT	persistence, bioaccumulation and toxicity
PD	Pharmacodynamic(s)
$PEC_{surfacewater}$	predicted environmental concentration in surface-water
PK	Pharmacokinetic(s)
PML	Progressive Multifocal Leukoencephalopathy
PO	Per Os (orally)
popPK	Population PK
PPLL	Placebo/cladribine low dose
PT	Preferred Term
RD	Risk difference
RMS	Relapsing Multiple Sclerosis
RR	Risk Ratio/Rate ratio
RRMS	Relapsing-Remitting Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
PT	Preferred Term
PY	Patient Years
SAE	Serious Adverse Event
s.c./SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form 36 Item
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
SIR	Standardized Incidence Ratio
$t_{1/2}$	Apparent elimination half-life
TB	Tuberculosis
TEAE	Treatment-Emergent Averse Event
t_{max}	Time to reach maximum plasma concentration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Serono Europe Limited submitted on 23 June 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for MAVENCLAD, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 June 2015. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication:

MAVENCLAD is indicated as a single disease modifying therapy for the treatment of adult patients with highly active relapsing-remitting multiple sclerosis (MS) as defined by clinical or imaging features.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that cladribine was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/101/2009 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 December 2014. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Hanne Lomholt Larsen Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 23 June 2016.
- The procedure started on 14 July 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 03 October 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 3 October 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 14 October 2016.
- During the meeting on 27 October 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 28 October 2016.
- During the meeting on 10 November 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 10 November 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 27 March 2017.
- During the PRAC meeting on 6 April 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 11 April 2017.
- During the CHMP meeting on 21 April 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 7 June 2017.
- During a meeting of Scientific Advisory Group (SAG) on 8 June 2017, experts were convened to address questions raised by the CHMP.
- During the meeting on 22 June 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to MAVENCLAD.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) resulting in neurological impairment and severe disability. The present application seeks approval of cladribine for the treatment of adult patients with highly active relapsing remitting multiple sclerosis (RRMS) as defined by clinical or imaging features. During the course of the procedure the target population was revised to adult patients with highly active relapsing MS (RMS).

2.1.2. Epidemiology

MS is the most common cause of serious neurological disability in young adults. It is estimated that more than 2.3 million people have MS worldwide. While MS is a global disease, its prevalence increases with distance from the equator. The prevalence of MS is highest in North America and Europe (140 and 108 per 100,000 respectively) and lowest in sub-Saharan Africa and East Asia at 2.1 and 2.2 per 100,000, respectively.

MS typically begins between the ages of 20 to 40 years. Overall, women are affected approximately twice as often as men, except in individuals with the primary-progressive form of the disease, where there is no gender prevalence difference. The vast majority of patients (approximately 85%) first present with the RRMS form (Lublin et al., 2014), which usually later evolves into secondary-progressive MS (SPMS). Within ten years more than 50% of patients who suffer from a relapsing-remitting form eventually develop SPMS, which is characterised by sustained disability with or without superimposed relapses.

2.1.3. Aetiology and pathogenesis

While the exact cause of MS is unknown, an autoimmune process has been implicated involving both a genetic predisposition and environmental triggers.

The neuropathology of the disease is marked by an aberrant activation of specific T and B cells that recognize self-antigens (i.e., myelin) expressed in the CNS. MS relapses are considered the clinical expression of acute inflammatory focal lesions associated with an influx of inflammatory T cells and B cells into the CNS, leading to breakdown of the blood-brain barrier, followed by entry of innate immune cells including B cells andmonocytes and macrophages. This leads to oligodendrocyte loss, demyelination, axonal damage, and neuronal loss.

In addition, disease progression irrespective of relapses can occur, which is considered due likely to a neurodegenerative process associated with demyelination, impaired remyelination, axonal loss and neuronal loss independent of CNS inflammation.

2.1.4. Clinical presentation and diagnosis

Relapsing MS is characterized by multifocal inflammatory lesions that can manifest clinically with neurological signs and symptoms with variable recovery (Phadke and Downie, 1987). The term comprises patients with RRMS and SPMS with superimposed relapses. In line with the CHMP Guideline on clinical investigations of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev. 2), it can be assumed that relapses in RRMS and SPMS have the same underlying inflammatory pathophysiology.

RRMS is characterized by periodic acute exacerbations of disease activity (relapses) and periods of remission, consisting of partial or complete recovery. The frequency of relapses and the incidence of brain lesions vary considerably in patients with RRMS; relapses and the presence of new brain lesions on magnetic resonance imaging (MRI) are used to define disease activity. With recurring relapses, disability tends to accumulate, and over time it may disrupt patients' family, social, and working lives, undermining their capacity to function in society. As the disease progresses, patients may experience fewer relapses but continue to accumulate disability, a stage referred to as SPMS. Patients with SPMS continue to steadily accumulate disability irrespective of the presence or absence of superimposed relapses.

Most countries in the world make use of the McDonald criteria for the diagnosis of MS, which are based on both clinical grounds and MRI imaging to demonstrate dissemination of lesions in space and time. A recent revision in 2010 resulted in a simplification of the criteria with fewer required MRI examinations.

2.1.5. Management

Currently there is no cure for MS, but the aberrant activation of self-specific T and B cells observed in MS has been shown to be affected by immunomodulatory treatments, which can favourable alter the course of the disease. These therapeutic interventions are referred to as disease modifying drugs (DMDs). The goal of treatment of RMS with DMDs is to reduce the rate and severity of relapses and to delay disease progression by preventing accumulation of disability.

MS therapies also include symptomatic treatment applied to improve symptoms and complications caused by the disease, e.g. fatigue, spasticity, ataxia, walking disability, weakness, bladder and bowel disturbances, and cognition disturbances etc. Furthermore, acute relapses can be treated with corticosteroids and the standard of care is methylprednisolone i.v.

There are number of approved DMDs with different efficacy and safety profiles for the treatment of RRMS. Glatiramer acetate and interferon-beta (INF-ß) are considered as having a relatively mild-moderate effect (relative reduction by 30-40% of annualised relapse rate [ARR]) but on the other hand having rather benign safety profiles. Some INF-ß products are having broad indications including RRMS patients, patients with a single demyelinating event and SPMS patients with relapses (e.g. Betaferon, Extavia). Despite a rather benign safety profile, intramuscular (i.m.) or subcutaneous (s.c.) administration every other day (e.g. Betaferon) or once a week (Avonex) often cause local administration-related adverse drug reactions affecting the acceptability and compliance to the treatment.

Other recently approved medicines like dimethylfumarate and teriflunomide are indicated for patients with RRMS and are considered to have modest efficacy (reduction of ARR approximately by 50% for dimethylfumarate and by 30% for teriflunomide). Despite convenient way of administration (per os [p.o.] once or twice daily), these medications have a more complex safety profile. Teriflunomide reduces white blood cell count approximately by 15 % from baseline values, requires frequent monitoring of liver function (every two weeks during the first 6 months of treatment, and every 8 weeks thereafter) and has very slow

plasma elimination, which could take up to 2 years. Dimethylfumarate lowers lymphocyte counts by approximately 30% from baseline values and cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients with moderate or severe prolonged lymphopenia. Daclizumab is also indicated for patients with RRMS and has moderate efficacy (approximately 46% relative reduction of ARR). It also induces reduction of total lymphocyte, T and B cell counts on average ≤10% from baseline during the first year of treatment.

Alemtuzumab is indicated for 'RRMS patients with active disease defined by clinical or imaging features', while natalizumab and fingolimod have been approved for 'highly active RRMS'. Disease activity was defined based on clinical and MRI parameters with or without prior DMD. Alemtuzumab is administered as intravenous (i.v.) infusions during two treatment courses lasting 3-5 days each and separated by 12 months with safety follow up for 48 months after the last infusion (relative reduction of ARR by approximately 50%). Infusion related reactions, infections as well as autoimmune disorders including immune thrombocytopenia, nephropathies and thyroid disorders (up to 36% of treated patients) were reported in clinical trials with alemtuzumab. Alemtuzumab depletes T and B lymphocytes and total lymphocyte counts return to lower limit of normal by 6 months after the last infusion in 40% of patients.

Natalizumab is administered as i.v. infusion every 4 weeks. It is very effective in highly active RRMS (relative reduction of ARR by approximately 70%). In contrast to other treatment alternatives in MS it is not inducing lymphopenia, but is associated with seriously increased risk of PML (varies from 0.1 to 10 per 1000 treated patient).

Fingolimod is another alternative for patients with highly active RRMS (relative reduction of ARR by approximately 50-55%). However, it induces reduction of the peripheral lymphocyte count by approximately 70-80% from baseline value. Fingolimod is also associated with the occurrence of PML cases, basal cell cancer and serious cardiac adverse reactions including bradycardia, as well as cases of QT prolongation and atrioventricular block.

In summary, available treatment alternatives for highly active RRMS patients are relatively limited and even it these options are effective, the substantial safety concerns limit their use. Furthermore, in spite of a number of approved drugs for the treatment of RRMS, there is still an unmet medical need for treatment options which are easy to use for the patient, e.g. oral administration and/or short treatment courses, and which have high efficacy with a benign safety profile.

About the product

Cladribine (2-chloro-2′-deoxyadenosine, 2-CdA) is a nucleoside analogue of deoxyadenosine. It belongs to the class of antimetabolites and was initially developed as a synthetic anti-neoplastic agent for the treatment of lymphoid malignancies. It is approved in the European Union (EU)/European Economic Area (EEA) under the trade name Litak® as a solution for injection for the treatment of hairy-cell leukaemia. In contrast to that, MAVENCLAD was developed as an oral formulation of cladribine to improve patient adherence and compliance.

Cladribine is a prodrug, which is activated after intracellular phosphorylation to 2-chlorodeoxyadenosine (CdATP). Cladribine through its active metabolite exerts reversible selective depletion of lymphocytes, which are thought to underlie the autoimmune processes involved in MS pathophysiology (see section 2.4.3. for a description of the mechanism of action).

Type of Application and aspects on development

This application was a complete and independent application submitted in accordance with Article 8.3 of Directive 2001/83/EC.

Scientific advice was given by the CHMP in 2014 on clinical aspects of the application including, amongst other, the choice of a suitable target population, risk minimisation measures and the need for post-authorisation studies.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate release tablet for oral administration containing 10 mg of cladribine as active substance.

Other ingredients of the tablet core are hydroxypropyl betadex (2 hydroxypropyl-ß cyclodextrin), sorbitol and magnesium stearate.

The product is available in oriented polyamide (OPA)/aluminium (Al)/polyvinyl chloride (PVC) – aluminium (Al) blister sealed in a cardboard wallet and fixed in a child-resistant outer carton as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of cladribine is 2-chloro-2`-deoxyadenosine corresponding to the molecular formula $C_{10}H_{12}ClN_5O_3$ and has a relative molecular mass 285.69 g/mol and has the following structure:

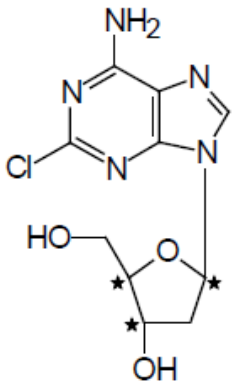


Figure 1. Structure of cladribine

The structure of the active substance was elucidated by a combination of IR spectroscopy, ^{1}H- and ^{13}C-NMR spectroscopy, mass spectrometry as well as elemental analysis. Cladribine is sufficiently characterised and its structure is adequately elucidated.

Cladribine appears as a white to off-white, non-hygroscopic, crystalline powder. It is slightly soluble in water and methanol and practically insoluble in acetonitrile.Its pka was found to be 1.21. Partition coefficient (logP) of 0.0595 was determined at pH 7. Cladribine is stable at slightly basic and at neutral pH.

Cladribine is a molecule with three stereogenic centres. Two stereoisomers are possible, 9-α and 9-β stereoisomer. Cladribine is the 9-β stereoisomer and is controlled by optical rotation according to the current Ph. Eur. monograph.

Cladribine exhibits polymorphism. At least two polymorphs are known. The XRPD patterns of all cladribine batches manufactured to date are consistent with the same polymorph. In addition no interconversion of the produced form into another polymorph has been observed.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The manufacturing process for cladribine active substance comprises two chemical steps and one purification step. The starting materials have been sufficiently justified, are well-defined and adequately controlled by acceptable specifications.

Critical steps and critical process parameters have been identified. Adequate in-process controls are applied during the synthesis.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. The fate and carry over of genotoxic impurities have been discussed satisfactorily.

The active substance is packed in two low density polyethylene (LDPE) bags (primary packaging material) inside a polyethylene drum and lid, which are constructed of high-density polyethylene (HDPE) (secondary packaging). All components used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual), identity (IR, Ph. Eur.), appearance of a solution (Ph. Eur.), pH of solution, specific rotation (Ph. Eur.), heavy metals, residue on ignition (Ph. Eur.), water content (Ph. Eur.), assay (Ph. Eur.), purity (HPLC, TLC, Ph. Eur.), residual solvents (GC), residual ammonia (ion chromatographic) and bacterial endotoxins (Ph. Eur.).

The specification of the active substance complies with the requirements in the Ph. Eur. monograph. The specified limits for genotoxic impurities are considered acceptable considering the indication and are in line with ICH M7 Guideline. The overall control strategy for the related impurities is acceptable; sufficient information has been provided on the control of the potential impurities (including genotoxic) and to demonstrate that potential impurities arising from the described route of synthesis are adequately removed.

The omission of a specific identification test for polymorphism has been satisfactorily justified considering that no interconversion has been observed and that the polymorphic form is not a critical quality attribute because cladribine is dissolved in the manufacture of the finished product.

The analytical methods used have been adequately described and compendial methods have been adopted where applicable. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from three production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot and seven production scale batches of cladribine from the proposed manufacturer stored in the intended commercial package up to 60 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 65% RH) has been provided according to the ICH guidelines. Pilot and production scale batches have been stored under accelerated condition (40 ºC / 75% RH) for 6 months. Results are all within specifications through the 24 month time point at 30 °C /65% RH condition.

Samples for the pilot scale batches were tested for appearance, moisture, specific optical rotation, assay and purity by HPLC. Samples for appearance, appearance of solution (clarity and color), water content, assay by HPLC and purity by HPLC and TLC were tested for the production scale batches. The analytical methods and acceptance criteria are the same as applied for release testing and have been shown to be stability indicating.

The stability of the polymorphic form of cladribine was also verified by XRPD analyses and it remains unchanged during 36 months of storage under the long term conditions and 3 months of storage under the accelerated conditions.

Results on stress conditions of two batches (heat, humidity, basic, acidic, and oxidation studies) were also provided. The conclusion of the forced degradation studies was that cladribine is a stable molecule.

Photostability testing following the ICH guideline Q1B was performed as part of forced degradation study on one batch. The results showed that cladribine is not sensitive to light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months of cladribine with no special storage conditions in the proposed container closure system.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as white, round and biconvex immediate release tablet, intended for oral administration. Each tablet contains 10 mg cladribine, sorbitol, hydroxypropyl betadex and magnesium stearate.

The aim of the pharmaceutical development strategy was to achieve a solid oral dosage form with high bioavailability for cladribine. The quality target product profile has been presented.

Cladribine active substance (AS) is classified as BCS class III compound (low permeability, high solubility). It is unstable in acidic media therefore initial formulations were designed to protect cladribine from the acidic conditions of the stomach and to ensure maximum drug bioavailability. Therefore, several different types of

formulations have been were developed and evaluated. The cladribine / hydroxypropyl betadex oral tablet formulation showed the most favourable PK profile and the lowest variability in the PK parameters estimated. The oral route of administration was pursued investigating two types of cyclodextrins.

Complexation with hydroxypropyl betadex (synonym: 2-hydroxypropyl-β-cyclodextrin, HPβCD) was selected and the process of complex formation was optimised (ratio and reaction temperature). The cladribine / hydroxypropyl betadex complex ratio was defined based on complexation studies at different ratios. Hydroxypropyl betadex is approved in Europe as food additive with an acceptable daily intake (ADI) of 5 mg/kg/day. The amount of hydroxypropyl betadex per tablet is well below the ADI. The excipient properties was considered to be critical material attributes with regard to the quality of the finished product have been presented. Cladribine / hydroxypropyl betadex complex was characterised by Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), solid-state Cross Polarization Magic Angle Spinning (CP-MAS) NMR and for properties in solution. The cladribine-hydroxypropyl betadex complex has been sufficiently characterised and its stability has been demonstrated.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The choice and function of the excipients in the formulation has been justified. Their material attributes (physical, chemical, microbiological properties) were assessed applying a risk assessment for their criticality to the product quality following the recommendations of ICH Q8.

The compatibility of cladribine with the excipients is demonstrated by stability studies carried out for cladribine finished product. No significant changes or variability over time and no degradation of cladribine or increase of degradation products was observed; therefore cladribine is regarded compatible with all the excipients employed.

The changes to formulation used for the Phase I/II/III clinical trials were presented. The excipients are qualitatively the same and quantitatively very similar compared to the clinical formulation. Bioavailability trials confirmed that the PK parameters were not affected by the changes in formulation during the development phases. The in vitro dissolution profiles of the commercial and clinical formulation showed very rapid dissolution and are similar across the pH range 1.2-6.8.

The choice of the dissolution method has been satisfactorily justified. The sink conditions were verified. The discriminatory power of a dissolution test method was evaluated by comparing several batches of different formulations and produced by different manufacturing processes. The provided dissolution data demonstrates that the dissolution method is discriminatory for differences in formulation and manufacturing processes.

Manufacturing process development for the formulation as well as for the commercial formulation was initiated at one manufacturing site and was subsequently transferred to the proposed site, where process validation studies were performed. The process is considered successfully transferred and the robustness of the process has been confirmed.

The tablet formulation was developed using a complexation technique where the complex is pre-milled, sieved and blended with excipients. The final blend is compressed into tablets. The complexation step was optimised with regard to hydroxypropyl betadex ratio, complexation time and temperature. The blending process has also been evaluated and optimised with regard to the relevant process parameters.During process transfer some further modifications in the manufacturing process were implemented. The process changes implemented were mainly due to the different batch size, while the process parameters remained

essentially unchanged. These minor modifications ensure a more robust production process in terms of improved compressibility.

The critical process parameters (CPPs) of the finished product manufacturing process were re-assessed at the proposed manufacturing site. The risk ranking method was presented and includes justification for the risk classification. CPPs have been identified for all the manufacturing steps.

The primary packaging of Cladribine 10 mg immediate release tablets is OPA/ Al /PVC – aluminium blisters (oriented polyamide/ aluminium/ polyvinyl chloride – aluminium blisters) which are sealed in a cardboard wallet and fixed in a child-resistant carton. The primary packaging is of food grade and complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

A usability study on the child-resistant packaging has also been submitted involving patients with mild or moderate dexterity impairments and testing all the handling steps that patients should perform in order to open the packaging and retrieve a tablet. In general the results showed that patients rated that packaging gets easier to open after each use (i.e. they become more experienced with the method to open the packaging). In addition, the testing shows that even under circumstances where patients either do not read the instructions or misunderstand them, the packaging is still intuitive enough that the tablet can be extracted.

Manufacture of the product and process controls

The manufacturing process for cladribine drug product comprises main steps: complexation, pre-milling, sieving/blending, compression, and packaging.

The manufacturing process follows the conventional approach for solid dosage forms, employing standard equipment and it can be considered as a standard process. Holding time for cladribine bulk tablets in a suitable container was established. Critical process steps have been identified and the respective CPPs were defined to control the critical steps. The IPCs during the manufacturing process have been presented and are adequately justified. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

Process validation data comprise a range of studies including among others three commercial scale batches. In conclusion, it has been demonstrated that the manufacturing process is sufficiently robust to provide assurance that immediate release tablets of consistent quality, complying with the designated specification, are produced.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), dimensions, identification by retention time (RP-HPLC), identification by UV spectrum (RP-HPLC), assay (RP-HPLC), degradation products (RP-HPLC), elemental impurities (ICP-MS), water content (Ph. Eur.), dissolution (Ph. Eur.), uniformity of dosage units (HPLC, Ph. Eur.), and microbiological purity (Ph. Eur.).

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data for a large number of batches (production and pilot scale) manufactured with the proposed commercial formulation of cladribine were presented. All batches are representative of the process and the results show that the finished product meets the proposed specification limits.

Stability of the product

Stability data from 5 commercial, 4 pilot and one laboratory scale batches of the finished product have been conducted in line with the ICH Stability Guidelines under long term conditions at 25 ºC / 60% RH for up to 36 months, under 30 ºC / 75% RH for up to 24 months and accelerated conditions at 40 ºC / 75% RH for 6 months. Appropriate post-approval stability commitments are provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Stability of cladribine bulk tablets when stored in the proposed container closure system (double low-density PE bags, with desiccant in between the two bags, placed in high-density polyethylene drums) has also been investigated. The proposed holding time is considered adequately supported by presented data.

The following parameters were investigated: description, water content, assay, related substances, dissolution test and microbial purity. The analytical procedures used for stability testing are the same as intended for release and are stability-indicating. No significant change in any of the tested parameters was observed during the study, as all the parameters tested met the acceptance criteria for all samples stored at long term and accelerated storage conditions. No trends were observed.

A photostability study was conducted on one production scale batch according to ICH Q1B Guideline. No significant change was observed in any of the tested parameters (appearance, identification, assay, degradation products, water content and dissolution) and the results confirm that the product is not photosensitive and no storage restriction against light is found necessary.

A thermal cycling study was performed with cladribine tablets packaged in aluminum/aluminium blisters to evaluate the effect of short-term excursions outside the proposed label storage condition that might occur during shipping. All stability data obtained after thermal cycling met the requirements of the shelf-life specification. No significant differences were observed for all parameters tested. The data are in line with the proposed shelf-life for the finished product.

Based on the provided stability data, the proposed shelf life of 36 months stored in the original package in order to protect from moisture, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

There are no materials of human or animal origin used in the manufacture of the finished product.

Satisfactory TSE/BSE certificates are provided covering the synthesis of hydroxypropyl betadex.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

Cladribine is a synthetic chlorinated analogue of the naturally occurring nucleoside deoxyadenosine, first developed for treatment of leukaemia and used for many years with parenteral formulations in patients with hairy cell leukaemia. An oral formulation (10mg tablets) was later developed for the treatment of MS.

The non-clinical development programme consisted of a battery of primary, secondary and safety pharmacology studies as well PK and toxicology studies and comprised various species including mice, rats, guinea pigs, dogs, and monkeys. Initial *in vivo* non-clinical studies were performed by IP, IV or SC routes. Later studies were conducted by oral route to support the advanced clinical development and marketing application for oral cladribine in MS patients.

All safety pharmacology, toxicology and toxicokinetic studies, as well as one secondary pharmacology study (*in vivo* study in dogs to evaluate cladribine effects on coagulation and platelets) were conducted in accordance with Good Laboratory Practice.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The T cell dependent, relapsing/remitting experimental autoimmune encephalomyelitis (EAE) model was chosen as a rodent model for MS in order to assess the potential of cladribine to reduce clinical symptoms of MS. The effects of cladribine on EAE were evaluated in two experiments in female SJL/J mice which were sensitized with whole mouse spinal cord homogenate in complete Freund's adjuvant and injected subsequently with pertussis toxin. In one experiment a total of 5 mg/kg cladribine was injected divided in five intraperitoneal (i.p.) injections (1mg/kg/day) after induction of EAE. In a second experiment cladribine was injected IV to three groups of EAE mice on day 0-9 with a total dose ranging from 5.0 – 30.0 mg/kg. All mice were evaluated for clinical signs of EAE. Furthermore, immunological and histological samples were collected. As clinical signs of EAE emerged within ten days after sensitization, samples were taken at day eight and at day fourteen. In neither of the studies cladribine exerted measurable effects on clinical signs of EAE.

Secondary pharmacodynamic studies

For the prediction of non-specific off-target binding of cladribine, 115 cell receptors, ion channels and enzymes were investigated in various in vitro receptor binding and enzyme assays. None of the investigated off-targets were affected to more than 50% at 10 µM cladribine except for the adenosine receptor A1. Furthermore, PDE2A and PDE4D were inhibited by 62% compared to control by cladribine. The IC_{50} values were higher compared to the expected exposure at the proposed human clinical dose in MS patients, and but no related signals (CNS, vomiting) were found in the non-clinical studies (see below). The clinical safety relevance of the *in vitro* results was thus considered not relevant.

Cladribine is structurally related to the endogeneous ligand adenosine. Therefore, and in light of the aforementioned results of receptor ligand binding assays, the affinity of cladribine for adenosine receptors A1, A2 and A3 were investigated on both rat and human material. Furthermore, the effects on adenosine uptake were investigated under *in vitro* conditions (guinea-pig). Compared to selective ligands for these receptor sites cladribine showed weak affinities to both adenosine receptors and the adenosine uptake site. The studies on human receptors demonstrated binding of cladribine to the hA1 receptor with Ki values of 1.5µM (agonistic radio-ligand) and 11µM (antagonistic radio-ligand). Less affinity was observed for hA2 and hA3 receptors. Overall, binding to adenosine receptors was only seen at concentrations well above clinical plasma concentrations found with therapeutic doses (22 –29 ng/ml in human plasma).

As part of general pharmacology studies the effects of cladribine on blood coagulation system (prothrombin time, activated partial thromboplastin, fibrinogen concentration), blood clotting time, ADP-induced platelet aggregation and haemolytic effects were studied using blood of rabbits and *in vivo* studies in dogs. At concentrations between 0.1 – 100 µM no effect was observed.

Safety pharmacology programme

The tests included the assessment of effects on cardiovascular, respiratory and central nervous system (CNS) and were supplemented by gastrointestinal and renal *in vivo* studies.

In vitro, a slight effect on hERG tail current in HEK-293 cells stably transfected with hERG cDNA was observed at 10^{-4} M cladribine. No effects on action potential duration, in particular at 90% of repolarization, were observed at concentrations ranging from 10^{-7} to 10^{-4} M in isolated canine purkinje fibers. This conclusion was supported by the results of a 3-month toxicology study in monkeys (oral or SC administration), which also did not show any effect on the duration of the heart rate-corrected QT interval.

In vivo cardiac safety was furthermore investigated in dogs and monkeys. In anaesthetised dogs, cladribine was investigated after cumulative IV administration of 0.1, 0.5, 1, 5 and 10 mg/kg. A slight decrease in systolic and diastolic systemic arterial blood pressure at doses ≥1 mg/kg coupled with an increase in heart rate and cardiac output at doses ≥0.5 mg/kg was observed. Furthermore, increased respiratory rate and volume were observed at doses ≥0.5 mg/kg. In awake dogs, on the contrary, oral administration of cladribine (80 mg/animal) did not induce any effect on heart rate, mean systolic and diastolic systemic arterial blood pressure. No ECG changes were seen and respiratory rate and rectal temperature did not change following administration of cladribine. Cladribine exposure in dogs (mean Cmax = 1775 ng/mL) was about 30 fold higher than the exposure in patients after oral administration of two 10 mg tablets for patients with a body weight ≥60 kg (i.e. maximum recommended human daily dose).

Cladribine had no effect on various different parameters addressing the function of the CNS in mice or rats after i.v. administration of 5 or 10 mg/kg. Additionally, no effects on gastrointestinal and renal function were seen up to 10 mg/kg IV.

Pharmacodynamic drug interactions

Cladribine is intended as a monotherapy. Therefore, no specific pharmacodynamic drug interaction studies were performed, which was considered acceptable.

2.3.3. Pharmacokinetics (PK)

The PK profile of cladribine was evaluated *in vitro* as well as *in vivo*. *In vivo* PK and toxicokinetic studies were performed in mice, rats, dogs and monkeys after oral administration, which is the intended route for human use, and in mice, rats, rabbits, dogs and monkeys after parenteral administration (SC and/or IV). In addition, blood plasma (mouse, rat, dog, monkey, human), hepatic microsomes and hepatocytes (rat, human) were utilised for metabolism studies. Analytical methods used for determination of plasma (mice, rats, rabbit, dog, monkey) urine (monkeys) concentration of cladribine and its major metabolites were validated and assessed.

Absorption studies have been done with different formulations of cladribine (cladribine in HPβCD water solution, HPβCD-tablets or capsules, cladribine dissolved in isotonic saline). Rate and extent of absorption of cladribine after oral administration were studied in rodents, dogs and monkeys. Oral bioavailability was determined for mice, rats and monkeys with the IV route as reference. Absorption was rapid in all species with a maximum plasma concentration (c_{max}) generally observed within 1h after administration, but the absolute bioavailability varied among the species: The highest values were found in mice (56%) and dogs (45%), whereas the values were lower in rats (27%) and monkeys (11%). Exposure to cladribine after oral dosing increased roughly in proportion to the increase in dose. No accumulation of the parent compound was found after repeated administration over 3 months.

In vitro plasma protein binding of cladribine in rats, dogs and monkeys was rather low (10 to 20%). Distribution in mice, monkeys and human whole blood showed that cladribine was almost equally distributed between blood cells and plasma. After i.v. administration of cladribine, the calculated volume of distribution at steady state was equivalent to about 2-3 fold the total body water in rats, dogs and monkeys indicating an extensive distribution into the tissues. Quantitative whole body autoradiography after SC administration of ^{3}H cladribine to mice showed that radioactivity was rapidly and widely distributed into most of the tissues, including the brain. Tissue distribution was rapid with a predominance of well-perfused organs and subsequently excretion organs including the gastrointestinal tract and bladder. Data in both dogs and monkeys also show that cladribine has the ability to distribute to the cerebrospinal fluid.

Following incubation of [^{14}C]-2-chlorodeoxyadenosine in hepatocyte cultures for 24 hours, the extent of metabolism was medium to low in all species (monkey, rabbit, rat, dog, mouse and human). The major routes of biotransformation were similar across the species but rather low in quantities and involved oxidative cleavage of adenine-deoxyribose bond to 2-chloroadenine, which was further oxidized, most likely via N-oxidation or hydroxylation at the pyrimidine moiety. Parent compound also underwent N-oxidation or hydroxylation. In addition, four glucuronide conjugates of 2-chloroadenine were observed in varying amounts across the species and are likely to be a mixture of N- and O-glucuronides. In whole blood, after incubation of 10 µM [^{14}C]-cladribine for up to 24 h, cladribine was extensively metabolized. Prominent metabolites included 2-chlorohypoxanthine in human and monkey plasma (43% of the total radioactivity) and the corresponding

nucleoside 2-chlorodeoxyinosine (14 to 18%). In human and monkey blood cells the main constituent was 2-chlorohypoxanthine besides parent drug with about remaining 23 to 25% of total radioactivity.

In vivo, unchanged cladribine and up to 10 metabolites were identified in plasma, red blood cells, urine and faeces in mouse and monkey with similar metabolic profiles between species. No human mass balance study was performed, but given the very short exposure of the parent drug (2 treatment weeks per year one month apart), the rapid excretion (see below) and the similarity between the urine metabolites in mouse, monkey and human, this was accepted.

The elimination of cladribine from plasma after parenteral administration was rapid in mouse, rat and rabbit with terminal plasma disposition half-life ($t_{1/2}$) values of 1.28, 0.92 and 0.64 hours, respectively, but slower in monkeys and dogs with a half-life of about 5.7 and 10.3 hours, respectively. After oral administration, cladribine elimination was in general relatively rapid in mice ($t_{1/2}$=1.17h), rats ($t_{1/2}$=1.16h), dogs ($t_{1/2}$=13.7h) and monkeys ($t_{1/2}$=3.6h). The mean systemic clearance after parenteral administration was moderate in rabbits (15.2 mL/min/kg) and moderate to high in monkeys (21.5 mL/min/kg) while it was high in mice, rats and dogs (70 mL/min/kg, 48.6 and 24.4 mL/min/kg respectively). In humans, systemic clearance was around 45.4 L/h and was considered as moderate to high.

Results indicated that urinary excretion was the primary route of elimination for cladribine in the mouse. Approximately 74% of the ^{3}H labelled dose was recovered in urine, faeces, and carcasses during a 96-hour period. Elimination appeared to be rapid, with approximately 62% of the administered radioactivity excreted in urine during the first 24 hours post-dose in both males and females. A biliar excretion study was not performed. In humans, elimination was also rapid with 59% of administered dose recovered unchanged in urine in the 0-24h fractions.

Studies related to possible drug–drug interactions have been done at the level of absorption and metabolism, respectively. Collectively, cytochrome (CYP) P450 mediated biotransformation of cladribine is considered of minor significance. Only very limited metabolism was observed at all concentration levels tested. Only incubation with CYPP1A1, CYP1A2 and CYP2D6 minor cladribine transformation was detected (1%, 2-chloroadine). Furthermore, in human hepatocytes there was no evidence of any cladribine derived induction of the major CYP P450 enzymes, i.e CYP1A2 and CYP3A4 (including 2C9 and 2C19). Likewise, no marked inhibitory interactions were observed with CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 in human liver microsomes was observed at concentrations of up to 10 µM.

Cladribine did not display any significant *in vivo* systemic inhibition potential of important transporter-proteins [P-gp (ABCB1), BCRP (ABCG2), MRP2 (ABCC2), MRP4 (ABCC4), MRP5 (ABCC5), OCT2, OAT1, OAT3, OAT4]. Similarly, a significant *in vivo* inhibition of the hepatic uptake transporters OATP1B1 and OATP1B3 seems unlikely. Furthermore, significant alterations of transporter-functions at the intestinal level are considered unlikely for BCRP (ABCG2), and P-gp (ABCB1) at the clinical dose level.

2.3.4. Toxicology

The nonclinical toxicology profile of cladribine was characterized in a number of studies by parenteral and oral administration, including single-dose and repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, antigenicity studies and studies on the excipient hydroxypropylbetadex (HPßCD) and on the metabolite 2-chloroadenine. Studies were conducted in both rodent (mice, rats) and non-rodent species (dog, cynomolgus monkey).

A summary of the studies is provided below with a focus on the studies using the intended route of administration (oral).

Single dose toxicity

Single dose toxicity studies have been performed with cladribine administered by IV or SC route to mice, rats and dogs. Mortality was observed at cladribine doses ranging from about 100 to 200 mg/kg regardless of the route of administration. The highest non-lethal dose in mice was 90 and 150 mg/kg by IV and SC routes, respectively. In rats the highest non-lethal dose was 48 mg/kg in males and 96 mg/kg in females by i.v. route and 100 mg/kg by s.c. route in both males and females. The main clinical signs observed at these doses consisted of prostration, decrease in activity and piloerection. In dogs, neither lethality nor clinical changes (except for foamy emesis) were seen after a single IV dose of 25 mg/kg, the highest feasible dose.

Repeat dose toxicity

The initial repeat-dose studies were conducted by i.v. or s.c. route using a daily dosing regimen or cyclic regimen. The pivotal studies designed to evaluate the repeat-dose toxicity of cladribine were conducted in mice and monkeys that are considered appropriate species due to similarities in plasma deoxycytidine level profile to humans.

Repeated dose toxicity studies including toxicokinetic investigations were performed after both parenteral and oral administration in mice and cynomolgus monkey. The species were chosen due to similarities in plasma deoxycytidine (DKC) levels compared to humans, given that DKC can compete for enzymatic binding sites of cladribine within cells). Generally, the toxic effects observed in mice and monkeys were dose-dependent and reversible. The main symptoms observed in the studies were anaemia, leucopenia, lymphoid depletion of lymphoid system (spleen, thymus and lymph nodes) and bone marrow cellular depletion. Longer administration of cladribine at 1 mg/kg/day had also effects on the kidney (karyomegaly of renal tubular epithelium) and adrenals (adrenal cortex atrophy and decreased vacuolation). Additional microscopic changes were observed in the animals sacrificed early and included atrophy of gastric and small intestinal mucosa and testicular degeneration. Therefore, the target organs were the immune system (at 0.3 mg/kg/day), bone marrow, skin, mucous membranes, and testes (≥ 0.6 mg/kg/day) and kidneys (≥ 1 mg/kg/day).

Safety margins (at least a factor of 1.6) were established based on the extrapolated exposure at the no-observed-adverse-effect-level (NOAEL) versus the projected human exposure at the anticipated oral clinical dose (i.e. 10 mg tablet/day corresponding to 0.175 mg/kg/day for a person of around 55-60 kg). No toxic effects were observed when cladribine was administered by oral route up to 20 mg/kg/day in mice and up to 6 mg/kg/days in cynomolgus monkeys, respectively. The daily exposure associated to these NOAELs exceeded the daily human exposure at the oral clinical dose (10 mg /day) by a factor of at least 3.9-fold based on AUC_{0-24} and 8.2-fold based on projected cumulative $AUC_{0-\infty}$ (200 mg/year). Both values refer to the NOAEL found in monkeys.

Furthermore, as HPßCD has previously been described to induce an increase in tumours of the exocrine pancreas in a carcinogenicity study, the application included a dedicated repeat-dose study in mice of the excipient alone in order to establish the relevance of the finding in relation to the proposed formulation and posology. The NOAEL with the cyclical regimen was 500 mg/kg/day corresponding to about 100 times the daily dose for a person weighing 60 kg and taking two 10 mg tablets.

Genotoxicity

The genotoxic potential of cladribine was tested in standard *in vitro* and *in vivo* tests. Cladribine was negative in bacterial and mammalian mutations assays and did not induce unscheduled DNA synthesis. However, it

was shown to be genotoxic, causing chromosomal damage in the bone marrow of mice *in vivo* and in Chinese hamster ovary-wbl cells *in vitro*. These findings are not unexpected, since cladribine inhibits DNA repair and causes DNA double strand breaks. Cladribine did not induce gene mutations but it was clastogenic in mammalian cells.

Carcinogenicity

Cladribine was tested for its carcinogenic potential in a single 22-month study in mice (s.c., up to 10mg/kg/day). Additionally, a 26-week transgenic bioassay in transgenic rasH2 mice (TgrasH2, administration by oral gavage, 5, 15 and 30 mg/kg/day) was conducted.

A significant increase in Harderian gland tumours was observed in the long-term mouse study at a dose of 10mg/kg/day. Although the majority of the tumours were benign adenomas, there were also three adenocarcinomas. No histomorphological signs of progression states to adenocarcinomas were found in any of the adenomas observed. This occurrence is not considered to have clinical relevance, as humans do not have a comparable anatomical structure (Carlton, 1991). No cladribine-related neoplastic findings were observed in TgrasH2 mice at any dose tested, either with cladribine tablet or with cladribine drug substance. Preliminary tumour findings in a dose-range study are considered as having occurred by chance.

Reproduction Toxicity

Studies investigating the effects of cladribine on male and female fertility in mice, embryofoetal development in mice and rabbits, and pre- and postnatal development were performed. The routes of administration were SC and IV. As these routes ensure high systemic administration, the lack of oral studies was accepted.

In males, testes weights and the percentage of motile sperms were significantly decreased by cladribine at 30 mg/kg/day. Testicular effects (marked testicular atrophy and the complete absence of spermatogenesis) have also been observed in one out of two monkeys in a repeated dose study after SC dosing of cladribine at 1 mg/kg/day. Testicular (non-neoplastic) effects were also observed in the oral 26-week carcinogenicity study in TgrasH2 mice with cladribine tablets at 30 mg/kg/day consisting of reduced testes weights and degeneration of seminifeorus tubules or signs of atrophy of germinal epithelium. No effects were observed by cladribine up to 30 mg/kg on male libido or fertility. Given the mechanism of action of cladribine, together with these data, the potential of cladribine to affect male fertility in humans seems likely. When male mice had been treated with cladribine four weeks prior to mating and throughout mating, single instances of embryos with skeletal malformations similar to those found in the embryofoetal development studies in mice and rabbits were observed.

Early embryo development was studied in mice at dosed up to 8 mg/kg/day (SC). Embryotoxicity was observed at the high dose group only, without maternal toxicity. NOAELs were determined to be 4 mg/kg/day (embryo) and 8 mg/kg/day (dams). Embryofetal development effects in mice and rabbits of i.v. administration of cladribine was also studied. In mice, the NOAEL for embryofetal development was 0.5 mg/kg, whereas maternal NOAEL was 3.0 mg/kg/day. Maternal NOAEL was similar in rabbits (3.0 mg/kg/day), whereas the NOAEL for the embryofetal development was 1.0 mg/kg/day.

In the pre- and postnatal development cladribine induced lethal effects in the offspring of mice at all stages of in utero development and was clearly teratogenic in mice and rabbits. Skeletal malformations were confirmed in a subset of pups. However, surviving pups did not show any effect on postnatal development including attainment of developmental milestones, behaviour, learning and reproductive functions.

No juvenile toxicity studies were performed as cladribine is only intended for use in adults.

Local Tolerance

Local tolerability studies were done using Syrian golden hamster treated in the cheek pouch, single dose SC irritation in mouse, intra and para-venous injection in rabbits, and intra-arterial injection in rabbits. The results of these irritation studies did not indicate any concerns about the clinical use of this compound by these routes of administration.

Other toxicity studies

Antigenicity of cladribine was studied in guinea pigs. In the active systemic anaphylaxis and the passive cutaneous anaphylaxis tests, cladribine did not show any antigenic potential. Analysis of the ultraviolet absorption spectrum showed that cladribine did not absorb light within the range of natural sunlight (290-700 nm). No concern for direct phototoxicity was identified and no further studies evaluating the phototoxic potential of cladribine were performed.

2.3.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment (ERA) according to Guideline EMEA/CHMP/4447/00 was provided. The n-octanol-water partition coefficient (log K_{ow}) for cladribine was 0.0595 at pH=7 (OECD 107; Lange, 2009). The predicted environmental concentration in surface-water ($PEC_{surfacewater}$) was calculated at 0.00027 µg/L based on a refined market penetration factor (Fpen) taking into account the proposed treatment regime (maximum of 10 treatment days per year, 20 treatment days in total over two years and dosing up to 20 mg/treatment day). Notably, cladribine is also approved for the treatment of hairy cell leukemia and the combined $PEC_{surfacewater}$ for both indications is 0.00028 µg/L.

Table 1 – Summary of ERA results

Substance: Cladribine			
CAS-number: 4291-63-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	0.0595	Not B Potential PBT (N)
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00027	µg/L	> 0.01 threshold (Y/**N**)
Other concerns (e.g. chemical class)	-	-	(Y/**N**)

Cladribine $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L and is not a persistence, bioaccumulation and toxicity (PBT) substance as log Kow does not exceed 4.5.

Therefore cladribine is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Cladribine is a well-known active substance with the ability to induce apoptosis in lymphocytes and used for the treatment of hairy cell leukaemia. Cladribine was extensively investigated in a variety of non-clinical studies aimed to characterize the pharmacological and PK profile as well as with regards to safety and

toxicology. Safety pharmacology, toxicology and toxicokinetic studies conducted were done in accordance with GLP.

In general, the pharmacology, PK, safety pharmacology and toxicology program was considered adequate to support the present application.

The experimental autoimmune encephalomyelitis (EAE) model was chosen as a rodent model for MS. In this model the applicant was unable to show exerted measurable effects on clinical signs of EAE or on histopathological and immunological parameters. It is speculated that this might be due to pharmacogenetic differences between rodents and humans affecting PK and pharmacodynamics (PD). It is hypothesized that the levels of cladribine (and of its active triphosphate form) necessary to suppress an immune response was either not achieved or not sustained for sufficient time to have an effect. While this explanation remains speculative, taking into consideration the limited predictive value of the EAE model, the missing proof of concept did not raise further concerns given the available evidence of efficacy from clinical trials (see sections 2.4.3. and 2.5.).

In anaesthetized beagle dogs a slight decrease in systolic and diastolic systemic arterial blood pressure at doses ≥1 mg/kg coupled with an increase in heart rate and cardiac output at doses ≥0.5 mg/kg was observed. In a new study, performed in awake dogs, cladribine did not induce any effect on cardiovascular parameters. In this study the exposure was about 30 fold higher than the exposure in patients. The applicants speculates that the difference between anaesthetized and awake dogs in relation to the cardiovascular effects could be due to the presence of compensatory mechanisms in awake dogs and the mode of application in the study performed in awake dogs (oral) compared to anaesthetized animals (IV) and subsequent different PK profiles. It is agreed with the applicant that these are possible explanations and that the newly performed study in awake dogs is of greater relevance than the study performed in anaesthetized dogs. Based on these data it seems that the potential of cladribine to elicit cardiotoxic effects under therapeutic conditions is low.

The additional safety pharmacology screening did not reveal any alterations including absence of any adverse CNS effect. The results of these studies support a considerable safety margin compared to doses and exposures intended for human use.

Data pertaining to the absorption, distribution, metabolism and excretion of cladribine have been gathered in a series of studies conducted in mice, rats, rabbits, dogs and monkeys via three routes of administration: IV, SC and oral. Absorption was rapid in all species but oral bioavailability was clearly different among the species. However, rapid absorption and moderate oral bioavailability has been found in humans (see section 2.3.3.). Exposure to cladribine after oral dosing increased roughly in proportion to the increase in dose. The volume of distribution was large and distribution was rapid and wide including the brain.

Metabolism studies revealed that cladribine is metabolized only to a small extent by phase I and II enzymes and neither induction nor marked inhibition of CYP450 enzymes has been found. Furthermore, the available data support a low potential for interaction with drug transporters.

Unchanged cladribine and up to 10 metabolites were identified in plasma, red blood cells, urine and faeces in mouse and monkey, with similar metabolic profiles. However, no human mass balance study has been performed and there is insufficient understanding of any human specific drug related material in human plasma. Consequently, no comparable plasma metabolite exposures data between human and the species was available for safety testing. The applicant argued that since the metabolites found in mouse and monkey plasma are similar as well as the metabolites found in mouse, monkey and human urine, the metabolic pathways proposed for mice and monkey is also relevant for humans. Taking also into consideration the very

short exposure of the parent drug (two treatments weeks per year, one month apart), and the rapid excretion, the issue was not further pursued.

Non-clinical toxicology of cladribine was characterized in a set of single dose and repeat dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance and antigenicity studies in different species (mouse, rat, rabbit, monkey and guinea pig). Most toxicology studies were performed by SC or IV routes, which, based on exposure were also considered relevant.

The single-dose toxicity studies conducted demonstrate that cladribine is only moderately toxic following parenteral administration. The pivotal studies designed to evaluate the repeat-dose toxicity of cladribine were conducted in mice and cynomolgus monkeys. The toxic effects observed in mice and monkeys were generally dose-dependent and reversible. The primary target organs were the immune system, bone marrow, skin, mucous membranes, testes and kidneys. No toxic effects were observed when cladribine was administered by oral route up to 20 mg/kg/day in mice and up to 6 mg/kg/days in cynomolgus monkeys, respectively. The safety margin to intended clinical human exposure following oral administration in mice and monkeys at these NOAEL was 4 times or more (when considering the cumulative exposure).

As part of its primary pharmacodynamic effects, cladribine causes DNA strand breaks and has DNA repair inhibiting effects. Thus, there is a risk for genotoxicity. In the long-term carcinogenicity study with mice, cladribine caused increased tumours only in the Harderian glands at an exposure exceeding the expected maximum human exposure by 15-fold. These tumours were considered clinically irrelevant as humans do not have a comparable anatomical structure. In addition, no tumours were observed in the short-term carcinogenicity study in Tg.rasH2 mice at an exposure exceeding the expected maximum human exposure up to 25-fold. Hence, no evidence for a relevant carcinogenic risk to humans was revealed in the mouse models. However, in the carcinogenicity studies with Tg.rasH2 mice also no cladribine-induced lymphopenia was observed.

In reproductive and developmental toxicity studies in animals, cladribine was shown to be embryolethal and to induce fetal malformations. The adverse effects on development occurred at dosage levels lower than those causing maternal toxicity. Furthermore, while no effect on female fertility was observed, reduced testes weights and increased numbers of non-motile sperm was observed in a study with male mice, although no actual detrimental effects on fertility was seen. Testicular changes were also seen in monkeys. The potential of cladribine to affect male fertility in humans is unknown. However, based on cladribine genotoxicity, a potential risk that cladribine can affect maturing germ cells cannot be excluded.

Based on these data, use of cladribine is contraindicated in pregnant and lactating women. Due to the genotoxic potential of cladribine and possible effects on spermatogonia and stem cells, an adequate timing to prevent pregnancies after end of treatment is recommended not only for women being treated with cladribine, but also for female partners of male patients. An access margin of 6 months after administration of the last cladribine dose was considered acceptable. Further information is provided in a prescribers and patient guide including advice for use of effective contraception.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical program was considered acceptable and adequate in order to support the present application for use of cladribine in the treatment of adult patients with highly active RMS. The findings from non-clinical pharmacology studies were in line with the mechanism of action of cladribine with the main target organs being lymphoid and haematopoietic systems. The non-clinical PK studies suggest a low

potential of cladribine for drug-drug interaction. Toxicology studies showed a genotoxic and a teratogenic potential of cladribine. Based on the ERA results, cladribine is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

In total, 21 clinical studies have been conducted with cladribine for the treatment of Multiple Sclerosis; 12 involving oral cladribine and 9 involving parenteral cladribine. An overview of the clinical program is presented in Table 2.

Good Clinical Practice (GCP)

The applicant confirmed that the clinical trials were performed in accordance with Good Clinical Practice as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2 Tabular Overview of Clinical Studies

Study identifier or no.	Phase	Route of administra-tion	Indication	Dose / Formulation	Included in integrated safety analyses	Included in integrated efficacy analyses
Main studies: oral cladribine						
Protocol 25643 (CLARITY)	III	Oral	RRMS	10 mg oral cladribine; clinical	Yes	Yes
Protocol 27820 (CLARITY EXT)	IIIb	Oral	RRMS	10 mg oral cladribine; clinical	Yes	Yes
Protocol 26593 (ONWARD)	IIb	Oral	Relapsing MS	10 mg oral cladribine; clinical Add-on to IFN-β-1a/--1	Yes	Yes
Protocol 28821 (ORACLE MS)	III	Oral	At high risk of converting to MS	10 mg oral cladribine; commercial	Yes	Yes
Supportive studies: oral cladribine						
PREMIERE Registry [a]	Obser-vational	None [a]	Participated in ≥1 of 5 oral cladribine studies[b]	None [a]	Yes [a]	No
RECORD MS Registry	Obser-vational	Oral	Cladribine-naïve MS	10 mg oral cladribine,	No	No

Study identifier or no.	Phase	Route of administra-tion	Indication	Dose / Formulation	Included in integrated safety analyses	Included in integrated efficacy analyses
				commercial		
Other supportive studies (Phase I and II): iv and sc cladribine						
6226	I	iv	Incurable hematologic malignancy	1 mg/mL solution	No	No
6414	I	iv	Refractory/ untreatable solid tumors	1 mg/mL solution	No	No
93-220	I	Oral and iv	Advanced malignancies	1 mg/mL solution	No	No
JK-6251-1	I	iv	Lymphoid malignancies	1 mg/mL solution	No	No
2-CdA-MS-SCRIPP (MS-Scripps)	II	iv	Progressive MS	1 mg/mL solution	Yes	No
2-CdA-MS-SCRIPA (Scripps-A)	II	iv	Progressive MS	1 mg/mL solution	Yes	No
2-CdA-MS-SCRIPB (Scripps-B)	II	sc	Progressive MS	1 mg/mL solution	Yes	No
2-CdA-MS-SCRIPC (Scripps-C)	II	sc	RRMS	1 mg/mL solution	Yes	No
2-CdA-MS-001 (MS-001)	III	sc	Progressive MS	1 mg/mL solution	Yes	No
Other supportive studies (Phase I): oral cladribine						
Protocol No. IXR 101-09-186	I	Oral and sc	MS	Two 3 mg tablet formulations 3 mg capsule sc 1 mg/mL solution	No	No
Protocol No. IXR 102-09-186	I	Oral and iv	MS	2 mg tablet formulation 10 mg tablet formulation 1 mg/mL solution	No	No
Protocol No. 25803	I	Oral and iv	MS	10 mg tablet formulation 1 mg/mL solution	No	No
Protocol No. 26127	I	Oral	MS	10 mg tablet formulation	No	No
Protocol No.	I	Oral	MS	10 mg tablet	No	No

Study identifier or no.	Phase	Route of administra-tion	Indication	Dose / Formulation	Included in integrated safety analyses	Included in integrated efficacy analyses
26486				formulation 44 µg IFN-ß-1a		
Protocol No. 27967	I	Oral	MS	10 mg tablet formulation; 40 mg tablets pantoprazole	No	No

DDI=drug-drug interaction; IFN=interferon; iv=intravenous; MS=multiple sclerosis; RRMS=relapsing-remitting MS; sc=subcutaneous

[a] Although the subjects had received cladribine in other studies, within the PREMIERE Registry no cladribine was administered

2.4.2. Pharmacokinetics

All clinical pharmacology studies were carried out in subjects with MS or haematological malignancies since it was not considered appropriate to conduct these in healthy volunteers in view of the nucleotide-related cytotoxicity of cladribine, especially on lymphocytes.

A total of 10 phase I trials have been conducted to investigate the clinical pharmacology of cladribine (see Table 2). Furthermore, population pharmacokinetic (popPK) analyses based on the clinical pharmacology studies and a sub-population from the phase III trial CLARITY, as well as PK/PD modelling have been performed using pooled data pooled from Phase II and III studies in MS patients. In addition, 19 *in vitro* studies with human biomaterial have been performed. Validated methods have been applied for the analysis of cladribine and the metabolite 2-chloroadenine in human plasma or urine.

The clinical pharmacology program aimed at describing the absorption and disposition of cladribine. Furthermore, clinical trials were conducted with the aim to identify factors, which may alter exposure and to reveal potential interactions with food and with other medical products.

Absorption

Different oral formulations were tested in biopharmaceutical studies. These oral formulations comprised HPβCD cladribine tablets, hard gelatin capsule formulations, as well as a mucoadhesive tablet formulation, with varying excipients, aimed at further increasing the bioavailability of cladribine and reducing variability. As a result of these studies the tablet employing HPβCD with a strength of 10 mg cladribine was selected based on its bioavailability and low variability as the clinical trial formulation.

Cladribine is rapidly absorbed, with a median t_{max} of 0.5h (range 0.5-1.5 h) following a single dose of a 10 mg HPβCD tablets. Cladribine showed moderate permeability and high solubility. Administration of 10 mg cladribine resulted in a cladribine 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.

The absolute oral bioavailability in MS subjects is approximately 40%, which is mainly explained by incomplete absorption due to transporter-mediated efflux. According to *in vitro* studies, cladribine is a substrate of BCRP (ABCG2) transporter proteins, which is abundantly expressed in the small intestine. Cladribine was also shown to be a weak substrate of P-glycoprotein (P-gp), however the significance is likely low. Furthermore, it was a substrate of the nucleoside transporters CNTs (Concentrative Nucleoside Transporters) and ENTs (Equilibrative Nucleoside Transporters) more specifically ENT1 and CNT3.

In vitro and *in vivo* data showing lack of appreciable CYP-mediated drug metabolism suggest that any contribution of a pre-systemic metabolism/first pass effect to the intermediate bioavailability of cladribine is negligible.

In comparing the tablet formulation intended for commercial use with the clinical trial formulation used in the pivotal studies, there were some differences in the composition. No comparative clinical bioavailability / bioequivalence study has been conducted comparing these two formulations. Instead, *in vitro* dissolution studies have shown comparable dissolution profiles. Furthermore, *in vivo* studies with different oral cladribine formulations showed that varying sorbitol contents across the range of both the cladribine clinical trials tablet formulation and the formulation intended for commercial use did not substantially alter the oral bioavailability of cladribine.

Data from food-interaction studies

When cladribine was administered together with a high fat meal, the absorption was delayed (t_{max} 1.5h), C_{max} was lower (by 29%), while the area under the curve (AUC) was minimally affected ($AUC_{0-\infty}$ reduced by 4%).

Distribution

The applicant performed two *in vitro* studies to assess protein binding and blood/plasma distribution.

The volume of distribution was found to be large (with a mean of 480–490 L), indicating extensive tissue distribution and intracellular uptake. *In vitro* experiments showed that cladribine and its phosphorylated metabolites were retained in lymphocytes isolated from healthy blood donors. The accumulation occurred almost completely in the first hour of incubation. Maximum concentrations of cladribine and/or its metabolites in lymphocytes at 0.1 µM incubations are about 30 to 40 times greater than in the total cell suspension.

After entering the target cells, cladribine is phosphorylated to cladribine monophosphate (Cd-AMP) by DCK (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'-NTase. In a study of the intracellular PK 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 half-life of Cd-AMP was 15 h. Intracellular half-life of Cd-ATP was 10 h.

The plasma protein binding of cladribine is low (20%) and independent of plasma concentration. In a small study in cancer patients, the CSF/plasma ratio was approximately 0.25 following an IV infusion, indicating that cladribine penetrates the blood brain barrier.

Elimination

No radioactive labelled human mass balance study was performed due to the long retention of cladribine in lymphocytes.

The metabolic profiles of cladribine were investigated in urine and plasma after IV and oral administration to humans. A total of 10 possible metabolites have been identified. These metabolites were formed by the following proposed pathways: oxidative cleavage at the adeninedeoxyribose bond, oxidation at the adenine or the deoxyribose moiety, and conjugation. Following both oral and IV administration, the parent compound cladribine was the main component present in plasma and urine (approximately 60% of a single dose was excreted as unchanged cladribine). No major plasma metabolites (i.e. exceeding 10% of the parent drug AUC) have been identified. The most notable metabolite, 2-chloroadenine, actually represents a minor metabolite in both plasma and urine and accounts for around 3% of parent drug exposure after oral

administration. This metabolite is reported as being several fold less cytotoxic in different types of leukocytes compared to cladribine (Lindemalm et al., 2004). Low levels of carboxy-cladribine and N-oxide-2-chloroadenine were also found in plasma. Additional metabolites detected at low levels in urine were carboxy-cladribine after oral and IV administration, and N-oxide-cladribine and N-oxide-2-chloroadenine after oral administration.

These metabolic characteristics are further supported by *in vitro* studies investigating potential CYP450 enzymes in pooled human liver microsomes and in human hepatic S9 fractions, which showed limited metabolism with 92-100% of cladribine remaining as unchanged cladribine. However, based on *in vitro* cDNA expressed enzyme systems cladribine could be metabolised by CYP1A1, CYP1A2 and CYP2D6.

Based on the popPK analysis, total mean clearance (CL) and typical $t_{1/2}$ in patients with MS was determined to be 45.8 L/h and 23h, respectively. The median values for elimination were 22.2 L/h for renal clearance and 23.4 L/h for non-renal clearance. The renal clearance of cladribine exceeds the glomerular filtration rate, indicating active renal tubular secretion of cladribine. The non-renal elimination consists predominantly of intracellular metabolism and elimination of cladribine and phosphorylated forms of cladribine. Hepatic metabolism plays only a minor role (i.e. <10% of the total cladribine CL). There was no excretion data from faeces.

From the population PK analysis, variability in cladribine pharmacokinetics parameters appears to be relatively small.

Dose proportionality and time dependencies

After oral administration of cladribine across a dose range from 3 to 20 mg, C_{max} and AUC increased in a dose-proportional fashion. No time dependence of cladribine exposure has been observed after multiple dosing. No significant accumulation of cladribine concentration in plasma has been observed after repeated dosing.

Special populations

No dedicated clinical pharmacology study has been performed to investigate potential PK differences for males or females. A trend towards a higher cladribine exposure in female subjects has however been observed in the popPK and PK/PD models. No specific study or population PK analysis comparing cladribine PK in different ethnic groups has been provided. This was accepted as no clinically relevant influence of ethnic differences on oral cladribine PK is expected.

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. Likewise, no studies were conducted in the paediatric population. This is in line with the PIP waiver from birth to less than 18 years of age based on the ground that MAVENCLAD is likely to be unsafe in the paediatric population.

The popPK model analysis did not show any effect of age (range 18 to 65 years) or gender on cladribine PK.

Impaired renal and hepatic function

No dedicated studies have been performed in patients with renal or hepatic impairment. Given that cladribine is not excreted via the faeces and in light of its metabolism characteristics, hepatic impairment was not expected to have any substantial impact on the elimination of cladribine rendering any further study unnecessary.

Overall, approximately 30 patients in the clinical pharmacology program had a calculated creatinine clearance (Cockgroft-Gault, CLcr) < 90 mL/min and would be categorized as having mild renal impairment. The number of patients with moderate renal impairment was very low.

In the population PK analysis in subjects with MS approximately half of the elimination of cladribine is related to renal elimination (CLR: 23.1 L/h, CLNR: 22.7 L/h). Of the 173 patients included in the analysis, 151 had normal renal function, 21 patients had mild renal impairment, and 1 patient had moderate renal impairment. The median (range) CLcr was 107.9 (49.6 -244.4) mL/min. According to the popPK model, the predicted total clearance is 45.8 L/h at a CLcr of 90 mL/min and 37.4 L/h at a CLcr of 60 mL/min. This corresponds to a 22% increase in exposure. 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 (CLcr= 65 ml/min), 30% in moderate renal impairment (CLcr = 40 ml/min), and 40% in severe renal impairment (CLcr = 20ml/min).

PK interaction studies

The potential for cladribine to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 was investigated *in vitro* in pooled human liver microsomes. There was no signal of CYP inhibition up to 5 µM (covering systemic inhibition potential), however too low cladribine concentration compared to the intestinal cut-off concentration was used for CYP3A4. A new *in vitro* study was conducted with acceptable study set up including appropriate incubation concentration to cover intestine concentration. The study confirmed that the risk of clinically relevant inhibitory effect on CYP3A4 is very low.

The results from investigation whether cladribine is an inducer of CYP2B6 and CYP3A were inconclusive. An induction of CYP1A2 based on mRNA increases was a borderline *in vitro* finding. The clinical experience using cladribine within oncology is vast and no report of CYP induction is known.

Cladribine was not an in vitro inhibitor of OATP1B1, OATP1B3, OCT1, OAT4, MRP2, MRP4 and OAT1. However, it appears to be an inhibitor in vitro of BCRP, MRP5 and OAT3. Based on the estimated systemic and intestinal cut-offs the risk of clinically relevant interaction was however limited.

Two clinical drug-drug-interaction studies were performed.

The interaction between cladribine and IFN-β1a was studied in 15 patients with MS. This was a three-period open-label multiple dose study. The subjects received cladribine orally at 10 to 20 mg/day for five consecutive days (Days 1 to 5). After at least 2 days following the last dose of cladribine, subjects received IFN-β1a at different doses. The study suggests that co-administration of cladribine with IFN-β-1a has a small effect on cladribine clearance. However, the 11% increase in total clearance was not considered to be clinically relevant.

The other study was an open label single-dose cross-over study in 18 MS patients. In one period, 10 mg cladribine was administered alone. In the other period, subjects received a dose of 40 mg pantoprazole on Days 1 and 2 and a single dose of cladribine on Day 2, 3 h after having received pantoprazole. The study showed that repeated oral pantoprazole 40 mg single doses administered 15h and 3h prior to administration of cladribine had no influence on the PK profile of cladribine. Therefore, a change in gastric pH induced by the concomitant administration of a proton pump inhibitor does not affect the rate and extent of cladribine absorption.

Finally, the potential for complex formation between free cyclodextrin (HPßCD), released from the cladribine tablet formulation, and concomitant drugs (ibuprofen, furosemide, gabapentin) was investigated *in vitro*.

Complexation of these drugs with HPßCD was seen, however, no firm conclusions could be drawn from the study results.

2.4.3. Pharmacodynamics

Mechanism of action

Cladribine is a synthetic analogue of the nucleoside deoxyadenosine. It differs from deoxyadenosine only by the substitution of a chlorine for hydrogen in the 2-position of the purine ring. The chlorine substitution in the purine ring protects cladribine from degradation by adenosine deaminase, increasing the intracellular residence time (Beutler 1992, Sipe 2005). Cladribine is a product and activation requires intracellular phosphorylation to its active triphosphate form 2-CdATP. This is particularly efficiently achieved in lymphocytes, due to their constitutively high deoxycytidine kinase (DCK) and relatively low 5'-nucleotidase levels. A high DCK to 5'-nucleotidase ratio favours accumulation of 2-CdATP, making lymphocytes particularly susceptible to the effects of compound and differences in in expression levels of DCK and 5'-nucleotidase between immune cell subtypes may explain differences in immune cell sensitivity to cladribine (Salvat 2009; Leist and Weissert 2011).

The molecular mechanism of action of 2-CdATP was studied in dividing and non-dividing lymphocytes and leukaemia cells including direct and indirect actions on DNA and pro-apoptotic effects on mitochondria (Freyer et al, 2015). In dividing cells, 2-CdATP can interfere with DNA synthesis via inhibition of ribonucleotide reductase and competes with deoxyadenosine triphosphate (dATP) for incorporation into DNA by DNA polymerases. In resting immune cells, cladribine causes DNA single-strand breaks, rapid nicotinamide adenine dinucleotide (NAD) consumption, adenosine triphosphate (ATP) depletion and cell death (Carson et al, 1983; Seto et al, 1985; Seto et al, 1986). In addition, cladribine can cause direct caspase dependent and independent apoptosis via the release of cytochrome C and apoptosis-inducing factor into the cytosol of non-dividing cells (Leoni et al, 1998; Genini et al, 2000).

MS involves a complex chain of events with a contribution from different immune cell types, with autoreactive T and B cells being the key players in the pathophysiological disease processes (Sipe 2010, Hemmer 2015). The mechanisms by which cladribine exerts its therapeutic effects in MS is not fully elucidated but its preferential effect on lymphocytes could potentially interrupt the cascade of immune events central to MS.

Primary and Secondary pharmacology

No dedicated primary pharmacology studies have been performed in support of this application. However, the PD effects of parenteral cladribine have previously been extensively investigated in the setting of lymphoid malignancies. Furthermore, clinical studies performed with parenteral cladribine in MS have been performed and showed a preferential and sustained reduction in lymphocytes, with only minor effects on neutrophils, platelets, hemoglobin and hematocrit levels (Beutler et al., 1996; Romine et al., 1999; Rice et al., 2000). These effects of oral cladribine on haematologic parameters and in particular lymphocytes were also assessed in the phase III oral cladribine studies CLARITY, CLARITY EXTENSION and ORACLE MS. Furthermore, a popPK/PD model was developed in order to describe the time course of absolute lymphocyte count (ALC). Finally, a time-to-event population model was developed to support the choice of dose and the re-treatment criteria including a delay in case of insufficient recovery of lymphocyte counts.

Cladribine has been shown to cause selective depletion of T and B cells, with a greater effect on CD4+ and CD8+ cells, with comparably low activity against other haematologic and immune cell types (Beutler et al., 1996; Rice et al.,2000; Grieb et al., 2001). CD8+ T cells have a less pronounced decrease and a faster

recovery, resulting in a decreased CD4:CD8 ratio. CD19+ B cells and CD14+/CD56+ natural killer cells are also affected but more transiently reduced than T cells. Changes in neutrophils, eosinophils, erythrocytes and platelets are relatively low and minimal (Sipe 2010, Leist and Weissert 2011).

In terms of lymphocyte depletion dynamics, treatment with oral cladribine in CLARITY resulted in a dose dependent decrease of lymphocyte counts when compared to baseline levels, followed by a gradual increase. At first nadir (Week 16) following start of treatment in year 1 and second nadir (Week 55) following start of treatment in year 2, the median lymphocyte counts decreased by 42% and 58%, respectively, from baseline pre-treatment levels. Similar results were obtained in the ORACLE study and in the group of subjects of the CLARITY EXT study who received cladribine treatment for the first time after receiving placebo in CLARITY. Exploratory lymphocyte subset analyses in patient subgroups helped to better understand the effect of cladribine on absolute numbers of naïve and central memory CD4+ and CD8+ T cells, CD19+ B cells and CD16+/CD56+ natural killer cells. Treatment with oral cladribine 3.5 mg/kg resulted in a moderate, sustained decline in absolute numbers of circulating T-cell counts (as assessed by CD3, CD4, and CD8 markers). In CLARITY, the median reduction seen at first and second nadir for the CD4+ subset was -56% and -72% respectively and, thus, higher than the reduction for the CD8+ subset at first nadir (-31%) and second nadir (-39%), consequently decreasing the CD4/CD8 ratio (see also laboratory findings in section 2.6.). Similarly, absolute numbers of median CD4+ T cell counts were more affected than CD8+ cell counts in CLARITY EXT (subjects who received cladribine treatment for the first time after receiving placebo in CLARITY) and ORACLE trials, and also took longer to recover, again leading to a decrease in CD4/CD8 ratio. In summary, the absolute median numbers of CD4+ lymphocytes are decreased more than CD8+ cell counts, and the recovery of the latter is faster. Treatment with cladribine is therefore associated with a temporarily decreased CD4/CD8 ratio.

To evaluate the dose- (exposure)-response relationship with respect to ALC following administration of cladribine, a popPK/PD model was developed. Data from CLARITY, CLARITY EXT and ORACLE MS were included in the analysis. The analysis dataset included 47,959 ALC observations from 1931 subjects. Hereof, 508 observations were missing and a further 203 observations were ignored as some subjects had multiple recorded ALC observations at time 0. Accordingly, the total number of ALC measurements included in the analysis summed to 47,248. The analyses were performed using the non-linear mixed effects modelling approach. The final model described the ALC dynamics observed following cladribine administration by use of an indirect response model with cladribine stimulating the loss of ALC through an inhibitory maximum exposure (Emax) drug-effect relationship. According to the model, the time course of ALC response was characterized by a slow turnover of cells corresponding to a mean residence time of lymphocytes 2.4 years. Women were estimated to have a 17% lower nadir value compared to men due to a higher sensitivity to cladribine exposure. The inter-individual variability in C50 parameter was approximately 65%. This indicates that the individual response to a certain cladribine exposure level is highly variable. Concomitant administration of IFN-β-1a was associated with an additional 19% drop in ALC compared to cladribine alone, whilst concomitant glucocorticoids had no influence on ALC response to cladribine.

Based on the long lasting PD properties of cladribine, the proposed posology consists of 2 treatment courses, each comprising 2 treatment weeks. To support the choice of dose to be used in clinical practice, the applicant developed a repeated time-to-event population model, initially using data from CLARITY and later extended to also include data from CLARITY EXT and ORACLE MS. The analysis dataset included a total of 1542 subjects (1319 from CLARITY, 867 from CLARITY EXT and 223 from ORACLE MS [fulfilling McDonald 2010 criteria]) and 753 relapse observations. The model described the time to occurrence and re-occurrence of qualifying relapses using a Weibull distribution with a decreasing hazard over time. The effect of cladribine was implemented on the hazard function using an Emax drug-effect relationship, whereby the effect is driven

by a (decaying) effect compartment exposure related to the cumulative amount of cladribine administered adjusted for individual creatinine clearance. The number of relapses in the year prior to receiving cladribine treatment was included in the covariate model as a proportional increase of the scale parameter of the Weibull distribution. The model showed that a dose of 3.5 mg/kg over 2 years is appropriate in reducing the risk of relapses: increasing the dose above 3.5 mg/kg did not rapidly and substantially increase the effect on the underlying hazard, whilst decreasing it to lower doses moves the exposure to the steeper part of the curve, and quickly leads to a marked drop in efficacy. The relation between the hazard and the effect compartment exposure was derived at different times (Month 1, 3, 6, 9, 12, 15, 18, 21, and 24) following the first dose for the typical subject. The predicted relationships during the first 2 years of treatment with 3.5mg/kg cumulative dose showed that the hazard of having a relapse decreases with time for any drug exposure, and decreases with the drug exposure at any time.

Simulations based on the relapse rate model jointly with the ALC model, have been applied to investigate the effect of treatment postponement in the second year (re-treatment criteria), allowing more time for the ALC to recover for those subjects who have not done so by the end of the first year. These simulations have shown that i) only very few subjects (1% or less) would not recover to Grade 1 or 0 within an additional 6 months before re-treatment in year 2, ii) in those subjects qualifying for postponement, the proportion reaching Grade 3-4 lymphopenia at some time in the study is decreased (from 23% to 15%) when the mitigation rule is applied, and iii) such a delay of up to 6 months has essentially no effect on the probability of experiencing relapses during the second year of cladribine treatment. In particular, the percentages of subjects not experiencing a certain (1 to 6) number of relapses, as well as the mean predicted relapse-free survival and its probability distribution over time, were comparable across the different scenarios considered during the analysis. This means that if drug administration needs to be interrupted for lymphopenia, the effect on efficacy is sustained.

With regards to secondary pharmacology, the effect of cladribine on QTc has been subject to detailed analyses based on a subpopulation of 143 patients from the CLARITY trial. This ECG sub-study in the target population of MS patients was designed to evaluate potential acute and/or cumulative effects of cladribine on the ECG time-intervals (RR, PR, QRS, QT, QTcB and QTcF) and T-wave morphology, with a particular emphasis on the heart rate corrected QT interval (QTcF primary, QTcB supportive), as a well-accepted surrogate measure signifying delay or heterogeneity in cardiac ventricular repolarization, which may be possibly associated with proarrhythmic product characteristics. QTcF was considered the primary outcome variable. According to the results, cladribine does not appear to influence the QTc interval to a clinically relevant extent.

2.4.1. Discussion on clinical pharmacology

Cladribine's mechanism of action is based on 2 possible actions of the intracellularly formed metabolite CdATP, affecting both dividing and quiescent lymphocytes. It exerts reversible and long lasting selective depletion of lymphocytes, which are thought to underlie the autoimmune processes involved in MS pathophysiology. As a result, the design and conduct of a classical clinical pharmacology developmental program in healthy adult subjects was not feasible. Therefore, all clinical pharmacology and biopharmaceutical studies were designed and conducted in patients in the targeted indications of MS or haematological malignancies. For this very reason, it was acknowledged that not all typical elements of clinical pharmacology programs for non-cytotoxic new molecular entities could be conducted.

Results from PK studies show that the absolute bioavailability of oral tablets of HPβCD cladribine is approximately 40% and is mainly determined by the absorption process. The variability in exposure was acceptable. Following oral administration of tablets absorption was rapid, with a time to maximum concentration in the range of 0.5-1.5 hours. Intake of cladribine tablets with food resulted in a small delay of the absorption (t_{max} 1.5h), and a small reduction in exposure requiring no dose adjustments.

Furthermore, the exposure of cladribine was shown to be dose dependent over the investigated dose range. The volume of distribution is large and complex with specific accumulation of the phosphorylated forms of cladribine in lymphocytes. Plasma/serum protein binding of cladribine is overall low and concentration independent.

The elimination of cladribine is equally dependent on renal (60% of dose excreted as parent compound) and non-renal routes, where the non-renal elimination consists predominantly of intracellular metabolism, non-hepatic extra-cellular metabolism and only to a minor extent hepatic metabolism. The majority of the non-renal elimination is likely related to the rapid uptake in lymphocytes and further forming phosphates. Cladribine has three chiral centres. Adenosine as well as 2-deoxy-D-ribose are natural compounds and their stereochemistry is well understood. With the introduction of the chlorine in the 2-position of the adenine moiety, the stereochemistry of the molecule is unlikely to be affected, while it renders the molecule more stable against metabolism by adenosine deaminase. Although this has not been studied, it appears plausible that cladribine does not have different properties from analogues like adenosine, which has well-known stereochemistry.

Due to the lack of a human mass balance, there is insufficient understanding of the existence of any human specific circulating drug-related material in human plasma or any major circulating metabolite. Overall, this gap was addressed by the available *in vitro* data and identification of metabolites in human plasma, which showed that cladribine is not metabolised to a meaningful extent.

While the turnover of cladribine in microsomes was low, the available data suggest some role of CYP1A1, CYP1A2 and CYP2D6 in the metabolism of cladribine. Overall, the importance of CYP enzymes in the elimination of cladribine was considered to be likely low. Renal clearance of cladribine exceeds the glomerular filtration rate, indicating the drug undergoes net tubular secretion in addition to glomerular filtration. This was consistently observed throughout the clinical pharmacology program. While no dedicated studies in patients with renal impairment have been conducted, there was some evidence for a dependence of total cladribine clearance on creatinine clearance based on popPK analyses. A modest reduction in total clearance for subjects with mild renal impairment is predicted. Cladribine is not recommended in patients with moderate or severe renal impairment. There is no experience in patients with hepatic impairment, which was considered acceptable given that cladribine is not excreted via the faeces and in light of its metabolism characteristics.

No *in vitro* evidence for either inhibition or induction of CYP450 enzymes has been observed. This is confirmed by the drug-drug interaction studies with IFN-β-1a and pantoprazole showing that concomitant administration of these drugs does not lead to relevant PK interactions. At the level of cladribine absorption, the only conceivable interaction pathway of clinical relevance appears to be breast cancer resistance protein (BCRP or ABCG2). A possible decrease in cladribine exposure could thus occur if potent BCRP transporter inducers are co-administered. *In vitro* studies also indicate that cladribine is a substrate of the ENT1 and CNT3 transport proteins. Although the net contribution to cladribine exposure is not known, it could theoretically be altered by potent ENT1 and CNT3 transporter inhibitors. This information is reflected in SmPC section 4.5. Furthermore, the CHMP noted that the effect of cladribine on hormonal contraceptives is

currently unknown. The CHMP therefore recommended that the applicant performed a drug-drug interaction study after approval.

Complexation of other medicinal products with HPßCD was seen, however, no firm conclusions could be drawn from the study results. Besides, in the absence of *in vivo* interaction studies, clinically relevant drug interaction scenarios cannot be excluded. As a precautionary measure, administration of any other oral medicinal product should be separated from cladribine by at least 3hours.

There is no clear evidence of gender-related differences in the PK of cladribine. Both the PK and PK/PD model suggest a small impact of age and/or weight on exposure and response. It is worth considering the observed gender difference as an effect of differing size/body composition of men and women leading to higher exposure in women. In the pop PK/PD model, ALC nadir was approximately 17% lower in women compared to men. This finding was in less than 50% explained by the higher exposure in women resulting from lower body weight and lower renal clearance. The difference in ALC nadir is therefore likely to reflect a higher sensitivity in women in terms of pharmacodynamic response to treatment. Overall, the level of evidence was limited and the effect was small. No dose-adjustment was considered necessary.

Modelling and simulation outcomes also showed that ALC decreases as a function of cladribine exposure. Simulations furthermore suggested that cumulative cladribine doses lower than 3.5 mg/kg would result in lower efficacy outcomes and would not substantially reduce the risk of adverse events. Simulations based on the relapse rate model jointly with the ALC model furthermore showed that a delay of re-treatment in year 2 of 6 months had no adverse effect on efficacy, while the majority of patients were likely to recover from severe lymphopenia during such period resulting in a reduced risk for future severe lymphopenia. These data thus supported the re-treatment guidelines.

With regards to secondary pharmacology, the effect of cladribine on QTc has been studied based on a subpopulation of 143 patients from the CLARITY trial. According to the results, cladribine does not appear to influence the QTc interval to a clinically relevant extent. The design of the ECG study was not in accordance with the ICH E4 guideline, especially with respect to timing of ECG and the construction with serial ECG assessments following long-time on-treatment. These issues were however not considered to preclude a conclusion of an absence of a risk taking also into account the lack of signal from the integrated safety analysis and non-clinical studies.

2.4.2. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data were considered adequate to support the present application.

2.5. Clinical efficacy

To evaluate the clinical efficacy of cladribine, four clinical trials were conducted, including the pivotal Phase III trial and its 2-year extension study CLARITY and CLARITY-EXT in adult patients with RRMS.

A summary of the study design, methods and main results is provided in this section.

2.5.1. Dose response study

No specific dose response studies in the target population have been conducted.

The choice of dose in the pivotal CLARITY trial was mainly based on the data from the initial Scripps studies, which investigated the use of a parenteral formulation of cladribine in the treatment of MS, in particular taking into account the risk of lymphopenia and herpes zoster infections. Safety data of the pooled Scripps studies Scripps-C, MS-Scripps, and MS-001 suggested that the risk of herpes zoster infections was dose-related, increasing in frequency among cladribine-treated subjects who received parenteral doses of 2.8 mg/kg or higher compared with subjects who received placebo or lower. Therefore, the doses selected to be carried forward in future studies were 2.1 mg/kg total cumulative dose and 1.4 mg/kg total cumulative dose, the lowest dose that had shown sustained beneficial MRI outcomes.

Given that the absolute bioavailability achieved with oral dosage forms was approximately 40%, as demonstrated for the 10 mg cladribine HPβCD tablet (see section 2.4.), the estimated corresponding oral dose to the parenteral cumulative dose of 2.1 mg/kg/year was 5.25 mg/kg and the oral equivalent to a parenteral cumulative dose of 1.4 mg/kg/year was 3.5 mg/kg.

(Re-)treatment regimens, either two or four courses in the first year with repeat dosing of two courses in the second year, were also based on previous parenteral studies and were chosen to optimize the benefit-risk profile for the oral formulation of cladribine.

A brief summary of the Scripps studies is provided below.

Scripps-B (2-CdA-MS-SCRIPB) Cladribine (2-CdA) Treatment of Multiple Sclerosis: A Multicenter Trial

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled phase II study to evaluate safety and efficacy of immunosuppression with cladribine in subjects with chronic progressive multiple sclerosis. Subjects were randomized to one of these treatment groups: 2.1 mg/kg cladribine (total dose), 0.7 mg/kg cladribine (total dose), or placebo. A total of 11 subjects were enrolled in the study; 4 received cladribine 0.7 mg/kg, 4 received cladribine 2.1 mg/kg and 3 received placebo.

Cladribine was administered at 0.07 mg/kg/day by SC injection for 5 consecutive days per course every 28 days. In the cladribine 2.1 mg/kg group, a maximum of 6 courses were to be active drug and 2 courses were placebo. In the cladribine 0.7 mg/kg group, a maximum of 2 courses were to be active drug and the remaining 6 courses were placebo.

After completing the double-blind phase, subjects who had been treated with placebo or cladribine 0.7 mg/kg were eligible to receive 3 monthly courses of cladribine (0.14 mg/kg/day for 5 days every 28 days) for a total retreatment dose of 2.1 mg/kg. Subjects who were initially treated with cladribine 2.1 mg/kg received 4 courses of placebo. All 11 subjects entered the crossover re-treatment phase.

Treatment with cladribine induced lymphopenia, which reached Grade 3-4 levels in all the subjects receiving the higher dose of cladribine. Infections, particularly urinary tract infections, were also commonly observed. No statistical analysis was performed on the efficacy data.

Scripps-C (2CdA-MS-SCRIPC) Cladribine (2CdA) Treatment of Relapsing-Remitting Multiple Sclerosis

This was a single-center, randomized, double-blind, placebo-controlled Phase II study designed to evaluate the efficacy and safety of cladribine in subjects with RRMS. This study utilized retrospective data collection and analysis. Subjects with RRMS were randomized to 1 of 2 treatment groups: Cladribine 2.1 mg/kg or placebo. Subjects in the cladribine group received 6 courses of cladribine, given as 5 consecutive daily SC

injections at a dose of 0.07 mg/kg/day, every 28 days. The 6 courses were followed by 2 courses of placebo. Subjects in the placebo group were to receive 8 courses of placebo.

The total duration of the double-blind phase of the study was 18 months, including an 8 month treatment period and a 10 month follow-up period.

A total of 52 subjects were enrolled and randomized to receive study treatment. Of the 52 enrolled subjects, 49 subjects (26 in the cladribine group and 23 in the placebo group) were included in the analysis population. Treatment with 2.1 mg/kg cladribine SC was superior to treatment with placebo in most of the trial efficacy endpoints: the annualized clinical relapse rate (ARR, cladribine 0.699, placebo 1.22; p=0.0125) , the proportion of subjects who were relapse free at Month 18 (cladribine 10/26, placebo 3/23; p=0.0223), the median number of active T1 Gd+ lesions at Month 18 per subject (cladribine 0.0, placebo 1.0; p=0.0004), and the median change from baseline in T2 lesion volumes at Month 18 (cladribine -0.12, placebo 1.42; p=0.0119). No statistically significant difference was observed for total relapse count between groups.

As expected, more subjects in the cladribine group experienced Grade 3 or Grade 4 lymphopenia and more cladribine-treated subjects reported an infection as an adverse event.

Notably, according to an independent third party audit at the study site, several major GCP violations and irregularities were revealed, based on which the US Food and Drug Administration concluded that the data generated from this site were not reliable to support a New Drug Application.

MS-Scripps (2-CdA-MS-SCRIPP): Cladribine Clinical Trial in the Treatment of Chronic Progressive Multiple Sclerosis

This was a single-center, randomized, double-blind, placebo-controlled, parallel-group Phase IIb study designed to evaluate safety and efficacy of cladribine 2.8 mg/kg compared with placebo in subjects with CPMS. This study utilized retrospective data collection and analysis. The trial included 3 phases: screening, double-blind, and follow-up. Subjects who qualified for the study were matched in pairs according to age, sex, and severity of disease. The subjects in each pair were randomly assigned to different treatment groups for the 2-year double-blind interval.

During Months 1 through 4 of Year 1, each subject received 4 monthly 7-day infusions of cladribine 0.1 mg/kg per day or placebo, followed by an 8-month observation interval. Cladribine-treated subjects received a total dosage of 2.8 mg/kg. In the second year of the study, subjects initially randomized to placebo received a total dosage of cladribine 1.4 mg/kg for 4 months. Subjects who initially received cladribine in Year 1 received placebo during these 4 months of Year 2. Subjects were then observed for 7 months with no treatment.

The analysis included 49 subjects: 24 patients receiving placebo, then cladribine 1.4 mg/kg, and 25 patients receiving cladribine 2.8 mg/kg, then placebo. The results of the efficacy analyses of Year 1 data showed that cladribine 2.8 mg/kg was superior to placebo as indicated by the lower volume of T1 enhanced lesions (cladribine 1.25, placebo 200; p<0.001) and a lesser increase from baseline in MRI T2 lesion volume (cladribine -0.44, placebo 2.3; p=0.003). There was also a lower cumulative progression rate with cladribine measured as the change in EDSS score (cladribine 0.0, placebo 0.5; p=0.006) and Scripps Neurologic Rating Scale (SNRS) scores (cladribine 4.0, placebo -5.0; p<0.001).

Adverse events reported for cladribine during this study, and changes in laboratory test results, were generally in line with the expected pharmacologic effects of cladribine on lymphocytes. The severity and persistence of most cladribine adverse effects appeared to be dose-related, with the exception of the degree

of decrease in lymphocyte count, which was similar following treatment with cladribine 1.4 mg/kg and 2.8 mg/kg.

MS-001 (2-CdA-MS-001): Cladribine Clinical Trial in Chronic Non-Remitting Progressive Multiple Sclerosis

The objective of this study was to evaluate the safety and efficacy of cladribine in subjects with CPMS and to evaluate the dose-response relationship. This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter study designed to compare cladribine 0.7 mg/kg and 2.1 mg/kg with placebo. Subjects received either a maximum of 2 weekly courses of cladribine 0.07 mg/kg per day (each treatment week consisting of 5 consecutive days) at 4 week intervals (plus 6 courses of placebo: total dose 0.7 mg/kg), or a maximum of 6 weekly courses of cladribine 0.07 mg/kg per day (each treatment week consisting of 5 consecutive days) at 4 week intervals (plus 2 courses of placebo: total dose, 2.1 mg/kg), or 8 weekly courses of placebo.

There were 54 subjects in the placebo group, 53 in the 0.7 mg/kg cladribine group, and 52 in the 2.1 mg/kg cladribine group. Both cladribine 0.7 mg/kg and 2.1 mg/kg treatments were superior to placebo treatment in subjects with CPMS with respect to the proportion of subjects having detectable MRI T1 enhanced lesions (0.7 mg/kg cladribine: 10% [5/53], 2.1 mg/kg cladribine: 6% [3/52], and placebo 31% [17/54], p=0.0080 and p=0.0009, respectively). A significant difference in favour of both cladribine groups compared to placebo was also observed for the mean volume and number of such lesions.

With regards to safety, a reduction in lymphocyte counts was observed, which was long-lasting and dose-related.

2.5.2. Main studies

One main pivotal trial along with its 2-year extension study has been conducted to support the claimed indication.

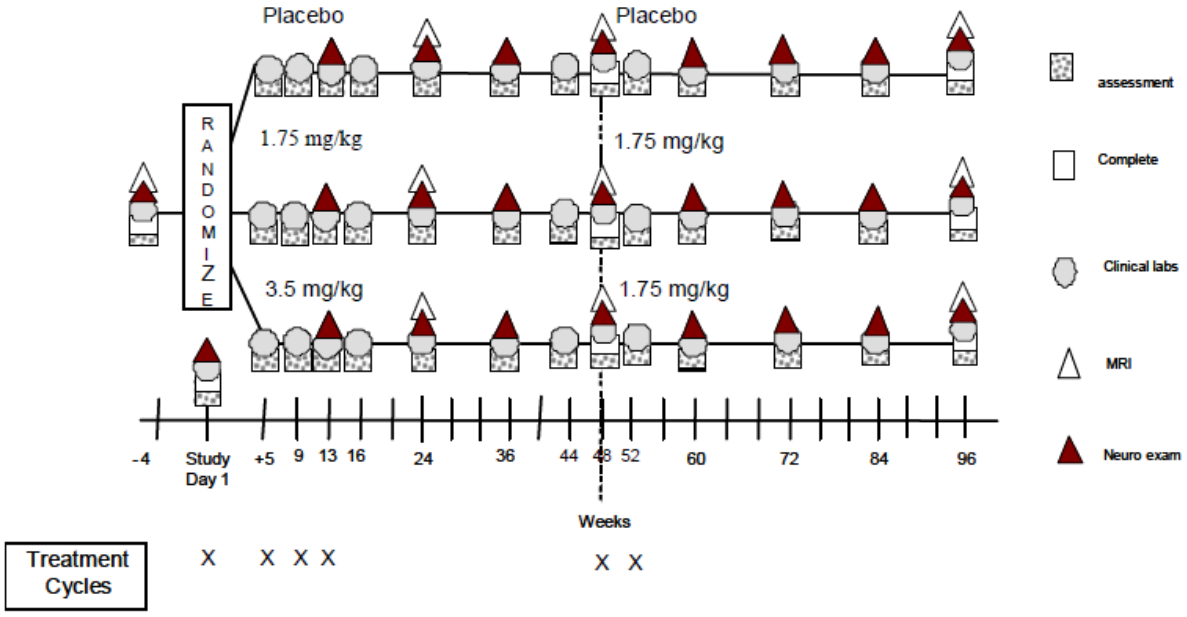
2.5.2.1. CLARITY

Study 25643 (CLARITY): A phase III, randomized, double-blind, three-arm, placebo-controlled, multi-center study to evaluate the safety and efficacy of oral cladribine in subjects with relapsing-remitting multiple sclerosis (RRMS)

This was a 96 week, Phase III, randomized, double-blind, 3-arm, placebo-controlled, multicentre study to evaluate the safety and efficacy of 2 doses of oral cladribine (3.5 mg/kg and 5.25 mg/kg) 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 Week 0-48; and a retreatment period during Week 48-96.

The overall trial design is displayed in Figure 1.

Figure 1 Schematic Overview of CLARITY Trial Design



Methods

Study Participants

Main Inclusion Criteria

- Male or female 18-65 years of age
- Had definite RRMS according to the 2005 McDonald criteria
- MRI consistent with MS at the pre-trial evaluation, according to the Fazekas criteria
- EDSS from 0-5.5
- Use of contraception (including males)

Main Exclusion Criteria

- Had Secondary Progressive MS (SPMS) or Primary Progressive MS (PPMS)
- Had received disease modifying drugs (DMDs) within the last three months prior to Trial Day 1
- Had previously failed treatment with two or more DMDs on the basis of efficacy (could have previously failed treatment based on tolerability and/or convenience)
- Had prior or current history of malignancy
- Had a history of persistent anaemia, leukopenia, neutropenia, or thrombocytopenia after immunosuppressive therapy

Treatments

Enrolled subjects were equally randomized into 3 groups to receive:

- Cladribine tablets 3.5 mg/kg (administered per os [p.o.] as 0.875 mg/kg/course for two courses plus placebo p.o. for two courses during the first 48 weeks and 0.875 mg/kg/course for two courses during the second 48 weeks), or
- Cladribine tablets 5.25 mg/kg (administered p.o. as 0.875 mg/kg/course for four courses during the first 48 weeks and 0.875 mg/kg/course for two courses during the second 48 weeks), or
- Matching placebo (administered p.o. for four courses during the first 48 weeks and two courses during the second 48 weeks).

A course was defined as daily administration given consecutively over four to five days. Initial treatment during Week 0-48 was administered in two or four separate courses starting at Trial Day 1, Week 5, Week 9 and Week 13. Retreatment during the Week 48-96 period was administered in two separate courses starting at Weeks 48 and 52. During the Week 48-96 period, those patients who received cladribine during Week 0-48 (both cladribine 3.5 mg/kg and cladribine 5.25 mg/kg) continued to receive cladribine 3.5 mg/kg, and those patients who received placebo during Week 0-48 continued to receive placebo.

Figure 2 displays the dosing courses for the three treatment groups. Study medication was administrated after an overnight fast on an empty stomach, and once administered, the patients were to wait at least one hour before eating.

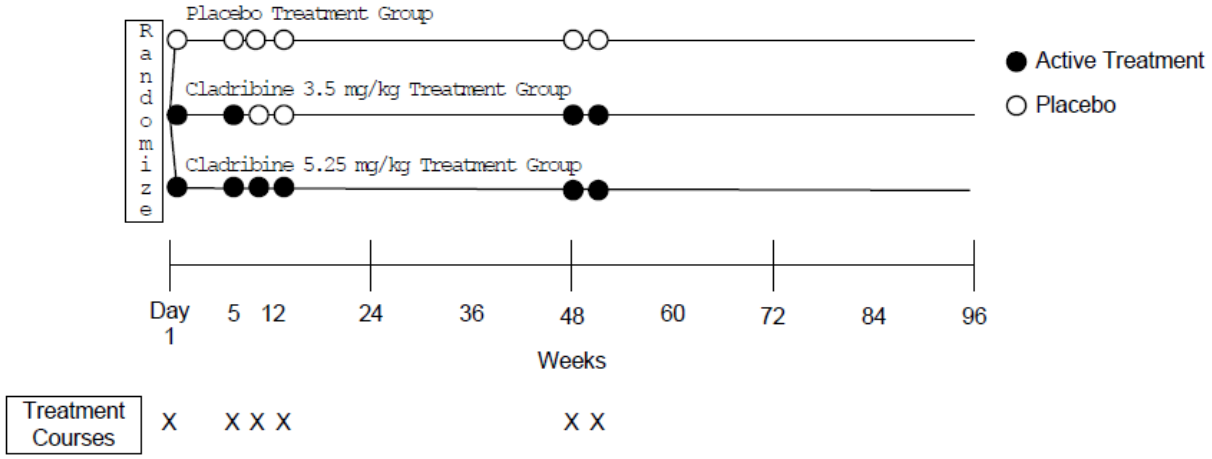


Figure 2 Treatment Dosing Diagram

Permitted Medicines

Corticosteroids were permitted for the treatment of acute relapses at the discretion of the Treating Physician. Steroid treatments for relapses were to consist of 1g i.v. solumedrol for three days. If not possible, oral steroids could be utilised for no more than fourteen days following a relapse. Any MRI scans conducted during the trial were to be performed before administration of steroids or at least seven days after the last dose of steroids.

Prohibited Medicines

Prohibited medicines included immunomodulatory therapy, immunosuppressive therapy, cytokine or anti-cytokine therapy and medication suspected to interact with cladribine.

Rescue Medication

Beginning at Week 24, rescue medication became an option and patients who experienced greater than one qualifying relapse (see definition below) and/or a sustained increase in EDSS of ≥1, or ≥1.5 points if baseline EDSS was 0 (over a period of at least three months) during a calendar year qualified to receive rescue medication. Rebif® was the preferred rescue medication in the trial but the Investigator and patient may have elected to take another disease modifying drug. Any patient who accepted rescue medication was permanently discontinued from trial medication and was to remain in the trial and perform all the scheduled assessments according to the visit schedule.

Objectives

Primary objective

The primary objective was to evaluate the efficacy of cladribine versus placebo in the reduction of qualifying relapse rate during 96 weeks of treatment in patients with RRMS.

Secondary objectives

The secondary objectives were to assess the effect of cladribine in patients with RRMS on progression of disability, and in reducing lesion activity as measured by MRI.

Outcomes/endpoints

Primary endpoint

The primary endpoint was the qualifying relapse rate at 96 weeks. A qualifying relapse was 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 at least 30 days of clinical stability or improvement

Secondary endpoints:

- Proportion of patients qualifying relapse-free at 96 weeks
- Disability progression at 96 weeks (time to sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0, over a period of at least 3 months)
- Mean number of active T1 gadolinium-enhanced lesions per patient per scan at 96 Weeks
- Mean number of active T2 lesions per patient per scan at 96 weeks
- Mean number of combined unique (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 “CU lesions”) per patient per scan at 96 weeks

Tertiary endpoints

Tertiary endpoints included, amongst other, time to first qualifying relapse at 96 weeks, proportion of subjects rescued at 96 weeks and the assessment of patient health related quality of life (HRQL) and health care resource utilisation (HRU).

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, 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 (i.e., 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%.

Randomisation

Subjects who satisfied the entry criteria were equally randomized (1:1:1) by a central randomization system and allocated a computer-generated treatment randomization number. Randomization occurred within the investigational sites.

Blinding (masking)

This was a double-blind trial. A Treating Physician viewed clinical laboratory evaluations and assessed adverse events (AEs) and safety information, while an independent Evaluating Physician, who was blinded to treatment, performed neurological examinations. A central neuroradiology center, also blinded to treatment, assessed MRIs.

Subjects received cladribine tablets or matching placebo. All subjects within a specific weight range received the same number of tablets per course. Subjects in the cladribine 3.5 mg/kg group received placebo tablets in courses three and four to maintain blinding with the cladribine 5.25 mg/kg group.

The blinding could only be broken for an individual subject in the case of an emergency, when knowledge of the investigational medicinal product (IMP) was essential for the clinical management of the subject.

Statistical methods

Analysis Populations

The analysis sets defined by the protocol consisted of:

- Intent-to-treat (ITT) population, comprising all subjects who were randomized into the trial.
- Evaluable population composed of the subjects who completed treatment without a major protocol deviation with 96-week data.
- Safety population, including 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 utilized as the supportive analysis population.

Evaluation of Efficacy

All tests were two-sided and performed at the 5% significance level. For the analysis of baseline continuous parameters, confirmation of the ANOVA model assumptions (normality) was conducted. Normality was assessed using the normal probability plot and the Shapiro-Wilk statistic. If the model assumptions were satisfied, the ANOVA model with fixed effects for treatment and region was performed on the raw data; otherwise, the ANOVA model with fixed effects for treatment and region was performed on the ranked data. Primary and secondary efficacy analyses were performed on the ITT population.

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.

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 superior to placebo for the primary efficacy parameter. If both of the cladribine doses were determined to be significantly superior to placebo, then an α of 5% was used in the testing of these MRI parameters. If only one of the doses was significantly different from placebo, then only that dose at α of 2.5% was tested for these MRI parameters.

These MRI parameters were analysed using a non-parametric ANCOVA (analysis of covariance) model on ranked data with fixed effects for treatment group and region with adjustment for T1 Gd+ lesion, as there was no available baseline data for baseline T2 or CU lesions.

The proportion of qualifying relapse-free subjects at the end of 96 weeks was analysed using a logistic regression model with fixed effects for treatment group and region. The odds ratio of being qualifying relapse-free in each of the cladribine groups versus the placebo group and the associated 95% (97.5%) CI was estimated.

Time to 3-month sustained change in EDSS score was analysed using a Cox proportional hazards model with fixed effects for treatment group and region. An approximate Chi-square test based on Wald statistic was used to compare each cladribine group versus the placebo group. The hazard ratio of time to 3-month sustained change in EDSS score in each of the cladribine groups versus the placebo group and the associated 95% (97.5%) CI was estimated. Kaplan-Meier plots of time to 3-month sustained change in EDSS score (survival function) were presented by treatment group.

Results

Participant flow

A total of 1,641 patients were screened for enrollment into the trial. Of these patients, 1,326 were randomized (1:1:1) into the trial and 315 were screening failures.

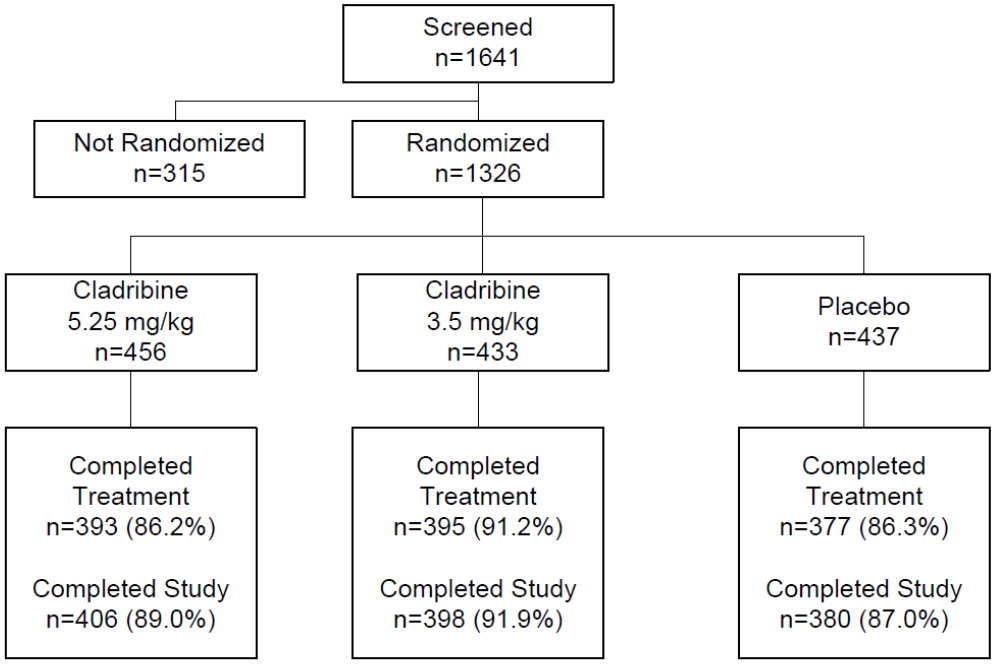


Figure 3 - Disposition of Subjects for Treatment Completion and Study Completion

The most common reason for treatment discontinuation was the "adverse event" for which the cladribine 5.25 mg/kg group displayed a higher rate (7.7%) compared to the cladribine 3.5 mg/kg (3.5%) and placebo (2.1%) groups.

Table 3 summarises the reasons for premature treatment withdrawal during the trial.

Table 3 - Treatment Termination by Treatment Group – ITT Population

	Status	Cladribine 5.25 mg/kg (n=456) n (%)	Cladribine 3.5 mg/kg (n=433) n (%)	Placebo (n=437) n (%)	Total (n=1326) n (%)
Completed Treatment	Yes	393 (86.2)	395 (91.2)	377 (86.3)	1165 (87.9)
	No	63 (13.8)	38 (8.8)	60 (13.7)	161 (12.1)
Reasons for Withdrawing from Treatment Prematurely	Adverse event	35 (7.7)	15 (3.5)	9 (2.1)	59 (4.4)
	Lost to follow-up	4 (0.9)	2 (0.5)	3 (0.7)	9 (0.7)
	Protocol violation	5 (1.1)	5 (1.2)	9 (2.1)	19 (1.4)
	Death	1 (0.2)	1 (0.2)	2 (0.5)	4 (0.3)
	Disease progression	5 (1.1)	5 (1.2)	24 (5.5)	34 (2.6)
	Other	13 (2.9)	10 (2.3)	13 (3.0)	36 (2.7)

Recruitment

A total of 1,326 patients were randomized into the trial from 155 investigative sites across 32 countries worldwide. Date of first patient first visit was 20 Apr 2005 and date of last patient last visit was 12 Nov 2008.

Conduct of the study

Nine protocol amendments were issued for this trial. Four of them were to adapt the protocol to country-specific regulations. The rest of them included smaller modifications, e.g. further specifying the MRI criteria for MS, introducing additional pregnancy testing prior to retreatment and including mean brain atrophy measurements at baseline and at 48 weeks.

The major protocol deviations were established prior to database lock. Subjects in the ITT population with major protocol deviations were excluded from the Evaluable population. Some of these protocol deviations were: history of malignancy (n=2), compromised blinding (n=4) and reports of pregnancy (n=23).

Baseline data

Demographic characteristics

Demographic characteristics were well balanced for the cladribine 5.25 mg/kg, cladribine 3.5 mg/kg, and placebo groups (see Table 4). No statistically significant differences were observed among any of the demographic characteristics. The mean age (years) was 39.1 for the cladribine 5.25 mg/k group, 37.9 for the cladribine 3.5 mg/kg group and 38.7 for the placebo group. Most subjects were white (>97%) and approximately 70% were female. Demographic characteristics for the Evaluable population were similar to those in the ITT population.

Table 4 - Demographics by Treatment Group – ITT Population

Demographic Characteristic	Statistics	Cladribine 5.25 mg/kg (n=456)	Cladribine 3.5 mg/kg (n=433)	Placebo (n=437)	p-value
Age (yr)	n (missing)	456 (0)	433 (0)	437 (0)	0.172[a]
	Mean (SD)	39.1 (9.9)	37.9 (10.3)	38.7 (9.9)	
	Median	39.0	38.0	38.0	
	Min; Max	18.0; 65.0	18.0; 65.0	18.0; 64.0	
Sex, n (%)	n (missing)	456 (0)	433 (0)	437 (0)	0.598[b]
	Male	144 (31.6)	135 (31.2)	149 (34.1)	
	Female	312 (68.4)	298 (68.8)	288 (65.9)	
Race, n (%)	n (missing)	456 (0)	433 (0)	437 (0)	0.838[b]
	White	446 (97.8)	425 (98.2)	429 (98.2)	
	Black	4 (0.9)	2 (0.5)	1 (0.2)	
	Asian	2 (0.4)	2 (0.5)	1 (0.2)	
	Other	4 (0.9)	4 (0.9)	6 (1.4)	
Weight (kg)	n (missing)	456 (0)	433 (0)	437 (0)	0.098[a]
	Mean (SD)	69.3 (14.8)	68.1 (14.6)	70.3 (15.4)	
	Median	67.0	66.0	68.9	
	Min; Max	41.2; 119.9	40.0; 117.0	40.0; 119.7	

(a) From a two-way ANOVA model on ranked data with fixed effects for treatment group and region
(b) From Cochran-Mantel-Haenszel general association test, adjusted for region

Multiple Sclerosis History

In general, MS history characteristics were well balanced across the 3 treatment groups (see Table 5). There was a shorter median time from first attack prior to Trial Day 1 in the cladribine 3.5 mg/kg treatment group compared to the other two groups. The majority (>94%) of the patients experienced one or two relapses

within the 12 months prior to Study Day 1. Only one or two patients in each treatment group received treatment in the 3 months prior to Study Day 1.

MS history characteristics for the Evaluable population were similar to those in the ITT population.

Table 5 - Multiple Sclerosis History by Treatment Group – ITT Population

Multiple Sclerosis Characteristic	Statistics	Cladribine 5.25 mg/kg (n=456)	Cladribine 3.5 mg/kg (n=433)	Placebo (n=437)	p-value
Time since first attack (years) prior to Study Day 1	n (missing)	456 (0)	433 (0)	437 (0)	0.005[a]
	Mean (SD)	9.3(7.6)	7.9(7.2)	8.9(7.4)	
	Median	7.2	5.8	7.1	
	Min; Max	0.4; 35.2	0.3; 42.3	0.4; 39.5	
Time since most recent relapse (months) prior to Study Day 1	n (missing)	456 (0)	433 (0)	437 (0)	0.352[a]
	Mean (SD)	5.3(3.0)	5.4(2.9)	5.4(2.7)	
	Median	4.3	4.8	5.0	
	Min; Max	0.9; 13.3	1.1; 15.2	0.9; 12.8	
Number of relapses within the past 12 months prior to Study Day 1, n (%)	n (missing)	456 (0)	433 (0)	437 (0)	0.667[b]
	0	2 (0.4)	0	0	
	1	323 (70.8)	303 (70.0)	306 (70.0)	
	2	113 (24.8)	105 (24.2)	110 (25.2)	
	3	14 (3.1)	22 (5.1)	19 (4.3)	
	>=4	4 (0.9)	3 (0.7)	2 (0.5)	
Subjects who received treatment during the last 3 months prior to Study Day 1	n (missing)	456 (0)	433 (0)	437 (0)	0.836[c]
	Yes	2 (0.4)	1 (0.2)	1 (0.2)	
	No	454 (99.6)	432 (99.8)	436 (99.8)	
Subjects with abnormalities related to MS on neurological examination	n (missing)	456 (0)	433 (0)	437 (0)	0.834[c]
	Yes	442 (96.9)	418 (96.5)	425 (97.3)	
	No	14 (3.1)	15 (3.5)	12 (2.7)	
Subjects who have signs and symptoms related to MS	n (missing)	456 (0)	433 (0)	437 (0)	0.333[c]
	Yes	428 (93.9)	416 (96.1)	416 (95.2)	
	No	28 (6.1)	17 (3.9)	21 (4.8)	

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[a]From a two-way ANOVA model on ranked data with fixed effects for treatment group and region.

[b]From Cochran-Mantel-Haenszel row means score test, adjusted for region.

[c]From Cochran-Mantel-Haenszel general association test, adjusted for region.

Baseline Neurological and MRI assessment

The baseline MRI and neurological assessments were also well balanced across the 3 treatment groups with few exceptions (see Table 6). The mean (SD) number of T1 hypointense lesions was greater for the cladribine 5.25 mg/kg group compared to cladribine 3.5 mg/kg and placebo (8.5 [9.3], 7.1 [8.2] and 7.4 [8.0], respectively), and the mean T2 lesion volume (mm^3) was greater in the cladribine 5.25 mg/kg group compared to cladribine 3.5 mg/kg and placebo (17202.1 [17467.7], 14828.0 [16266.8], and 14287.6 [13104.8], respectively).

The baseline MRI and neurological assessments for the Evaluable population were similar to those in the ITT population.

Table 6 - Baseline MRI and Neurological Assessment by Treatment - ITT Population

Characteristic	Statistics	Cladribine 5.25 mg/kg (n=456)	Cladribine 3.5 mg/kg (n=433)	Placebo (n=437)	p-value
EDSS category, n (%)	n (missing)	456 (0)	433 (0)	437 (0)	0.149[a]
	0	11 (2.4)	12 (2.8)	13 (3.0)	
	1	80 (17.5)	75 (17.3)	70 (16.0)	
	2	119 (26.1)	133 (30.7)	127 (29.1)	
	3	108 (23.7)	108 (24.9)	96 (22.0)	
	4	84 (18.4)	71 (16.4)	83 (19.0)	
	>=5	54 (11.8)	34 (7.9)	48 (11.0)	
EDSS	Mean (SD)	3.0 (1.4)	2.8 (1.2)	2.9 (1.3)	
	Median	3.0	2.5	3.0	
	Min; Max	0.0; 5.5	0.0; 6.0	0.0; 5.5	
Number of T1 Gadolinium-enhanced Lesions	n (missing)	456 (0)	433 (0)	437 (0)	0.547[b]
	Mean (SD)	1.0 (2.3)	1.0 (2.7)	0.8 (2.1)	
	Median	0.0	0.0	0.0	
	Min; Max	0.0; 20.0	0.0; 32.0	0.0; 27.0	
Number of T1 Hypointense Lesions	n (missing)	456 (0)	433 (0)	437 (0)	0.058[b]
	Mean (SD)	8.5 (9.3)	7.1 (8.2)	7.4 (8.0)	
	Median	5.0	4.0	5.0	
	Min; Max	0.0; 57.0	0.0; 48.0	0.0; 44.0	
T2 Lesion Volume (mm^3)	n (missing)	456 (0)	433 (0)	437 (0)	0.058[b]
	Mean (SD)	17202.1 (17467.7)	14828.0 (16266.8)	14287.6 (13104.8)	
	Median	11106.0	9659.0	10140.5	
	Min; Max	236.0; 103645.0	106.0; 128747.0	150.0; 76770.0	

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[a] From Cochran-Mantel-Haenszel row means score test, adjusted for region.

[b] From a two-way ANOVA model on ranked data with fixed effects for treatment group and region.

Prior and Concomitant Medication

A greater proportion of patients in the cladribine 3.5 mg/kg group were naïve to DMD treatment compared to the cladribine 5.25 mg/kg and placebo groups (73.9%, 67.8%, and 67.5%, respectively). There was similar access across the spectrum of DMD agents previously used by patients within the three treatment groups, with prior treatment with Copaxone® varying the most (8.3%, 4.4%, and 6.6%, for the cladribine 5.25 mg/kg group, cladribine 3.5 mg/kg and placebo groups, respectively).

The majority of concomitant medications taken by subjects during the trial were treatments commonly used by MS patients to treat MS-related symptoms such as paracetamol, acetylsalicylic acid and methylprednisolone. Administration of antibiotics for systemic use was comparable in all three treatments groups (n=158 cladribine 5.25 mg/kg; n=147 cladribine 3.5 mg/kg; n=147 placebo). The placebo group utilized a greater amount of corticosteroids for systemic use (n=124 cladribine 5.25 mg/kg; n=113 cladribine 3.5 mg/kg; n=211 placebo).

Numbers analysed

Of the 1326 subjects included in the ITT population, 456 were randomized to the cladribine 5.25 mg/kg group, 433 were randomized to the cladribine 3.5 mg/kg group and 437 were randomized to the placebo group.

Table 7 - Subjects Populations and Evaluability

Analysis Set, n (%)	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
ITT	456	433	437
Safety Set	454 (99.6%)	430 (99.3%)	435 (99.5%)
Evaluable Population	377 (82.7%)	381 (88.0%)	364 (83.3%)

Outcomes and estimation

Primary Efficacy Endpoint

The annualized qualifying relapse rates (ARR) were 0.15 for cladribine 5.25 mg/kg, 0.14 for cladribine 3.5 mg/kg, and 0.33 for placebo. Treatment with cladribine 5.25 mg/kg resulted in a 54.5% relative reduction in annualized qualifying relapse rate compared to placebo ($p<0.001$). Treatment with cladribine 3.5 mg/kg resulted in a 57.6% relative reduction in annualized qualifying relapse rate compared to placebo ($p<0.001$). As compared to placebo, the relative risk of developing a qualifying relapse for each cladribine group was 35% and 54% for cladribine 5.25 mg/kg; and 34% and 54% for cladribine 3.5 mg/kg.

Table 8 - Qualifying Relapse Rate at week 96 by Treatment Group - ITT population

Characteristic	Statistics	Cladribine 5.25 mg/kg (n=456)	Cladribine 3.5 mg/kg (n=433)	Placebo (n=437)
Number of Qualifying Relapses	n (missing)	456 (0)	433 (0)	437 (0)
	Mean (SD)	0.25 (0.58)	0.25 (0.59)	0.56 (0.88)
	Median	0	0	0
	Min; Max	0; 4	0; 4	0; 6
Descriptive Statistics				
	Relapse Rate (Annualized)	0.15	0.14	0.33
	95% CI	(0.12, 0.17)	(0.12, 0.17)	(0.29, 0.38)
	97.5% CI	(0.12, 0.18)	(0.11, 0.17)	(0.29, 0.38)
	Relative Reduction[1] % (Cladribine vs Placebo)	54.5	57.6	
Inferential Statistics				
	Relative Risk (Cladribine/Placebo)			
	Point Estimate (SE[2])	0.43 (0.11)	0.43 (0.12)	
	95% CI	(0.35, 0.54)	(0.34, 0.54)	
	97.5% CI	(0.34, 0.56)	(0.33, 0.56)	
	p-value[3]	<0.001	<0.001	

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[1]Calculated as the ratio of the difference in annualized relapse rate (placebo - cladribine) relative to the annualized relapse rate in the placebo group.
[2]SE is presented on log scale.
[3]p-value based on Wald Chi-square test from analysis of number of qualifying relapses using a Poisson regression model with fixed effects for treatment group and region and with log of time on study as an offset variable

Secondary Efficacy Endpoints

- Proportion of Qualifying Relapse-free Subjects

A total of 78.9% of subjects in the cladribine 5.25 mg/kg group, 79.7% of subjects in the cladribine 3.5 mg/kg group, and 60.9% of subjects in the placebo group remained relapse-free at Week 96.

The OR was 2.43 (p<0.001; 95% CI of the OR=1.81; 3.27) for the cladribine 5.25 mg/kg group compared to the placebo group, indicating that the odds of subjects treated with cladribine 5.25 mg/kg remaining relapse-free during the 96 weeks of therapy were 2.43 times higher than 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 3.5 mg/kg group compared with the placebo group, indicating that the odds of subjects treated with cladribine 3.5 mg/kg remaining relapse-free during the 96 weeks of therapy were 2.53 times higher than the odds of subjects treated with placebo.

- Time to 3-month Confirmed EDSS Progression

Treatment with cladribine 5.25 mg/kg and cladribine 3.5 mg/kg significantly prolonged the time to 3-month sustained change in EDSS score over 96 weeks compared to placebo. The HR was 0.69 (p = 0.026; 95% CI of the HR=0.49; 0.96) for cladribine 5.25 mg/kg compared to placebo, indicating that subjects in the cladribine 5.25 mg/kg group had a 31% reduction in the risk of experiencing a 3-month sustained change in their EDSS score compared to placebo. The HR was 0.67 (p = 0.018; 95% CI of the HR=0.48; 0.93) for cladribine 3.5 mg/kg compared to placebo, indicating that subjects in the cladribine 3.5 mg/kg group had a 33% reduction in the risk to experience a 3-month sustained change in their EDSS score compared to placebo.

- Time to 6-month Confirmed EDSS Progression (*post-hoc analysis*)

Treatment with cladribine prolonged the time to 6-month sustained change in EDSS score over 96 weeks compared to placebo. The HR was 0.68 (p= 0.0332; 95% CI of the HR=0.47;0.97) for cladribine 5.25 mg/kg compared to placebo, indicating that subjects in the cladribine 5.25 mg/kg group had a 32% reduction in the risk of experiencing a 6-month sustained change in their EDSS score compared to placebo. The HR was 0.53 (p=0.0016; 95% CI of the HR=0.36;0.79) for cladribine 3.5 mg/kg compared to placebo, indicating that subjects in the cladribine 3.5 mg/kg group had a 47% reduction in the risk of experiencing a 6-month sustained change in their EDSS score compared to placebo.

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

The adjusted mean number of active T1 Gd+ lesions per subject per scan at Week 96 for the cladribine 5.25 mg/kg, cladribine 3.5 mg/kg, and placebo groups were 0.11, 0.12 and 0.91, respectively.

Subjects treated with cladribine 5.25 mg/kg had 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 (p<0.001). This represents an 88% relative reduction in mean number of active T1 Gd+ lesions per subject per scan for cladribine 5.25 mg/kg.

Similarly, subjects treated with cladribine 3.5 mg/kg 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 (p<0.001). This represents an 86% relative reduction in mean number of active T1 Gd+ lesions per subject per scan for cladribine 3.5 mg/kg.

- Mean Number of Active T2 Lesions per Subject per Scan at 96 weeks

The adjusted mean number of active T2 lesions per subject per scan at Week 96 for the cladribine 5.25 mg/kg, cladribine 3.5 mg/kg, and placebo groups were 0.33, 0.38 and 1.43, respectively.

Subjects treated with cladribine 5.25 mg/kg 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

(p<0.001). This represents a 77% relative reduction in the mean number of active T2 lesions per subject per scan.

Similarly, subjects treated with cladribine 3.5 mg/kg 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 (p<0.001). This represents a 73% relative reduction in the mean number of active T2 lesions per subject per scan.

- Mean Number of CU Lesions per Subject per Scan at 96 weeks

The mean number of CU lesions per subject per scan at Week 96 for the cladribine 5.25 mg/kg, cladribine 3.5 mg/kg, and placebo groups were 0.38, 0.43 and 1.72, respectively.

Subjects treated with cladribine 5.25 mg/kg 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 (p<0.001). This represents a relative reduction of 78% in the mean number of CU lesions per subject per scan.

Similarly, subjects treated with cladribine 3.5 mg/kg 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 (p<0.001). This represents a relative reduction of 74% in the mean number of CU lesions per subject per scan.

Post hoc analysis in patients with High Disease Activity (HDA)

The HDA definition was developed in line with a CHMP scientific advice using the definitions for highly active disease previously agreed for other DMDs, considering a number of clinical relapses in a previous year as well as a number of T1 Gd+ or T2 lesions as criteria to build this definition.

The resulting HDA subgroups are descripted below, and compared in Table 9:

- HDA1:
  - (a) Subjects with at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions, OR
  - (b) Subjects with 2 or more relapses in the previous year (no prior use of DMD at any time in subject history or duration of previous DMD therapy less than 1 year) and at least 1 T1 Gd+ lesion.
- HDA2: Subjects with 2 or more relapses in previous year (regardless of previous treatment status)
- HDA3: Subjects with 2 or more relapses in previous year (regardless of previous treatment status), AND at least: 1 T1 Gd+ lesion OR 9 T2 lesions.
- HDA4:
  - (a) Subjects with at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions, OR
  - (b) Subjects with 2 or more relapses in the previous year (regardless of previous treatment status).

Table 9 - Overview of HDA Definitions

Definition	HDA1	HDA2	HDA3	HDA4
	A and/or C	D	B and D	A and/or D
A. Subjects with ≥1 relapse in previous year while on DMD therapy and ≥1 T1 Gd+ or ≥9 T2	√			√
B. ≥1 T1 Gd+ or ≥9 T2 lesions			√	
C. Subjects with ≥2 relapses (no prior use of DMD at any time in subject's history or duration of previous DMD therapy <1 year)	√			
D. Subjects with ≥2 relapses in previous year regardless of treatment status		√	√	√

Disposition by HDA subgroup

Table 10 displays the number of subjects included in the overall study population and the HDA subgroups.

Table 10 - Number of Subjects in CLARITY by HDA Subgroup

Parameter N (%)	Placebo	Cladribine 3.5 mg/kg	Cladribine 5.25 mg/kg	Total
Overall population	437 (100)	433 (100)	456 (100)	1326 (100)
HDA1 subgroup	67 (15.3)	62 (14.3)	70 (15.4)	199 (15.0)
HDA2 subgroup	131 (30.0)	130 (30.0)	131 (28.7)	392 (29.6)
HDA3 subgroup	122 (27.9)	112 (25.9)	120 (26.3)	354 (26.7)
HDA4 subgroup	149 (34.1)	140 (32.3)	148 (32.5)	437 (33.0)

Results by HDA Subgroup

With regards to the **ARR** for HDA1, HDA2, HDA3, and HDA4 in subjects treated with 3.5 mg/kg cladribine in CLARITY, the relative risk ratios ranged from 0.38 to 0.32, indicating a relative risk reduction of 62% to 68%. The relative risk ratios in HDA subgroups with the 5.25 mg/kg cladribine dose ranged from 0.25 to 0.39.

In general, the effect of cladribine compared to placebo was larger across all HDA subgroups compared to the respective non-HDA groups. However, the differences did not reach statistical significance, although it became close for HDA2 versus non-HDA2 patients (p=0.0683 for cladribine 3.5mg/kg).

Table 11 - Annualized Qualifying Relapse Rate by Dose and HDA Subgroups - CLARITY

Subgroups	Measures	Placebo	Cladribine 3.5 mg/kg	Cladribine 5.25 mg/kg
HDA1 subgroup				
HDA	Relapse rate (95% CI)	0.57 (0.45; 0.73)	0.22 (0.14; 0.33)	0.14 (0.09; 0.23)
	RR (95% CI); p-value	-	0.38 (0.24; 0.61) p<0.0001	0.25 (0.15; 0.42) p<0.0001
Non HDA	Relapse rate (95% CI)	0.30 (0.26; 0.35)	0.13 (0.11; 0.16)	0.14 (0.12; 0.18)
	RR, (95% CI); p-value	-	0.43 (0.34; 0.56) p<0.0001	0.47 (0.37; 0.60) p<0.0001
HDA2 subgroup				
HDA	Relapse rate (95% CI)	0.50 (0.41; 0.60)	0.16 (0.11; 0.22)	0.18 (0.14; 0.25)
	RR (95% CI); p-value	-	0.32 (0.22; 0.47) p<0.0001	0.37 (0.26; 0.52) p<0.0001
Non HDA	Relapse rate (95% CI)	0.29 (0.24; 0.34)	0.14 (0.11; 0.18)	0.13 (0.10; 0.16)
	RR (95% CI); p-value	-	0.49 (0.37; 0.65) p<0.0001	0.45 (0.34; 0.60) p<0.0001
HDA3 subgroup				
HDA	Relapse rate (95% CI)	0.48 (0.39; 0.58)	0.18 (0.13; 0.25)	0.16 (0.12; 0.23)
	RR (95% CI); p-value	-	0.37 (0.25; 0.54) p<0.0001	0.34 (0.23; 0.50) p<0.0001
Non HDA	Relapse rate (95% CI)	0.29 (0.25; 0.34)	0.13 (0.10; 0.16)	0.14 (0.11; 0.17)
	RR, (95% CI); p-value	-	0.45 (0.34; 0.59) p<0.0001	0.46 (0.35; 0.60) p<0.0001
HDA4 subgroup				
HDA	Relapse rate (95% CI)	0.47 (0.40; 0.57)	0.16 (0.12; 0.22)	0.19 (0.14; 0.25)
	RR (95% CI); p-value	-	0.33 (0.23; 0.48) p<0.0001	0.39 (0.28; 0.55) p<0.0001
Non HDA	Relapse rate (95% CI)	0.29 (0.24; 0.34)	0.14 (0.11; 0.18)	0.13 (0.10; 0.16)
	RR, (95% CI); p-value]	-	0.49 (0.37; 0.65) p<0.0001	0.44 (0.33; 0.59) p<0.0001

For the **time to 3-month confirmed EDSS progression** in subjects treated with 3.5 mg/kg cladribine, the HRs (95% CI) for HDA2, HDA3 and HDA4 were 0.28 (0.15, 0.54), 0.30 (0.15, 0.59) and 0.28 (0.15, 0.54), respectively, indicating a risk reduction of 72%, 70% and 72%. HDA2, HDA3 and HDA4 showed higher responses to cladribine 3.5 mg/kg than their non-HDA complementary subgroups (subgroup by treatment interaction resulted in p=0.0061, p=0.0140, and p=0.0079, respectively). HDA1, with a smaller subject number and a wider confidence interval, had point estimates that also favoured cladribine 3.5 mg/kg over placebo (HR: 0.78, 95% CI: 0.35, 1.70), but no advantage compared to non-HDA1 was observed.

In subjects receiving the 5.25 mg/kg dose, the HRs in HDA subgroups ranged from 0.32 to 0.41, with risk reductions of 62%, 65%, 68% and 59% seen in the HDA1 to HDA4 subgroups, respectively, and 40% (HR 0.60) in the overall population.

For the **time to 6-month confirmed EDSS progression** in subjects treated with 3.5 mg/kg cladribine, the HR for the HDA2, HDA3, and HDA4 subgroups was 0.18 in each case, indicating a risk reduction of 82%. The

HDA2, HDA3 and HDA4 subgroups showed consistent and higher responses to cladribine 3.5 mg/kg than their non-HDA complementary subgroups. A subgroup by treatment interaction was nominally statistically significant for HDA2 (p=0.0036), HDA3 (p=0.0061) and HDA4 (p=0.0037) indicating better efficacy of cladribine in HDA subjects compared to non-HDA subjects. HDA1, with a smaller subject number and a wider confidence interval, had point estimates that also favoured cladribine 3.5 mg/kg over placebo, but did not reach significance compared to non-HDA1.

In subjects receiving the 5.25 mg/kg dose, the HRs in HDA subgroups ranged from 0.33 to 0.38, with risk reductions of 62%, 67%, 67% and 63% seen in the HDA1 to HDA4 subgroups, respectively, and 32% (HR 0.68) in the overall population.

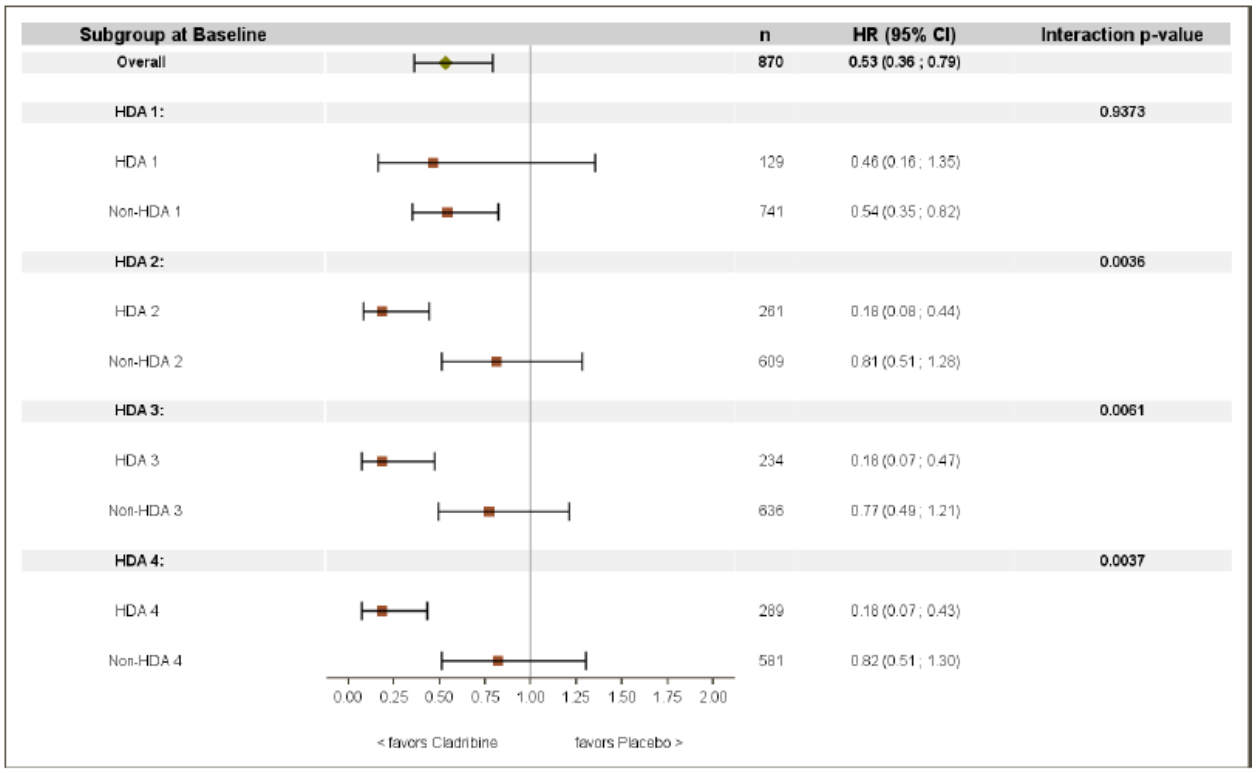


Figure 4 - Forest Plot of Hazard Ratio of Time to 6-Month Confirmed EDSS Progression in Subgroups for 3.5 mg/kg vs Placebo - CLARITY

For the relative risk of cumulative **new T1 Gd+ lesions** in subjects treated with 3.5 mg/kg cladribine the relative risk ratio (95% CI) for the HDA1, HDA2, HDA3, and HDA4 subgroups was 0.08 (0.042, 0.147), 0.09 (0.052, 0.144), 0.08 (0.045, 0.132) and 0.08 (0.046, 0.128), indicating a risk reduction of 92%, 91%, 92% and 92% in cumulative new T1 Gd+ lesions.

In subjects receiving the 5.25 mg/kg dose, the relative risk in HDA subgroups ranged from 0.02 to 0.03, with risk reductions of 97%, 98%, 98% and 97% seen in the HDA1 to HDA4 subgroups, respectively. No difference between HAD and non-HAD subgroups was observed. Similar results were seen for analyses performed **for active T2 lesions** and **CU lesions**.

For the assessment of disease-free status, **No Evidence of Disease Activity (NEDA)** was selected and defined as no relapses, no EDSS progression, no T1 Gd+ lesions and no active T2 lesions. For the proportion of subjects with NEDA in the 3.5 mg/kg cladribine group, the ORs (95% CI) for the HDA1, HDA2, HDA3, and

HDA4 subgroups were 5.49 (1.17, 17.58), 8.02 (3.93, 16.35), 7.06 (3.40, 14.65) and 7.82 (4.03, 15.19). Observed point estimates in HDA subgroups were systematically more favourable than the respective non-HDA subgroups although not reaching nominal significance except for HDA4 (p=0.0435).

In subjects receiving the 5.25 mg/kg dose, the ORs in HDA subgroups were 10.32, 7.91, 7.63 and 7.59 in the HDA1 to HDA4 subgroups, respectively, and 4.75 in the overall population. Observed point estimates in HDA subgroups were systematically more favourable than the respective non-HDA subgroups.

2.5.2.2. CLARITY EXT

Study 27820 (CLARITY EXT): A Phase IIIb, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Extension Trial to Evaluate the Safety and Tolerability of Oral Cladribine in Subjects with Relapsing-Remitting Multiple Sclerosis Who Have Completed Trial 25643 (CLARITY)

This was a double-blind, randomized, placebo-controlled, multicentre, parallel-group 96 week extension trial to Trial 25643 (CLARITY) to evaluate the safety, tolerability and efficacy of oral cladribine for up to 4 years (192 weeks, including the 96 weeks of CLARITY) in subjects with RRMS (see 2.5.2.1.) for a schematic overview of the study design). The trial included a pre-study evaluation period, two blinded 48-week treatment periods, and a 24-week supplemental follow-up phase during which subjects did not receive treatment with investigational medicinal product, for a total of 216 weeks of observation (including CLARITY).

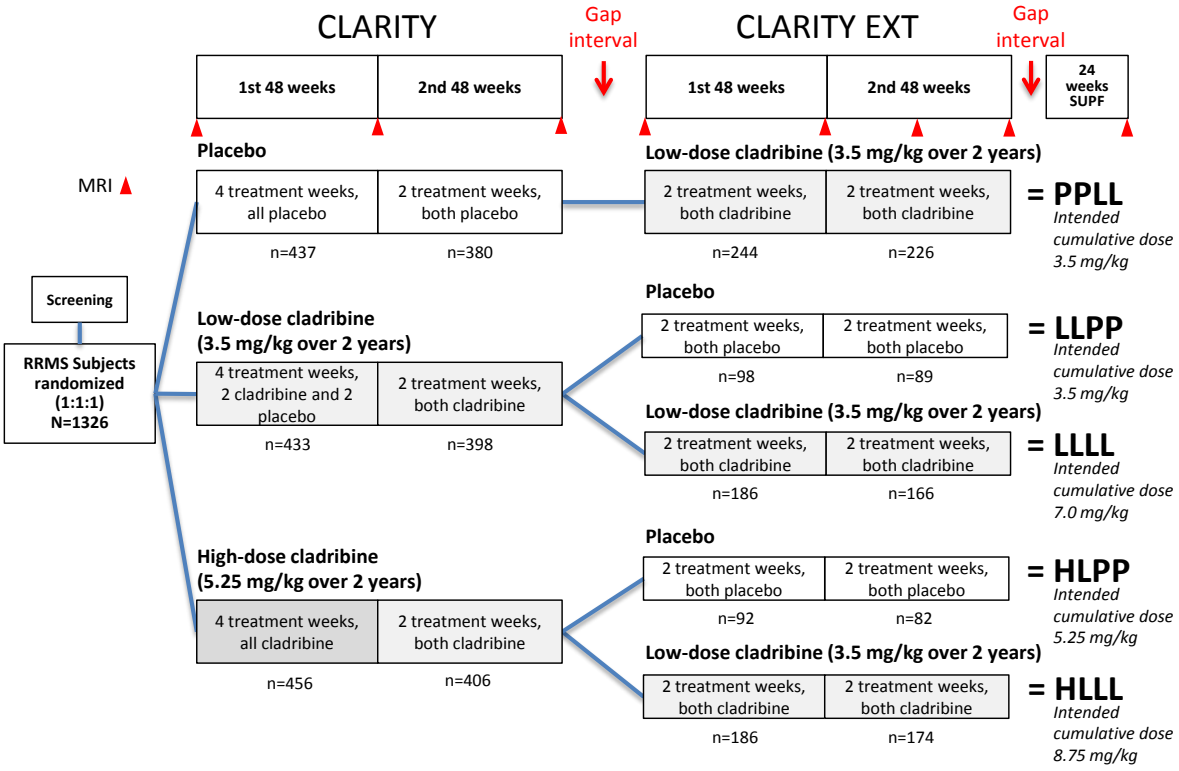


Figure 5 – Schematic Overview of CLARITY EXT Study Design

This extension trial was initiated after 723 of the subjects enrolled in CLARITY (54%) had already completed that trial, resulting in a gap in prospective data collection of varying length between these subjects' final visits in CLARITY and their first visits in CLARITY EXT. Similarly, 52 out of the 636 subjects who ultimately

entered the supplemental follow-up phase (8%) had completed the double-blind period of CLARITY EXT before this phase was introduced by Protocol Amendment 3 on 28 April 2010.

Methods

Study participants

Main inclusion criteria

- Randomization in CLARITY and completed scheduled visits for the full 96 weeks.
- No medical history or evidence of latent tuberculosis infection (LTBI) or TB, as evidenced by TB skin test or chest X-ray (this criterion was added in Amendment 2 to the Clinical Study Protocol).
- Following Protocol Amendment 2, subjects had to have all of the following laboratory haematologic parameters evaluated as normal (as defined below, inclusively) within 28 days of first dosing of blinded study medication at extension Study Day 1 for retreatment to occur:
    - Haemoglobin = 11.6 – 16.2 g/dL
    - Leukocyte (total white blood cell [WBC]) count = 4.1 – 12.3 × 10^3/µL
    - Absolute lymphocyte count (ALC) = 1.02 – 3.36 × 10^3/µL
    - Absolute neutrophil count (ANC) = 2.03 – 8.36 × 10^3/µL
    - Platelet count = 140-450 × 10^3/µL

Main Exclusion Criteria

- Inadequate liver function, defined by total bilirubin, aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase >2.5 times the upper limit of the nomal values
- History of active or chronic infectious disease or any disease which compromises immune function (e.g. HIV+, Lyme disease)
- Positive stool heme-occult test at Pre-Study Evaluation
- History of seizures not adequately controlled by medications

Treatments

During the 96-week double-blind phase of this extension study, cladribine and matching placebo were administered as 2 treatment courses separated by 1 year. Only the lower dose of cladribine used in CLARITY was administered (total cumulative dose of 3.5 mg/kg)

Each treatment course consisted of 2 treatment weeks separated by 1 month, and each treatment week consisted of 4 or 5 days on which eligible patients received 1 or 2 tablets (10 mg or 20 mg of cladribine or matching placebo) as a single daily dose, dependent on body weight.

Subjects randomized to placebo during CLARITY were assigned to low-dose oral cladribine.

Subjects randomized to oral cladribine during CLARITY were re-randomized in a 2:1 allocation ratio to receive either low-dose oral cladribine or placebo.

The randomized treatment groups were defined as follows:

- **Cladribine high/low dose (HLLL):** subjects randomized to high-dose cladribine in the first 48 weeks and low-dose cladribine in the second 48 weeks of CLARITY, and to low-dose cladribine in CLARITY EXT (the total cumulative dose expected was 8.75 mg/kg).
- **Cladribine low/low dose (LLLL):** subjects randomized to low-dose cladribine for all 96 weeks of CLARITY and in CLARITY EXT (the total cumulative dose expected was 7.0 mg/kg).
- **Cladribine high dose/placebo (HLPP):** subjects randomized to high-dose cladribine in the first 48 weeks and low-dose cladribine in the second 48 weeks of CLARITY, and to placebo in CLARITY EXT (the total cumulative dose expected was 5.25 mg/kg).
- **Cladribine low dose/placebo (LLPP):** subjects randomized to low-dose cladribine for all 96 weeks of CLARITY and to placebo in CLARITY EXT (the total cumulative dose expected was 3.5 mg/kg).
- **Placebo/cladribine low dose (PPLL):** Subjects randomized to placebo for all 96 weeks of CLARITY and assigned to low-dose cladribine in CLARITY EXT (the total cumulative dose expected was 3.5 mg/kg).

The requirements for permitted, prohibited and rescue medication were the same as for CLARITY.

For subjects who had to delay entry into the CLARITY Extension study or the 24-Week safety follow-up phase, whereby there was a gap interval of varying duration, and who during this interval received a DMD, the study protocol indicated that they had to discontinue the DMD for a period of at least 3 months prior to Study Day 1. Subjects who were unable or unwilling to discontinue their DMD could not be re-randomized to receive study medication. These subjects were encouraged to enter the study but could only be followed for safety.

Objectives

The primary objectives of the study were related to safety:

- To evaluate the safety of extended treatment with oral cladribine when administered according to a fixed annual dosing schedule to patients who completed CLARITY.
- To assess the safety of cladribine with an emphasis on cardiac repolarization as measured by changes in QT interval (in a subset of patients also participating in PK sampling and analysis).

Amongst the explorative objectives was to determine the long-term benefit of treatment with oral cladribine vs. placebo.

Outcomes/endpoints

Efficacy Endpoints (selected endpoints)

- Proportion of subjects “qualifying” relapse-free. A qualifying relapse was 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 at least 30 days of clinical stability or improvement
- Disability progression, defined as an increase in the EDSS scale of at least 1.0 point compared to baseline if baseline EDSS score was ≥0.5 or ≤4.5; ≥1.5 points if the baseline EDSS score was zero;

and ≥0.5 points if the baseline EDSS score was ≥5.0. The following two progression endpoints were to be used: (i) Time to confirmed EDSS progression, confirmed after 3 months, and (ii) Time to confirmed EDSS progression, confirmed after 6 months.

- Time to treatment start with rescue medication.
- Annualized "qualifying" relapse rate.
- Time to first "qualifying" relapse.
- MRI efficacy endpoints included:
  - Number of new T1 gadolinium-enhancing lesions.
  - Number of active T2 lesions.
  - Number of CU lesions, defined as (i) new T1 gadolinium-enhancing, or (ii) new or enlarging T2 lesions

Sample size

The number of subjects eligible to enter this study was limited by the enrolment, retention, and roll-over of patients from the preceding CLARITY study. Therefore, no statistical estimation of the sample size was performed.

Randomisation

Treatment allocation for the double-blind phase of CLARITY EXT was performed using a central randomization system, and depended on the subject's initial treatment randomization in CLARITY (see treatment above).

Subjects were assigned to treatment using a central interactive voice response system.

Blinding (masking)

This study was double-blinded. Cladribine tablets and matching placebo tablets were provided to the sites in identical blister packages, each containing up to 10 tablets.

Only the Treating Physician – but not the Evaluating Physician (responsible for the neurological assessment) – had access to laboratory data in order to make safety assessments.

The blind could be broken for an individual patient only in the case of an emergency when knowledge of the assigned treatment was essential for the clinical management of the patient.

Statistical methods

Analysis Sets

The protocol defined the following data sets for analysis:

- The Enrolled Analysis Set included all subjects who were enrolled in CLARITY EXT and signed an Informed Consent.

- The ITT Analysis Set consisted of all subjects who were randomized or assigned to treatment in CLARITY EXT, analysed as randomized/assigned.
- The Safety Analysis Set comprised all subjects who received at least one dose of IMP in CLARITY EXT and had at least one safety assessment during the double-blind phase, analyzed as randomized/assigned.
- The Safety Follow-up Analysis Set included all subjects who were enrolled and had at least one safety assessment, but were not randomized or assigned to treatment because they were not eligible to receive study medication: subjects were analysed as randomized in CLARITY.

All statistical tests comparing treatment arms were two-sided and conducted at the 2.5% level. CIs were two-sided with a confidence level of 97.5%, unless otherwise specified. A p-value less than 0.025 was considered to be "nominally" significant, given that all hypothesis tests were exploratory and were not pre-specified.

Efficacy data were summarised descriptively by randomised/assigned treatment group. Efficacy analyses were performed for the ITT analysis set only and included the following between-group comparisons:

- *Late treatment group* (PPLL) *vs. early treatment group* (LLPP)
- *192-week treatment group vs. 96-week treatment group:* two comparisons, low-dose (LLLL vs. LLPP) and high-dose (HLLL vs. HLPP)
- *Active treatment group (LLLL + HLLL) vs. placebo treatment group* (LLPP + HLPP).

Within-group comparisons of the effect of treatment during the CLARITY EXT period were also performed for HLLL, LLLL, PPLL and LLPP (with the exception of "time to event" endpoints), using data from both CLARITY and CLARITY EXT, i.e. 192 weeks vs. 96 weeks.

For the proportion of relapse-free subjects and the proportions of subjects with no lesions, the odds ratio for treatment effect (and 97.5% CI) was estimated for the between group comparisons using a logistic regression model with fixed effects for treatment group and region; treatment effect was tested using a Wald test. Within-group comparisons: The effect of treatment during the CLARITY EXT period on proportion of subjects relapse-free (or proportion with no lesions) was analysed using McNemar's test.

Kaplan-Meier plots of probability of surviving event-free were presented by treatment group and time-to-event percentiles (and 95% CIs) were reported for time to first and second relapses, time to confirmed progression in EDSS and time to start of rescue medication. Between-group comparisons were based on the hazard ratio for treatment effect (and 97.5% CI), which was estimated using a Cox proportional hazards model with fixed effects for treatment group and region; treatment effect was tested using a Wald test. No between-group comparisons were performed for time to start of rescue medication because only 7 of the 806 ITT subjects received any rescue medication.

Annualised "qualifying" relapse rate and associated 97.5% CI was presented by treatment group. Between-group comparisons included the relapse rate ratio for treatment effect (and 97.5% CI), which was estimated using a Poisson regression model with number of relapses as dependent variable, fixed effects for treatment group and region, and with the log of time on study as an offset variable; treatment effect was tested using a Wald test. Percent reduction in relapse rate was estimated using the same model. Within-group comparisons were performed using the Wilcoxon signed rank test (the null hypothesis was that the median difference between the pairs of rates was zero).

Between-group comparisons for the number of lesions were based on the lesion rate ratio for treatment effect (and 97.5% CI), which was estimated using a negative binomial model with cumulative number of lesions as dependent variable, fixed effects for treatment group and region, with baseline T1 Gd+ lesion count as a covariate, and with the log of the number of scans as an offset variable. Percent reduction in lesion rate was estimated using the same model. Within-group comparisons: were performed using the Wilcoxon signed rank test.

Results

Participant flow

A total of 1,326 patients were randomised into CLARITY. Of these, 883 patients were screened for participation in CLARITY EXT, 867 were enrolled and 806 were randomised or assigned to treatment (LLPP: 98, HLPP: 92, LLLL: 186, HLLL: 186, PPLL: 244). Of the 806 patients who were randomised/assigned to treatment, 738 completed the 96-week double-blind phase of the study and 650 completed the planned study treatment.

The most frequent reasons for study discontinuation were “other” (45 patients) and lost to follow-up (12 patients); 6 patients discontinued due to AEs, 3 patients died, and 2 were withdrawn because of protocol deviations. Of the 45 patients in the category “other,” the majority stated verbatim terms such as withdrawal of consent/patient’s decision/refusal (n=36).

The most frequent reasons for treatment discontinuation were AEs (89 patients) and “other” (53 patients); 9 patients were lost to follow-up, 3 patients died (the same patients for whom death was cited as the reason for study discontinuation), and 2 patients stopped treatment due to disease progression.

Patient disposition and reasons for discontinuation during the double-blind phase of the extension study are presented in Table 12.

Table 12 - Patient Disposition and Reasons for Discontinuation – CLARITY EXT

Characteristic	LLPP Cladribine 3.5 mg/kg/ Placebo (N=98)	HLPP Cladribine 5.25 mg/kg/ Placebo (N=92)	LLLL Cladribine 3.5 mg/kg/ Cladribine 3.5 mg/kg (N=186)	HLLL Cladribine 5.25 mg/kg/ Cladribine 3.5 mg/kg (N=186)	PPLL Placebo/ Cladribine 3.5 mg/kg (N=244)	Total
Number of subjects enrolled, n						867
Number of subjects not randomized, n						61
Randomized subjects, n (%)	98 (100.0)	92 (100.0)	186 (100.0)	186 (100.0)	244 (100.0)	806 (100.0)
Subjects who completed study drug, n (%)	86 (87.8)	82 (89.1)	144 (77.4)	139 (74.7)	199 (81.6)	650 (80.6)
Subjects who discontinued from study drug, n (%)	12 (12.2)	10 (10.9)	42 (22.6)	47 (25.3)	45 (18.4)	156 (19.4)
Reason for discontinuation of treatment, n (%)						
Adverse event	3 (3.1)	4 (4.3)	26 (14.0)	30 (16.1)	26 (10.7)	89 (11.0)
Lost to follow-up	2 (2.0)	1 (1.1)	0	2 (1.1)	4 (1.6)	9 (1.1)
Protocol violation	0	0	0	0	0	0
Disease progression	1 (1.0)	0	0	1 (0.5)	0	2 (0.2)
Death	2 (2.0)	0	1 (0.5)	0	0	3 (0.4)
Other	4 (4.1)	5 (5.4)	15 (8.1)	14 (7.5)	15 (6.1)	53 (6.6)
Subjects who completed the study, n (%)	89 (90.8)	82 (89.1)	166 (89.2)	174 (93.5)	227 (93.0)	738 (91.6)
Subjects who discontinued the study, n (%)	9 (9.2)	10 (10.9)	20 (10.8)	12 (6.5)	17 (7.0)	68 (8.4)
Reason for discontinuation of study, n (%)						
Adverse event	0	1 (1.1)	3 (1.6)	0	2 (0.8)	6 (0.7)
Lost to follow-up	3 (3.1)	1 (1.1)	2 (1.1)	2 (1.1)	4 (1.6)	12 (1.5)
Protocol violation	0	1 (1.1)	0	1 (0.5)	0	2 (0.2)
Disease progression	0	0	0	0	0	0
Death	2 (2.0)	0	1 (0.5)	0	0	3 (0.4)
Other	4 (4.1)	7 (7.6)	14 (7.5)	9 (4.8)	11 (4.5)	45 (5.6)

Recruitment

Patients were enrolled in 133 centers in 30 countries including Australia, the US and countries in Europe, Asia and South America.

The study period was February 2008 to December 2011 (first patient's first visit to last patient's last visit).

Conduct of the study

The original protocol, dated 03 July 2007, was amended four times. One amendment applied to France only (Amendment 1).

Protocol Amendment 2 (all countries; 16 December 2008) aimed at addressing potential safety issues identified by the Sponsor. To prevent the risk of treating a subject with a coincident laboratory haematological Grade 3 or Grade 4 toxicity, study procedures were amended to assure that a subject's

haematological status was known prior to dosing with blinded study medication. Changes included introduction of an entry criterion requiring haematological values within normal ranges, modification of laboratory criteria for retreatment, and specification that subjects were not to take the study medication dispensed at Weeks 5 and 52 until instructed to do so by site staff, following confirmation that laboratory values were within acceptable limits.

Protocol Amendment 3 (all countries; 28 April 2010) introduced an Interim Analysis and the 24-week supplemental follow-up phase that would provide extended monitoring and safety assessment of subjects who completed the double-blind phase.

Protocol Amendment 4 (all countries; 28 February 2011): The main purposes of this amendment were to clarify the roles of the Treating Physician and Evaluating Physician and to ensure consistent guidance regarding the use of contraception by female subjects following the last dose of study medication.

During the 96-week double-blind period of the study, a total of 27 major protocol deviations were identified in a total of 26 patients in the combined ITT Analysis Set. All deviations were identified prior to the database lock and described in the study report. The majority of protocol deviations (24) were related to use of another investigational drug, use of prohibited medications, use of DMD within 3 months of Study Day 1, extended use of steroids, or underdosing (insufficient compliance). Three patients continued study treatment despite a positive pregnancy test.

Baseline data

Demographic characteristics

Baseline age at entry into CLARITY EXT ranged from 20 to 67 years, with an overall mean (SD) of 41.1 (10.1) years and a median of 41.0 years. 65.9% were female and a great majority of patients were White (97.6% overall). Patient weight ranged from 40.0 to 120.4 kg at entry into CLARITY EXT, with an overall mean (SD) of 69.4 (14.8) kg and median of 67.0 kg.

Multiple Sclerosis History

Time since first MS attack ranged from 2.2 to 44.2 years, with an overall mean (SD) of 11.0 (7.3) years and median of 9.1 years and without substantial differences between treatment groups. Nearly all ITT patients (773 patients or 95.9% overall) had abnormalities related to MS on neurological examination. Three patients (0.4% overall) had received DMD treatment during the 3 months before study entry (all in the PPLL group).

Overall, 98 ITT patients (12.2%) had experienced a relapse between the end of CLARITY and the start of CLARITY EXT; the percentage of patients with relapses between studies was 18.9% in the PPLL group (i.e., those patients randomized to placebo in CLARITY) compared to 8.7%-9.7% in the other treatment groups.

Among patients experiencing relapse between studies, time since most recent relapse ranged from 0.1 to 21.9 months, with an overall mean (SD) of 5.6 (4.5) months and median of 4.6 months.

Baseline Neurological and MRI Assessment

Results of neurological assessment at baseline of CLARITY EXT revealed differences between the groups randomized to cladribine and to placebo in CLARITY, with higher EDSS scores and a higher proportion of patients reporting relapses since completion of CLARITY in the PPLL group (who had been randomized to placebo in CLARITY) than in the other treatment groups.

It is possible that this group included patients with relatively benign disease (less than 2 relapses and no sustained increase in EDSS) – who were thus able to complete the 96 weeks of CLARITY without need for

rescue medication which could only be offered after a second relapse or a sustained increase in EDSS had occurred– than the groups that received cladribine in CLARITY.

- EDSS ranged from 0.0 to 6.5 in the ITT Analysis Set, with an overall mean (SD) of 2.90 (1.52) and median of 2.50. Median EDSS scores were 2.50 in all treatment groups but the PPLL group, for which the median was 3.00.
- Distributions of EDSS scores by category were generally similar across treatment groups, but there was a slight tendency towards higher scores in the PPLL group: 22.1% of PPLL patients had EDSS scores of 3.0-3.5 compared to ≤19.4% in the other groups; the percentage of PPLL patients with EDSS 4.0-4.5 was comparable to or lower than those in other groups, but 15.2% of PPLL patients had EDSS ≥5.0 compared to ≤13.3 in the other groups (Table 11–6).

Results of MRI assessment at baseline of CLARITY EXT were generally similar across treatment groups in the ITT Analysis Set, although considerable variation was seen at the patient level.

Considering treatment group means, the PPLL group (who had been randomized to placebo in CLARITY) had higher numbers of T1 Gd+ lesions and higher T1 Gd+ lesion volumes. The mean (SD) was 0.77 (1.85) in the PPLL group compared to 0.10-0.31 in the other groups; for T1 Gd+ lesion volume, the mean (SD) was 132.30 (415.18) mm^3 for PPLL compared to 18.45-49.19 mm^3 in the other groups. Third quartiles showed the same pattern.

Prior and Concomitant Medications

In the ITT Analysis Set, a total of 610 subjects (75.7%) reported use of at least one concomitant medication during the double-blind phase. The kinds of medications reported were typical for an MS population, and were generally similar across treatment groups.

Duration of the Gap Interval between CLARITY and CLARITY EXT

CLARITY EXT was initiated after 54% of the patients enrolled in CLARITY had already completed the study, resulting in a gap interval of varying length between these patients' final visits in CLARITY and their first visits in CLARITY EXT. Gap duration was similar across treatment groups, with group median values ranging from 39.5 to 43.1 weeks, and group maximum values ranging from 111.0 to 118.0 weeks (Table 11–4). Overall, 86 patients (10.7%) had a gap of ≤4 weeks, while 361 patients (44.8%) had a gap of >4 to ≤43 weeks and 359 patients (44.5%) had a gap of >43 weeks.

Numbers analysed

A total of 883 subjects were screened, of whom 867 were enrolled and 806 were randomized or assigned to treatment. The number of patients in the ITT and Safety Analysis Set were the same between treatment groups (LLPP=98, HLPP=92, LLLL=186, HLLL=186 and PPLL=244). A total of 636 subjects entered the safety follow-up phase, and 621 subjects completed the 24 weeks follow-up. A total of 61 subjects who were not eligible to receive treatment were followed for safety only in the safety follow-up phase (placebo=22, cladribine 3.5 mg/kg= 17, cladribine 5.25 mg/kg=22).

Outcomes and estimation

- Annualized Qualifying Relapse Rate

Annualized qualifying relapse rates were broadly similar across treatment groups (≤ 0.15 in all groups: 0.15 for the LLPP group, 0.13 for the HLPP group, 0.10 for the LLLL group, 0.12 for the HLLL group, and 0.10 for the PPLL group). Of the within-group comparisons performed, the ARR during CLARITY differed significantly from that during CLARITY EXT only in the PPLL group where it decreased from 0.26 in Period 1 to 0.10 in Period 2 ($p<0.0001$).

There were no obvious differences in ARR between subgroups defined by gap duration. In subjects with gap duration >4 weeks and ≤43 weeks, the ARR ranged from 0.10 to 0.17, and in those with gap duration >43 weeks, ARR ranged from 0.10 to 0.14.

Table 13 - Qualifying Relapse Rates During CLARITY EXT by Treatment Group – (ITT)

Characteristic	Statistics	LLPP Cladribine 3.5 mg/kg/ Placebo (N=98)	HLPP Cladribine 5.25 mg/kg/ Placebo (N=92)	LLLL Cladribine 3.5 mg/kg/ Cladribine 3.5 mg/kg (N=186)	HLLL Cladribine 5.25 mg/kg/ Cladribine 3.5 mg/kg (N=186)	PPLL Placebo/ Cladribine 3.5 mg/kg (N=244)
Number of qualifying relapses	N (missing)	98 (0)	92 (0)	186 (0)	186 (0)	244 (0)
	Mean (SD)	0.35 (0.79)	0.30 (0.66)	0.23 (0.56)	0.28 (0.59)	0.25 (0.57)
	Median	0.00	0.00	0.00	0.00	0.00
	Min; Max	0.0; 5.0	0.0; 3.0	0.0; 3.0	0.0; 3.0	0.0; 3.0
	Qualifying relapse rate (Annualized)	0.15	0.13	0.10	0.12	0.10
	97.5% CI	0.09,0.21	0.08,0.19	0.06,0.13	0.08,0.16	0.07,0.13

- Proportion of Subjects Qualifying Relapse-Free

More than 75% of subjects in all treatment groups whose relapse status was known were “qualifying” relapse-free over the entire extension trial, including the safety follow-up phase phase: the proportions ranged from 75.3% and 81.2%, with no discernible difference between the LLPP and HLPP groups and the HLLL group where subjects received the highest cumulative (continuous) cladribine dose. Follow-up time was comparable across treatment groups: medians by treatment group ranged from 122.9 to 123.9 weeks.

Table 14 - Proportion of Subjects Qualifying Relapse-Free During CLARITY EXT by Treatment Group –CLARITY EXT (ITT Analysis Set)

Characteristic	Statistics	LLPP Cladribine 3.5mg/kg/ Placebo (N=98)	HLPP Cladribine 5.25mg/kg/ Placebo (N=92)	LLLL Cladribine 3.5mg/kg/ Cladribine 3.5mg/kg (N=186)	HLLL Cladribine 5.25mg/kg/ Cladribine 3.5mg/kg (N=186)	PPLL Placebo/ Cladribine 3.5mg/kg (N=244)
Subjects qualifying relapse-free, N (%)	Yes	68 (75.6)	61 (75.3)	134 (81.2)	132 (76.7)	180 (79.6)
	No	22 (24.4)	20 (24.7)	31 (18.8)	40 (23.3)	46 (20.4)
	Unknown	8	11	21	14	18

The percentage of subjects who were "qualifying" relapse-free during both trials was lower in the PPLL group (51.3%) than in the groups randomized to cladribine in CLARITY (≥61.1%, with a maximum of 68.5% for LLLL compared to 61.1% for LLPP and 62.2% for HLLL).

- Time to First Qualifying Relapse

Considering the entire period comprising CLARITY, CLARITY EXT, and the gap between these periods, the estimated time at which 25% of subjects had experienced a first "qualifying" relapse, measured from Study Day 1 of CLARITY, was longer for the LLLL group and shorter for the PPLL group compared to the other treatment groups: 25th percentiles for time to first "qualifying" relapse were 1291 days for the LLLL group (95% CI: 762, 1655) and 470 days for the PPLL group (95% CI: 323, 596). Time to first "qualifying" relapse in the LLPP group was similar to that in the LLLL group: the 25th percentile for LLPP was 1047 days (95% CI: 717, 1771).

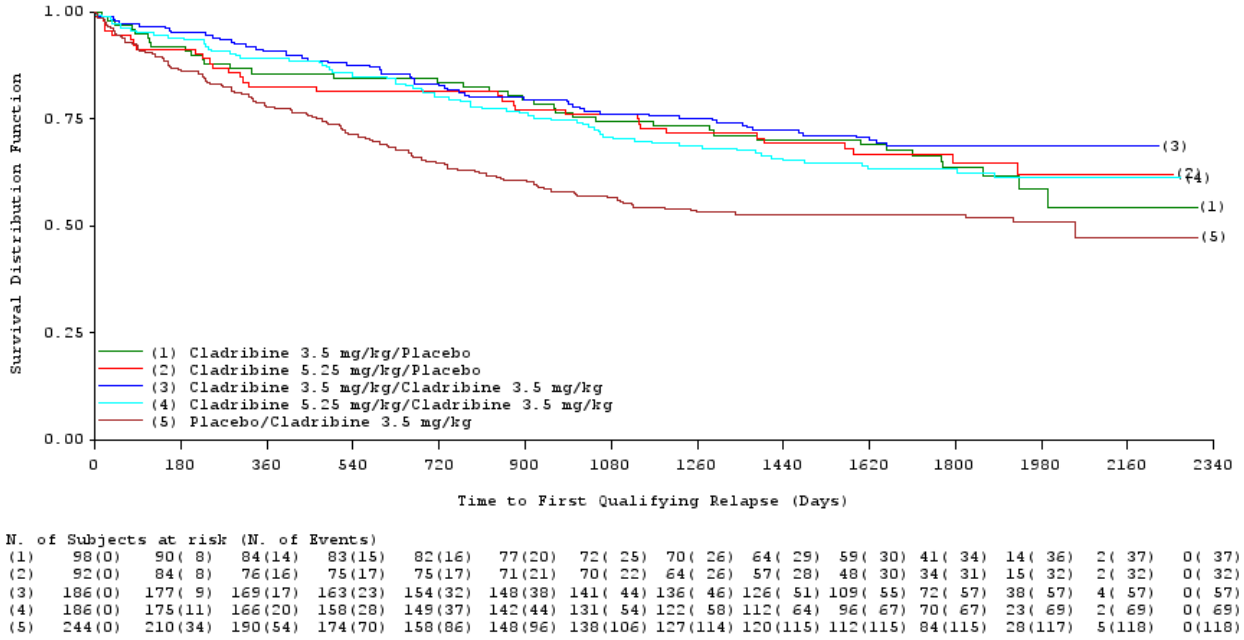


Figure 6 - Time to First qualifying relapse

- EDSS progression

During CLARITY EXT, between 9/92 (9.8%) (HLPP group) and 18/98 (18.4%) (LLPP group) of subjects, experienced 3 month confirmed progression in EDSS. An estimated 10% of subjects experienced 3-month confirmed EDSS progression by 533 days in the LLPP group, 1009 days in the HLPP group, 596 days in the LLLL group, 498 days in the HLLL group, and 429 days in the PPLL group. Between-group comparisons based on the HR for treatment effect, adjusted for region, did not show statistically significant differences in time to 3-month confirmed progression in EDSS during CLARITY EXT between the active and placebo treatment groups (HLLL and LLLL, and HLPP and LLPP), the high-dose 192 week and 96 week treatment groups (HLLL and HLPP), the low-dose 192 week and 96 week treatment groups (LLLL and LLPP), or the late and early treatment groups (PPLL and LLPP).

Percentages of subjects experiencing 6-month confirmed progression in EDSS during CLARITY EXT were ≤13.3% for all treatment groups. Between-group comparisons did not show nominally significant differences in time to 6-month confirmed progression in EDSS between the active and placebo treatment groups (HLLL and LLLL, and HLPP and LLPP), the high-dose 192 week and 96 week treatment groups (HLLL and HLPP), the low-dose 192 week and 96 week treatment groups (LLLL and LLPP), or the late and early treatment groups (PPLL and LLPP).

Table 15 - Time to Confirmed 6-months EDSS Progression during CLARITY EXT by Treatment Group – ITT Analysis Set

Statistics	LLPP Cladribine 3.5 mg/kg/ Placebo (N=98)	HLPP Cladribine 5.25 mg/kg/ Placebo (N=92)	LLLL Cladribine 3.5 mg/kg/ Cladribine 3.5 mg/kg (N=186)	HLLL Cladribine 5.25 mg/kg/ Cladribine 3.5 mg/kg (N=186)	PPLL Placebo/ Cladribine 3.5 mg/kg (N=244)
Subjects at Risk, n (missing)	98 (0)	92 (0)	186 (0)	186 (0)	244 (0)
Subjects with event, n (%)	13 (13.3)	6 (6.5)	15 (8.1)	22 (11.8)	32 (13.1)
Subjects censored, n (%)	85 (86.7)	86 (93.5)	171 (91.9)	164 (88.2)	212 (86.9)
K-M estimate at last event	84.8	93.1	91.3	87.5	84.5
(95% CI)	(75.0; 91.0)	(85.3; 96.9)	(85.9; 94.7)	(81.6; 91.6)	(77.8; 89.3)
Time to Confirmed 6-month EDSS Progression[1]					
10th percentile	665	NE	NE	580	582
(95% CI)[2]	(168; NE)			(246; NE)	(415; 1009)
20th percentile	NE	NE	NE	NE	NE
(95% CI)					
25th percentile	NE	NE	NE	NE	NE
(95% CI)					
Median	NE	NE	NE	NE	NE
(95% CI)					
75th percentile	NE	NE	NE	NE	NE
(95% CI)					

[1] Time to Confirmed 6-month EDSS Progression is measured relative to Study Day 1 of CLARITY Extension.
[2] The percentiles are estimated from a Kaplan-Meier survival curve; NE indicates that the percentile and / or 95% Lower / Upper CI were not estimable.
Table T-EDSS3-ITT produced on 27OCT2015

- Mean number of New T1 Gadolinium-Enhanced Lesions

During CLARITY EXT, the mean number of new T1 Gd+ lesions per subject per scan ranged from 0.0 to 12.2 overall (see Table 16).

Between-group comparisons for mean number of new T1 Gd+ lesions per subject per scan during CLARITY EXT were nominally significant for the active vs placebo groups (HLLL and LLLL, and HLPP and LLPP; $p<0.001$), the low-dose 192 week vs 96 week treatment groups (LLLL and LLPP; $p<0.001$), and the late vs early treatment groups (PPLL and LLPP; $p=0.003$), but not for the high-dose 192 week vs 96 week treatment groups (HLLL and HLPP; $p=0.047$).

Table 16 - Mean Number of New T1 Gd+ Lesions per Subject per Scan During CLARITY EXT by Treatment Group (ITT)

Characteristic	Statistics	LLPP Cladribine 3.5mg/kg / Placebo (N=98)	HLPP Cladribine 5.25mg/kg/ Placebo (N=92)	LLLL Cladribine 3.5mg/kg/ Cladribine 3.5mg/kg (N=186)	HLLL Cladribine 5.25mg/kg/ Cladribine 3.5mg/kg (N=186)	PPLL Placebo/ Cladribine 3.5mg/kg (N=244)
Mean number of new T1 Gd+ lesions per subject per scan	N (missing)	95 (3)	90 (2)	178 (8)	180 (6)	236 (8)
	Mean (SD)	0.28 (0.87)	0.29 (1.14)	0.03 (0.08)	0.17 (1.04)	0.07 (0.38)
	Median	0.00	0.00	0.00	0.00	0.00
	Q1; Q3	0.00; 0.17	0.00; 0.00	0.00; 0.00	0.00; 0.00	0.00; 0.00
	Min; Max	0.0; 6.4	0.0; 9.0	0.0; 0.5	0.0; 12.2	0.0; 5.5

Examination of the distribution of subjects with different mean numbers of lesions per subject per scan during CLARITY EXT showed higher proportions of subjects with mean values ≥1.0 in the groups randomized to placebo in CLARITY EXT - and particularly in the LLPP group - compared to those randomized to cladribine (11.6% for the LLPP group and 6.6% for the HLPP group, compared to ≤2.9% in the other groups). No subject in the LLLL group had a mean value of 1.0 or higher

In the LLPP group, mean numbers of new T1 Gd+ lesions were higher among subjects with gap duration >43 weeks than among subjects with gap duration between 4 and 43 weeks or subjects with gap duration ≤4 weeks. Proportions of subjects with a mean of ≥1 new T1 Gd+ lesion per scan were also higher among subjects with gap duration >43 weeks compared to the other subgroups.

- Mean number of active T2 Lesions

The mean number of active T2 lesions per subject per scan ranged from 0.0 to 32.3 overall (mean number ± SD: LLPP 1.42 ± 3.64; HLPP 1.44 ± 2.40; LLLL 0.88 ± 1.63; HLLL 1.13 ± 2.78; PPLL 1.07 ± 1.84). There was an initial increase in active T2 lesions observed in all treatment groups during the first year of CLARITY EXT. Between-group comparisons for mean number of active T2 lesions per subject per scan during CLARITY EXT were nominally significant for the active vs. placebo groups (HLLL + LLLL vs. HLPP + LLPP; p=0.019), with nominally significantly lower mean numbers of active T2 lesions per subject per scan in the group randomized to cladribine in CLARITY EXT, but not for the high-dose 192-week vs. 96-week treatment groups (HLLL vs. HLPP; p=0.028), the low-dose 192-week vs. 96-week treatment groups (LLLL vs. LLPP; p=0.260), or the late vs. early treatment groups (PPLL vs. LLPP; p=0.470).

- Mean number of CU Lesions

The mean number of CU lesions per subject per scan ranged from 0.0 to 34.0 overall (mean number ± SD: LLPP 1.49 ± 3.82; HLPP 1.52 ± 2.59; LLLL 0.88 ± 1.63; HLLL 1.19 ± 3.07; PPLL 1.08 ± 1.86). Between-group comparisons for mean number of CU lesions per subject per scan during CLARITY EXT showed lower mean numbers of lesions per subject per scan for the groups randomized to cladribine in CLARITY EXT. The difference was nominally significant for the active vs. placebo groups (HLLL + LLLL vs. HLPP + LLPP; p=0.016), but not for the high-dose 192-week vs. 96-week treatment groups (HLLL vs. HLPP; p=0.027), the low-dose 192-week vs. 96-week treatment groups (LLLL vs. LLPP; p=0.214), or the late vs. early treatment groups (PPLL vs. LLPP; p=0.387).

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17 - Summary of Efficacy for Trial 25643 (CLARITY)

Title: CLARITY: A phase III, randomized, double-blind, three-arm, placebo-controlled, multi-center study to evaluate the safety and efficacy of oral cladribine in subjects with relapsing-remitting multiple sclerosis (RRMS)			
Study identifier	25643		
Design	Multicentre, double-blind, randomized, placebo-controlled, parallel-group study		
	Duration of main phase:		48 weeks initial treatment period 48 weeks retreatment period
	Duration of Run-in phase:		Pre-trial evaluation period: Up to 28 days
	Duration of Extension phase:		96 weeks (CLARITY EXT – see)
Hypothesis	Superiority		
Treatments groups	Cladribine 3.5 mg/kg		Cumulative dose of 3.5 mg/kg oral cladribine, administered as two courses of cladribine (total dose of 1.75 mg/kg), followed by two courses of placebo during the first 48 weeks (Day 1, Week 5, Week 9 and Week 13) and two courses of cladribine during the second 48 weeks (total dose of 1.75 mg/kg, Week 48 and 52). 433 patients randomized
	Cladribine 5.25 mg/kg		Cumulative dose of 5.25 mg/kg oral cladribine, administered as four courses during the first 48 weeks (total dose of 3.5 mg/kg Day 1, Week 5, Week 9 and Week 13) and two courses during the second 48 weeks (total dose of 1.75 mg/kg, Week 48 and 52). 456 patients randomized
	Placebo		Matching placebo, administered as four courses during the first 48 weeks and two courses during the second 48 weeks (Day 1, Week 5, Week 9, Week 13, Week 48 and 52). 437 patients randomized
Endpoints and definitions	Primary endpoint	ARR	Annualized qualifying relapse rate at 96 weeks. 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 at least 30 days of clinical stability or improvement. The annualized relapse rate for each treatment group was calculated as the total number of confirmed relapses divided by the total number of days on study multiplied by 365.25.
	Secondary endpoint	Relapse-free rate	Proportion of subjects qualifying relapse-free at 96 weeks

	Secondary endpoint	Time to 3-months/6-months confirmed EDSS progression	Time to sustained change in Expanded Disability Status Score (EDSS) ≥ one point, or ≥ 1.5 points if baseline EDSS was 0, over a period of (i) at least three and (ii) at least six months (*post-hoc* analysis)
	Secondary endpoint	T1 Gd+ lesions	Mean number of gadolinium-enhancing T1-weighted lesions per subject per scan at 96 weeks
	Secondary endpoint	T2-weighted lesions	Mean number of active T2-weighted lesions per subject per scan at 96 weeks
	Secondary endpoint	CU lesions	Mean number of new gadolinium-enhancing T1-weighted lesions or new non-enhancing or enlarging T2-weighted lesions per subject per scan at 96 weeks
Database lock	Last subject last visit: 12 November 2008		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Analysis population: intention-to-treat (ITT). The ITT population included all subjects who were randomized into the trial.			
Descriptive statistics and estimate variability	**Treatment group**	**Placebo**	**Cladribine 3.5 mg/kg**	**Cladribine 5.25 mg/kg**
	Number of subjects	**437**	**433**	**456**
	ARR (relapses/year)	0.33	0.14	0.15
	95% CI	(0.29, 0.38)	(0.12, 0.17)	0.12, 0.17)
	Relapse-free rate (%)	60.9%	79.7%	78.9%
	Time to 3 months confirmed EDSS progression (% patients)	18.8	13.4	13.6
	10^{th} percentile	330	414	414
	Time to 6 months confirmed EDSS progression (% patients)	15.8	9.0	11.6
	10^{th} percentile	245	NE	433
	T1 Gd+ lesions, mean number	0.86	0.09	0.07
	SD	(1.78)	(0.30)	(0.37)
	T2-weighted lesions, mean number	1.38	0.35	0.29
	SD	(2.11)	(0.66)	(0.56)
	CU lesions, mean number	1.65	0.39	0.33
	SD	(2.55)	(0.71)	(0.64)
Effect estimate per comparison	Comparison groups		Cladribine 3.5 mg/kg vs placebo	Cladribine 5.25 mg/kg vs placebo

	Primary endpoint: ARR	ARR ratio	0.43	0.43
		95% CI	0.34-0.54	0.35-0.54
		P-value	<0.001	<0.001
	Secondary endpoint: Relapse-free rate	Odds Ratio	2.53	2.43
		95% CI	1.87, 3.43	1.81, 3.27
		P-value	<0.001	<0.001
	Secondary endpoint: Time to 3 months confirmed EDSS progression	Hazard Ratio	0.67	0.69
		95% CI	0.48, 0.93	0.49, 0.96
		P-value	0.018	0.026
	Secondary endpoint: Time to 6 months confirmed EDSS progression	Hazard Ratio	0.68	0.53
		95% CI	0.47, 0.97	0.36, 0.79
		P-value	0.0332	0.0016
	Secondary endpoint: T1 Gd+ lesions	Treatment Difference	-0.78	-0.80
		95% CI	-0.92, -0.65	-0.94, -0.66
		P-value	<0.001	<0.001
	Secondary endpoint: T2-weighted lesions	Treatment Difference	-1.05	-1.10
		95% CI	-1.22, -0.87	-1.27, -0.94
		P-value	<0.001	<0.001
	Secondary endpoint: CU lesions	Treatment Difference	-1.28	-1.34
		95% CI	-1.49, -1.08	-1.54, -1.14
		P-value	<0.001	<0.001

Analysis description	**Subgroup analysis by High Disease Activity (HDA)**								
Analysis population and time point description	Analysis population: subjects with HDA from CLARITY, defined as follows: • HDA1: o Subjects with at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions, OR o Subjects with 2 or more relapses in the previous year (no prior use of DMD at any time in subject history or duration of previous DMD therapy less than 1 year) and at least 1 T1 Gd+ lesion. • HDA2: o Subjects with 2 or more relapses in previous year (regardless of previous treatment status). • HDA3: o Subjects with 2 or more relapses in previous year (regardless of previous treatment status), AND at least: 1 T1 Gd+ lesion OR 9 T2 lesions. • HDA4: o Subjects with at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions, OR o Subjects with 2 or more relapses in the previous year (regardless of previous treatment status).								
Descriptive statistics and estimate	**Treatment group**	**Placebo**				**Cladribine 3.5 mg/kg**			
		HDA1	HDA2	HDA3	HDA4	HDA1	HDA2	HDA3	HDA4

variability	**Number of subjects**	67	131	122	149	62	130	112	140
	ARR, (relapses/ year)	0.57	0.50	0.48	0.47	0.22	0.16	0.18	0.16
	95% CI	0.45, 0.73	0.41, 0.60	0.39, 0.58	0.40, 0.57	0.14, 0.33	0.11, 0.22	0.13, 0.25	0.12, 0.22
	Time to 3 months confirmed EDSS progression (K-M estimate at last event)	75.7	69.6	69.3	71.7	80.9	90.3	89.6	91.0
	95% CI	62.8, 84.6	60.5, 77.0	59.8, 76.9	63.4, 78.5	68.1, 88.9	83.5, 94.4	81.9, 94.1	84.7, 94.8
	Time to 6 months confirmed EDSS progression (K-M estimate at last event)	82.2	76.5	76.5	77.7	91.2	95.1	95.2	95.5
	95% CI	70.1, 89.7	67.9, 83.1	67.6, 83.3	69.8, 83.8	80.2, 96.3	89.4, 97.8	89.0, 98.0	90.2, 97.9
Effect estimate per comparison	Comparison groups (HDA versus placebo)					HDA1	HDA2	HDA3	HDA4
	Annualized relapse rate	Relative risk ratio				0.38	0.32	0.37	0.33
		95% CI				(0.24, 0.61)	(0.22, 0.47)	(0.25, 0.54)	(0.23, 0.48)
		P-value				<0.0001			
	Time to 3 months confirmed EDSS progression	Comparison groups (HDA subgroup versus placebo)				HDA1	HDA2	HDA3	HDA4
		Hazard ratio				0.78	0.28	0.30	0.28
		95% CI				(0.35, 1.70)	(0.15, 0.54)	(0.15, 0.59)	(0.15, 0.54)
		P-value				0.5239	0.0001	0.0005	0.0001
	Time to 6 months confirmed EDSS progression	Hazard ratio				0.46	0.18	0.18	0.18
		95% CI				(0.16, 1.35)	(0.08, 0.44)	(0.07, 0.47	(0.07, 0.43)
		P-value				0.1576	0.0002	0.0004	0.0001
Notes	*The chart summarises the subgroup analysis for both placebo and Cladribine 3.5 mg/kg for the primary endpoint and the key secondary endpoint. The highest dose (5.25 mg/kg) is not included in the chart as it is not proposed for clinical use.*								

Table 18 - Summary of Efficacy for Trial 27820 (CLARITY EXT)

Title: A Phase IIIb, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Extension Trial to Evaluate the Safety and Tolerability of Oral Cladribine in Subjects with Relapsing-Remitting Multiple Sclerosis Who Have Completed Trial 25643 (CLARITY)							
Study identifier	Trial No.: 27820						
Design	A randomised, double-blind, placebo-controlled, parallel group, multicenter 96-week extension study to CLARITY.						
	Duration of main phase:		Main phase: 96 weeks				
	Duration of Run-in phase:		No run-in phase				
	Duration of Supplemental follow-up period		24 weeks				
Hypothesis	Exploratory						
Treatments groups	LLPP		Treatment in CLARITY: Low dose cladribine (3.5 mg/kg), randomised to placebo in CLARITY EXT N (randomized) =98; duration=96 weeks				
	HLPP		Treatment in CLARITY: High dose cladribine (5.25 mg/kg), randomised to placebo in CLARITY EXT N=92; duration=96 weeks				
	LLLL		Treatment in CLARITY: Low dose cladribine (3.5 mg/kg), randomised to low dose cladribine (3.5 mg/kg) in CLARITY EXT N=186; duration=96 weeks				
	HLLL		Treatment in CLARITY: High dose cladribine (5.25 mg/kg), randomised to low dose cladribine (3.5 mg/kg) in CLARITY EXT N=186; duration=96 weeks				
	PPLL		Treatment in CLARITY: Placebo, randomised to low dose cladribine (3.5 mg/kg) in CLARITY EXT N=244; duration=96 weeks				
Endpoints and definitions	Clinical Efficacy Endpoint	ARR	Annualized qualifying relapse rate at 96 weeks				
	Clinical Efficacy Endpoint	Time to 3 months/ 6 months confirmed EDSS progression	Time to sustained change in Expanded Disability Status Score (EDSS) ≥ one point, or ≥ 1.5 points if baseline EDSS was 0, over a period of at least (i) 3 months, and (ii) 6 months				
Database lock	Last subject last visit: 08 December 2011						
Results and Analysis							
Analysis description	**Primary Analysis**						
Analysis population and time point description	Intent to treat (ITT) population						
Descriptive statistics and estimate variability	Treatment group	LLPP	HLPP	LLLL	HLLL	PPLL	
	Number of subjects (ITT)	98	92	186	186	244	
Explorative efficacy endpoints	ARR (relapses/year)	0.15	0.13	0.10	0.12	0.10	
	97.5% CI	0.09; 0.21	0.08; 0.19	0.06; 0.13	0.08; 0.16	0.07; 0.13	

	Time to 3-Month Sustained Change in EDSS Score (10^{th} Percentile)		533	1009	596	498	429
	95% CI		168; 781	162; NE	328; NE	246; 673	330; 582
	Time to 6-Month Sustained Change in EDSS Score (10^{th} Percentile)		665	NE	NE	580	582
	95% CI		168; NE	NE	NE	246; NE	415; 1009
Effect estimate per comparison	Comparison groups		(1) Active treatment groups (LLLL + HLLL) vs. placebo treatment group (LLPP + HLPP) (2) 192-week vs. 96-week high dose treatment group (HLLL vs. HLPP) (3) 192-week vs. 96-week low dose treatment group (LLLL vs. LLPP) (4) Late treatment group (PPLL) vs. early treatment group (LLPP)			
			Comparison Group (1): LLLL+HLLL vs. LLPP+HLPP	**Comparison Group (2): HLLL vs. HLPP**	**Comparison Group (3): LLLL vs. LLPP**	**Comparison Group (4): PPLL vs. LLPP**
	ARR	Relative Risk	0.76	0.89	0.65	0.68
		97.5% CI	0.53,1.10	0.53,1.51	0.39,1.08	0.42,1.11
		P-value	0.096	0.634	0.059	0.078
	Time to 3-Month Sustained Change in EDSS Score	Hazard Ratio	1.24	1.72	0.62	0.91
		97.5% CI	0.32,4.78	0.73,4.05	0.30,1.27	0.48,1.71
		P-value	0.479	0.152	0.134	0.728
	Time to 6-Month Sustained Change in EDSS Score	Hazard Ratio	0.99	1.88	0.58	0.96
		97.5% CI	0.53,1.87	0.67,5.29	0.25,1.36	0.46,2.00
		P-value	0.974	0.169	0.153	0.895

2.5.3. Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy data from the CLARITY, CLARITY EXT, and ONWARD studies (see section on supportive studies) were pooled to assess ARR, EDSS progression and MRI endpoints across these studies. The ORACLE MS study was not included as it included patients with clinically isolated syndrome (CIS) and utilized an event driven study design that did not provide the consistent 2 year observation period for all study subjects provided by CLARITY, CLARITY EXT, and ONWARD. The intention of the pooling was to increase the number of patients in order to evaluate long term efficacy of treatment.

Statistical analyses were conducted using 2 cohorts, as follows:

1. 96 Weeks Double-Blind was an integrated analysis of CLARITY and ONWARD double-blind period only.

2. DB plus EXT was an integrated analysis of CLARITY, CLARITY EXT, and ONWARD including all periods. The DB plus EXT cohort was conducted to allow reporting of long term efficacy endpoints.

Furthermore, analyses were conducted for the overall pooled population as well as for subgroups by baseline characteristics and HDAs (same definition as in CLARITY).

An overview of the number of subjects in the pooled analysis is presented below:

Table 19 - Overview of Subjects in the Pooled Analysis

Study	Placebo	Cladribine 3.5 mg/kg	Cladribine 5.25 mg/kg	TOTAL
CLARITY	437	433	456	1326
CLARITY EXT[1]	190	616	-	867
ONWARD[2]	57	140	17	214

1 A further 61 subjects were followed without any treatment. These 61 subjects did not receive cladribine, but were eligible to be administered other MS therapies.

2 All subjects received at least 1 dose of cladribine or placebo and IFN-β. It should be noted that 25 (14.5% of ONWARD subjects) subjects had SPMS.

Since there were no subjects treated with placebo for more than 2 years in the DB plus EXT cohort, comparisons with the active treatments groups were difficult to make. Considering this limitations, data are presented in the following for the 96 Week DB cohort only.

The same criteria and definitions of the HDA subgroups as for CLARITY were applied, with the following distribution:

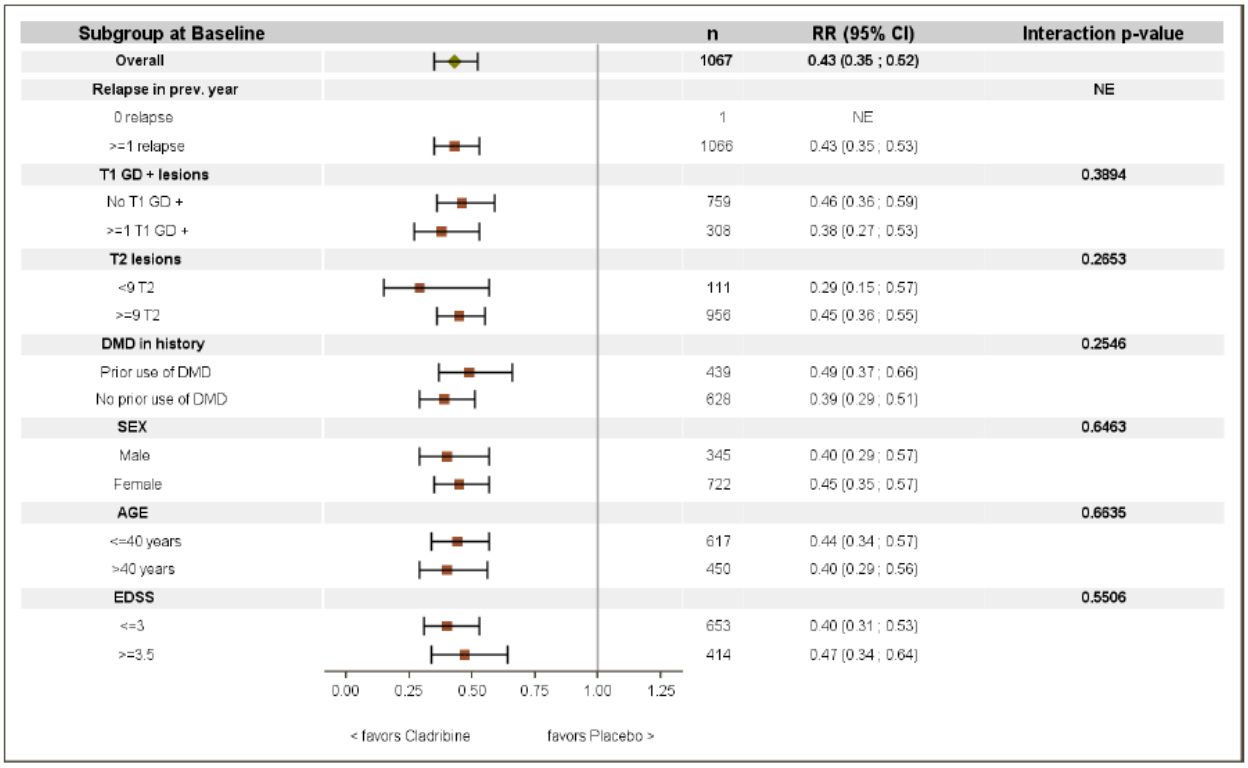
Table 20 - Numbers of Subjects in the Integrated Analysis by HDA Subgroup – 96 Week DB Cohort (CLARITY and ONWARD)

Parameter N (%)	Placebo	Cladribine 3.5 mg/kg	Cladribine 5.25 mg/kg	Total
Overall population	494 (100)	573 (100)	473 (100)	1540 (100)
HDA1 subgroup	114 (23.1)	180 (31.4)	78 (16.5)	372 (24.2)
HDA2 subgroup	150 (30.4)	164 (28.6)	136 (28.8)	450 (29.2)
HDA3 subgroup	140 (28.3)	144 (25.1)	125 (26.4)	409 (26.6)
HDA4 subgroup	197 (39.9)	262 (45.7)	159 (33.6)	618 (40.1)

The numbers in the analysis cohorts were generally balanced except for HDA1. This is due to the uneven contribution from the 5.25 mg/kg dose group as there were fewer patients in 5.25 mg/kg in ONWARD study following a protocol amendment removing this dose from the study.

Results *(CLARITY and ONWARD - 96 Weeks Double-Blind Cohort)*

The relative risks of **qualified ARR** in RRMS subjects were consistent with the efficacy shown in the analysis of CLARITY alone. For cladribine 3.5 mg/kg and 5.25 mg/kg, the HDA1, HDA2, HDA3, HDA4 and corresponding non-HDA subgroups were similar to the overall population in terms of ARR results (57% reduction) with statistically significant reductions ($p<0.0001$) seen in these subgroups. Observed point estimates in HDA2 to HDA4 subgroups were systematically more favourable than their non-HDA counterparts, reaching nominal significance for HDA2. The relative risk ratios for HDA-subgroups range from 0.44 to 0.33 indicating a risk reduction of 56% to 67% in ARR.



CI=Confidence interval; DB=double-blind; DMD=disease modifying drug; EDSS=expanded disability status scale; Gd+=gadolinium-enhanced; RR=relative risk

Figure 7 - Forest Plot of Relative Risk of Annualized Qualifying Relapse in Subgroups with Cladribine 3.5 mg/kg vs Placebo – 96 Week DB Cohort

The HRs for the **time to 3-month confirmed EDSS** progression for HDA1, HDA2, HDA3, and HDA4 subgroups treated with 3.5 mg/kg cladribine were 0.90, 0.40, 0.43 and 0.47, respectively, indicating a risk reduction of 10%, 60%, 57%, and 53% in time to 3-month confirmed EDSS progression. Observed point estimates in HDA2 to HDA4 subgroups were systematically more favourable than their non-HDA counterparts, reaching nominal significance for HDA2. In subjects receiving the 5.25 mg/kg dose, the HRs in HDA subgroups with the 5.25 mg/kg cladribine dose ranged from 0.33 to 0.51, with risk reductions of 49%, 64%, 67% and 51% seen in the HDA1 to HDA4 subgroups, respectively, and 37% (HR 0.63) in the overall population.

Consistent results in favour of both cladribine doses were observed across subgroups by baseline demographics; the results suggested greater effects in males compared to females (interaction p=0.0338) and in younger patients (≤40 years, interaction p=0.0422), however, this has to be interpreted with caution, given the multiplicity of testing.

For the **time to 6-month confirmed EDSS progression** HR for HDA1, HDA2, HDA3, HDA4 and their counterpart non-HDA subgroups in subjects treated with 3.5 mg/kg cladribine in the 96 Week DB period the HRs were 0.78, 0.29, 0.30, and 0.40 respectively, indicating a risk reduction of 22%; 71%; 70%; and 60% in time to 6-month confirmed EDSS progression. Observed point estimates in HDA2 to HDA4 subgroups were systematically more favourable than their non-HDA counterpart**s**, reaching nominal significance for HDA2 and HDA3. In subjects receiving the 5.25 mg/kg dose, the HRs in HDA subgroups with the 5.25 mg/kg cladribine dose ranged from 0.34 to 0.40, with risk reductions of 60%, 65%, 66%, and 60% seen in the HDA1-4

subgroups, respectively, and 30% (HR 0.70) in the overall population. Generally, consistent results in favour of cladribine (both doses) compared to placebo were observed across subgroups by baseline demographics.

The relative risk ratio for the HDA1, HDA2, HDA3, and HDA4 subgroups treated with 3.5 mg/kg cladribine was 0.10, 0.08, 0.07 and 0.09, indicating a risk reduction of 90%, 92%, 93% and 91% in **cumulative new T1 Gd+ lesions**. Similar results were shown for the non-HDA counterpart subgroups. Results in all subgroups are consistent with the findings in the overall population (relative risk ratio of 0.10), which had indicated a risk reduction of 90%. In subjects receiving the 5.25 mg/kg dose, the relative risk ratios in HDA subgroups were all 0.03, with risk reductions of 97% seen in the HDA1 to HDA4 subgroups and 94% (relative risk ratio 0.06) in the overall population. Subgroup analyses by baseline demographics suggest a greater effect in males compared to females (interaction p=0.0002).

Clinical studies in special populations

No dedicated clinical studies in special populations were performed. The main studies included adult patients up to the age of 65 years. No clinical studies were performed in the paediatric populations or in patients older than 65 years.

2.5.4. Supportive studies

Clinical study 26593 (ONWARD): A Phase II, multi-center, randomized, double-blind, placebo-controlled, safety, tolerability and efficacy study of add-on cladribine tablet therapy with Interferon-beta (IFN-β) treatment in multiple sclerosis (MS) subjects with active disease.

The ONWARD study was a Phase IIb, multicenter, randomized, double-blind, placebo-controlled, safety, tolerability and efficacy study of add-on cladribine and IFN-β in subjects with active RMS despite treatment with IFN-β therapy. Patients with active disease were defined as having experienced at least 1 relapse in the 48 weeks prior to study entry despite concurrent treatment with IFN-β. The study included subjects with RRMS and 14.5% of the subjects had secondary progressive MS (SPMS) with relapses.

According to the original protocol, subjects were randomized into 3 arms:

- Placebo + IFN-β (Rebif®)
- Cladribine 3.5 mg/kg (same course regimen as in CLARITY) + IFN-β
- Cladribine 5.25 mg/kg (same course regimen as in CLARITY) + IFN-β

The study protocol was amended following early safety signals related to haematologic toxicities and re-evaluation of procedures for re-dosing. The amendment resulted in elimination of the high dose cladribine treatment group (5.25 mg/kg), implementation of risk minimization procedures related to haematologic testing prior to blinded study medication dosing, expansion of entry criteria to allow the enrollment of subjects taking other IFN-β treatments. Furthermore, in June 2011, the Sponsor decided to no longer pursue new development plans for oral cladribine, resulting in discontinuation of treatment with cladribine (treatment with IFN-β was to continue), and reduction of the Extension period to a maximum of 48 weeks, for the purpose of collecting safety data.

After the protocol amendments, a total of 172 subjects were randomized to the double-blind period, 48 subjects to the placebo + IFN-β group and 124 subjects to the cladribine 3.5 mg/kg + IFN-β group. By

the time of study termination (October 2011), all subjects had completed the scheduled 96 weeks of the double-blind period, allowing analysis of the planned efficacy endpoints.

Overall, in the placebo and 3.5 mg/kg groups, a total of 197 SPMS or RRMS patients, all of whom had had superimposed relapses in the previous year, were randomized: 26 were SPMS and 171 were RRMS patients.

The primary objective was to evaluate the safety and tolerability of 3.5 mg/kg oral cladribine tablets as an add-on to injectable IFN-β treatments. The secondary objective was to explore the efficacy on qualifying relapse rate, progression of disability and lesion activity (MRI).

Results

With regard to patient demographics and baseline characteristics after protocol amendments, mean age and EDSS were similar across groups, although there was a notable difference in the mean number of T1 lesions between groups, explained by the inclusion of a few subjects with a high load of T1 lesions in the cladribine 3.5 mg/kg + IFN-β group with a maximum value of 34 whereas in the placebo + IFN-β group the maximum value was 6, while the median was zero in both groups.

Annualized Qualifying Relapse Rate (ITT Population)

The ARR for the placebo + IFN-β group and cladribine 3.5 mg/kg + IFN-β group were 0.32 and 0.12, respectively. The relative risk of 0.37 (95% CI: 0.22, 0.63) indicates that subjects in the cladribine 3.5 mg/kg + IFN-β group were 63% less likely to experience a qualifying relapse than subjects in the placebo + IFN-β group ($p<0.001$). In the SPMS subgroup, the relative risk was 0.11 (95% CI: 0.01, 0.94), indicating that subjects in the cladribine 3.5 mg/kg + IFN-β were 89% less likely to experience a qualifying relapse than subjects in the placebo + IFN-β group ($p=0.0439$). For patients in the RRMS subgroup with superimposed relapses, the relative risk was 0.50 (95% CI: 0.30, 0.84) in the cladribine over the placebo group, indicating that subjects in the cladribine 3.5 mg/kg + IFN-β were 50% less likely to experience a qualifying relapse than subjects in the placebo + IFN-β group ($p=0.0090$).

Subgroup analyses in SPMS and RRMS patients showed a statistically significant reduction in ARR with active treatment compared to placebo in both patient groups (see Table 21).

Table 21 - ARR for Patients classified as SPMS and RRMS

Statistic	SPMS Patients (N=26)		RRMS Patients N=171	
	Placebo + IFN-β (N=9)	Cladribine 3.5 mg/kg + IFN-β (N=17)	Placebo + IFN-β (N=48)	Cladribine 3.5 mg/kg + IFN-β (N=123)
Annualized relapse rate (adjusted)	0.30	0.03	0.31	0.15
95% CI	(0.13 ; 0.73)	(0.00 ; 0.24)	(0.21 ; 0.45)	(0.11 ; 0.22)
Risk ratio	-	0.11	-	0.50
95% CI	-	(0.01 ; 0.94)	-	(0.30 ; 0.84)

CI = confidence interval; IFN-β = interferon beta; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis (with relapses).

EDSS

In the placebo + IFN-β group, 6 (12.5%) of 48 subjects had a qualifying 3-month sustained EDSS disability progression compared with 19 (15.3%) of 124 subjects in the cladribine 3.5 mg/kg + IFN-β group (p=0.623). Similarly, no treatment effect was observed in either of the SPMS or RRMS subgroups, which is consistent with the overall study data and as expected given the low number of patients in the study.

MRI

There were 11 MRI efficacy endpoints. Of these, 7 MRI endpoints gave positive efficacy signals in favour of the cladribine 3.5 mg/kg + IFN-β group. There was a significant reduction in the mean (SD) number of new T1 Gd+ lesions per subject per scan during the 96 week double-blind period in the cladribine 3.5 mg/kg + IFN-β group (0.25 [1.46]) compared with the placebo + IFN-β group (1.27 [3.39]). For subjects in the SPMS subgroup, cladribine 3.5 mg/kg + IFN-β led to a reduction in both mean (SD) number of T1 Gd+ lesions (0.13±0.55) and mean number of active T2 lesions (0.29±0.52) per subject per scan compared to placebo + IFN-β (0.67±2.00 and 0.59±1.66 respectively). For subjects in the RRMS subgroup with superimposed relapses, cladribine 3.5 mg/kg + IFN-β showed superiority as well in reducing the mean (SD) number of T1 Gd+ (0.05±0.31) and T2 lesions (0.58±1.40) per subject per scan compared to placebo + IFN-β (0.29±0.64 and 1.31±2.36 respectively).

Clinical study 28821 (ORACLE): A Phase III, randomized, double-blind, placebo-controlled, multi-center clinical trial of oral cladribine in subjects with a first clinical event at high risk of converting to MS

The ORACLE MS study was a Phase III, randomized, double-blind study to evaluate the efficacy and safety of oral doses of cladribine (3.5 mg/kg and 5.25 mg/kg) vs placebo in subjects who had sustained a first clinical demyelinating event within 75 days prior to the screening visit. The study was terminated early in June 2011 (protocol amendment 5).

Subjects were randomized to either oral cladribine 5.25 mg/kg, oral cladribine 3.5 mg/kg, or matching placebo administered following the same course regime as in CLARITY. The treatment was administered over a total of 6 weeks, at the start of Year 1 (4 weeks of treatment) and Year 2 (2 weeks of treatment). This period was referred to as initial treatment period (96 weeks).

The primary objective was to evaluate the effect of oral cladribine on the time to conversion from CIS to clinically definite MS (CDMS, defined according to the Poser criteria by either a second attack or an increase in the EDSS score of ≥ 1 point if baseline was ≥1 and ≤ 4.5, or of ≥ 1.5 points if baseline EDSS was 0, or of ≥ 0.5 point if baseline EDSS was ≥ 5, sustained over a period of at least 3 months). CIS status was confirmed prior to randomisation by an adjudication committee applying the same standards in all regions. Subjects converting to CDMS within the initial treatment period were to discontinue blinded study medication at the time of conversion to CDMS and initiate maintenance treatment with INF-ß in an open-label fashion for 96 weeks.

Subjects who did not convert to CDMS during the initial treatment period were eligible to enroll in a long-term follow-up (LTFU) period. Subjects who developed MS according to the McDonald 2005 criteria received open-label cladribine 3.5 mg/kg upon entry into the LTFU. Subjects without signs of MS did not receive any treatment. After protocol amendment 5, subjects who converted to either MS diagnosis in the LTFU were to receive INF-ß. The original duration of the LTFU period was planned as a maximum of 96 weeks. Upon early termination of the study, the period was reduced to allow for follow-up of subjects for 24 weeks from the time of the last dose of cladribine.

A total of 617 subjects were randomized and 616 received at least 1 dose of blinded study medication (the ITT/Safety Population); 204 subjects in the cladribine 5.25 mg/kg group, 206 subjects in the cladribine 3.5 mg/kg group, and 206 subjects in the placebo group.

Results

Main patient demographics and baseline characteristics were balanced across treatment groups, except for a higher proportion of subjects with T1 lesions in the cladribine 5.25 mg/kg group. It also appeared that more severe cases of CIS were recruited in Russia/Eastern Europe.

Primary Endpoint - Conversion to CDMS

At the time of protocol amendment 5, which required subjects to discontinue cladribine treatment, only 6.8% of subjects had discontinued early from the initial treatment period. At the time of the primary analysis of the initial treatment period, a total of 122 subjects in the ORACLE MS study had converted to CDMS (122/127 [96.1%] of the planned number of events). Of the 122 subjects who converted to CDMS, 27 subjects had been treated with cladribine 3.5 mg/kg, 30 subjects had been treated with cladribine 5.25 mg/kg, and the remaining 65 subjects had been treated with placebo.

Treatment with cladribine 3.5 mg/kg and cladribine 5.25 mg/kg delayed the time to CDMS conversion compared to placebo ($p<0.0001$ for each comparison) during the initial treatment period. The estimated HR for CDMS conversion was 0.354 (95% CI: 0.226, 0.555; $p<0.0001$) for the cladribine 3.5 mg/kg group vs the placebo group, indicating a 64.6% risk reduction of CDMS conversion relative to the placebo group. The estimated HR for the time to CDMS conversion was 0.414 (95% CI: 0.269, 0.639; $p<0.0001$) for the cladribine 5.25 mg/kg group vs the placebo group, indicating a 58.6% risk reduction of CDMS conversion in the cladribine 5.25 mg/kg group relative to the placebo group.

The Kaplan-Meier estimates of the cumulative probability of CDMS conversion at the end of the double-blind period in the cladribine 3.5 mg/kg, cladribine 5.25 mg/kg, and placebo groups were 15.8%, 18.1%, and 40.1%, respectively (see Figure 8).

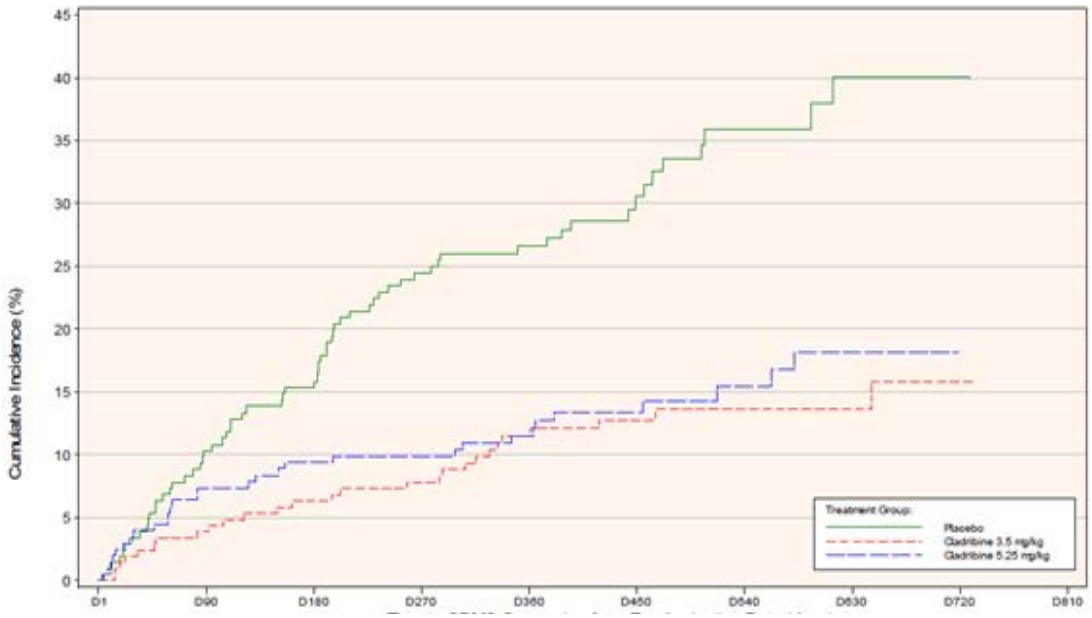


Figure 8 - Time to CDMS Conversion: Kaplan-Meier Incidence Curves – ORACLE MS

The number and percentage of subjects in the ITT analysis set who satisfied the 2010 McDonald MS Criteria at baseline were 83 (40.7%) subjects in the cladribine 5.25 mg/kg group, 68 (33.0%) subjects in the cladribine 3.5 mg/kg group, and 72 (35.0%) subjects in the placebo group. For these subjects, there was a significant difference in favour of the cladribine 3.5 mg/kg group compared with the placebo in the time to CDMS conversion during the initial treatment phase. The HR was 0.258 (95% CI 0.116, 0.575; p=0.0009), indicating a 74.2% risk reduction of CDMS conversion compared to placebo. Although the HR for cladribine 5.25 mg/kg versus placebo (0.628) was favourable for active treatment, it did not reach statistical significance (p=0.1364).

2.5.5. Discussion on clinical efficacy

Efficacy data from four randomized, double-blind, placebo-controlled phase II/III studies have been provided in support of the application for cladribine, covering a relatively broad spectrum of MS patients. Patients with RRMS were recruited in the pivotal Phase III study CLARITY along with its 2-year extension CLARITY EXT. While CLARITY mostly enrolled RRMS patients with low disease activity, the study also included a limited subset of patients with highly active RRMS, in line with the proposed target population. Supportive data were furthermore available in patients with SPMS and superimposed relapses, which were recruited in addition to RRMS patients in the ONWARD study. The use of cladribine was also evaluated in patients with CIS in the ORACLE study. Finally, additional data from the Scripps legacy studies were provided with parenteral cladribine. These studies were considered mainly in the context of the dose selection for the clinical trials with oral cladribine.

Design and conduct of clinical studies

All four clinical trials evaluated two cumulative doses of oral cladribine, 3.5mg/kg and 5.25 mg/kg. The choice of the doses was based on a number of small phase II studies (the Scripps studies) using parenteral cladribine and taking into account the bioavailability of cladribine after p.o. administration.

CLARITY

In CLARITY, RRMS patients were included in accordance with the McDonald's 2005 criteria. The total treatment period was 96 weeks, whereby active treatment was administered at the beginning of Year 1 and 2 in monthly courses of 0.875 mg/kg up to a cumulative dose of 3.5mg/kg and 5.25 mg/kg. The overall design of the study was considered acceptable.

The primary objective was to evaluate the efficacy of cladribine versus placebo in the reduction of the annualized qualifying relapse rate (ARR) at the end of the treatment period compared to baseline, which is in line with the CHMP Guideline on clinical investigations of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev. 2). According to the Guideline, progression of disability should be a key secondary endpoint, and was investigated in CLARITY as time to sustained change in EDSS over a period of at least 3 months, although only as a regular secondary endpoint. Disease progression over a period of 6 months was investigated in a *post-hoc* analysis, which was considered acceptable given that the study was conducted prior to the specification of the duration in the Guideline. The CHMP furthermore noted that the Guideline requires clinical global impression of change as well as patient reported outcomes to be included as secondary endpoints, which was not the case in CLARITY. However, as the tertiary endpoints included measurements to this end (e.g. health related quality of life [HRQL] and health care resource utilisation [HRU]), this was considered a minor issue.

For the statistical analyses, an ANOVA model with fixed effects for treatment group and region using a Chi-square test based on Wald statistics was used, which was considered acceptable. The choice of a fixed effect model rather than a random effect model was considered acceptable as the study population was limited to RRMS patients. For the secondary endpoints, the hierarchical testing procedure as well as the hierarchical ranking (T1, T2, and CU) was also considered appropriate.

In line with a CHMP Scientific Advice in December 2014, in order to identify a target population with a more favourable benefit-risk balance, *post-hoc* subgroup analyses were performed in patients with high disease activity (HDA). Four HDA groups were initially defined with high disease activity being measured in terms of occurrence of relapse and presence of MRI lesions with or without prior DMD treatment. The criteria defining the HDA4 subgroup of patients, i.e. at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions, OR with 2 or more relapses in the previous year (regardless of previous treatment status) resulted in the largest subgroups of patients in all three treatment groups. Still, the proportion of patients fulfilling this definition was limited.

CLARITY EXT

Patients who completed scheduled clinic visits for the full 96 weeks in the CLARITY study were eligible to participate in CLARITY EXT. The primary objective of this extension study was to investigate the long-term safety of oral cladribine, whereas efficacy was amongst the explorative objectives, which limits firm conclusions regarding efficacy.

Compared to CLARITY, more restrictions related to safety parameters like comorbidities (LTBI and TB) as well as threshold blood test values were introduced. The stricter inclusion/exclusion criteria did not negatively affect recruitment, whereas it would likely enhance the safety of cladribine in clinical practice for which reason they are reflected in the SmPC sections 4.2, 4.3, and 4.4 (see also section 2.6. on clinical safety).

The study included a 96-week double-blind period (divided into two 48-week periods during which treatment was given according to the same schedule as in the second year of CLARITY). Five treatment groups were investigated: LLPP (3.5 mg/kg during CLARITY, placebo in CLARITY EXT), HLPP (5.25 mg/kg during CLARITY, placebo in CLARITY EXT), LLLL (3.5 mg/kg during CLARITY, 3.5 mg/kg in CLARITY EXT), HLLL (5.25 mg/kg during CLARITY, 3.5 mg/kg in CLARITY EXT) and PPLL (placebo during CLARITY, 3.5 mg/kg in CLARITY EXT). The choice to only use the 3.5 mg/kg dose in CLARITY EXT was considered appropriate as no clinical meaningful difference in efficacy between doses had previously been observed in CLARITY (see also discussion on efficacy data below). Overall, the design of the study was considered suitable in order to examine persistence of the treatment effect and the need for additional treatment cycles in year 3 and 4.

With regards to the efficacy variables, which included both clinical and MRI endpoints, the CHMP noted that an extensive list of MRI parameters had been predefined, which increases the likelihood of chance-findings.

Supportive studies (ONWARD and ORACLE)

ONWARD was designed primarily to evaluate safety and tolerability of cladribine as add-on treatment to background INF-β treatment in patients with active RMS. The population studied in ONWARD was more advanced compared to CLARITY and ORACLE and included RMS patients, who despite treatment with INF-ß had at least one relapse during last 12 months. While the majority of patients had RRMS, 14.5% of patients recruited into this trial had SPMS with superimposed relapses (16.7% placebo; 13.7% cladribine 3.5mg/kg). All efficacy endpoints were secondary and included qualifying relapse rate, progression of disability and lesion activity (MRI) and the results were considered supportive for the present application. Moreover, although the

number of SPMS patients was low, subgroup analyses were considered relevant to support efficacy of cladribine in this population.

ORACLE was designed to test the efficacy of cladribine in preventing conversion of CIS to CDMS. Notably, some CIS patients (approximately 30%) could be retrospectively classified as RMS based on the 2010 McDonald criteria. The population tested in the ORACLE study was considered to be representative of patients with very early stage in the disease development. More severe cases of CIS were recruited in Russia/Eastern Europe, but this was not regarded as a major issue, given that the present application concerns a different target population (RRMS patients with high disease activity). The study was prematurely terminated collecting 122 instead of 127 conversion to CDMS cases and resulting in changes to patient follow up. While the shorter follow up may have had an impact on the study results, it was considered unlikely that the deviation from the originally planned conversion rate had an impact on the primary efficacy results.

Pooled analysis

In order to increase the number of patients for the evaluation of long term efficacy of cladribine treatment, data from CLARITY, CLARITY EXT, and ONWARD were pooled. The main focus was on the 96 Week DB cohort including data from the double-blind period of CLARITY and ONWARD. However, while the advantages of a larger analysis population were acknowledged, the value of a pooled analysis in a heterogeneous patient population as the one resulting from the combination of CLARITY and ORACLE could be questioned. ONWARD compared cladribine + IFN-β to placebo + IFN-β, whereby the effect of INF-β in the treatment in RRMS is well established. This means that efficacy seen in ORACLE (both in the active and the placebo arm) cannot be solely attributed to cladribine. Further, a small subset of subjects in ONWARD was classified as SPMS (14.5%) with superimposed relapses. On the other hand, it could be expected that in order to demonstrate efficacy on ARR, EDSS and MRI endpoints in a more heterogeneous patient population could actually be more challenging. With that said, patients included into CLARITY, CLARITY EXT and ONWARD were considered an adequate group to study efficacy of cladribine in RRMS (as well as RMS) and data pooling helped to increase the size of the HDA analysis population.

Efficacy data and additional analyses

CLARITY

A total of 1,326 patients were randomised into one of the treatment groups in CLARITY. Of these, 87.9% patients completed treatment and 89.3% completed the study, and the rates were comparable across treatment groups. In both cladribine groups, the most common reason for discontinuation of treatment was adverse events (AEs), whereas in the placebo-group the most common reason for discontinuation was disease progression (5.5%). Baseline demographics as well as MRI and neurological findings were generally well balanced across treatment groups, although T1 hypointense and T2 lesion load appeared to be greater in the cladribine 5.25 mg/kg group, suggesting that patients in this group may have had an increased disease burden at baseline.

The primary endpoint was met for both doses of cladribine. The ARRs were 0.15 for patients receiving cladribine 5.25 mg/kg, 0.14 for patients receiving cladribine 3.5 mg/kg, and 0.33 for the placebo group. The difference between both active arms and placebo was statistically significant ($p<0.001$) and of clinically relevance with a relative reduction of the ARR of 54.5% with cladribine 5.25 mg/kg and 57.6% with cladribine 3.5 mg/kg compared to placebo. No difference in the effect size was observed between the 2 cladribine doses, which supports the choice of the 3.5mg/kg dose for use in CLARITY EXT as well as in clinical practice. In general, the RRMS patients recruited in CLARITY were relatively mildly affected, which is reflected

in the low ARR in the placebo group, which was in fact somewhat lower compared to the ARR in the placebo group of clinical trials with recently approved MS treatments.

With regards to the time to 3-months sustained disability progression, the hazard ratios were 0.67 and 0.69 for cladribine 3.5 mg/kg and 5.25 mg/kg respectively versus placebo. The differences between the active arms and placebo were statistically significant and were considered clinically relevant, although in absolute figures for the 10th percentile, the difference between active treatment and placebo was only 84 days. There was no clinically meaningful difference between the two cladribine doses. Time to 6-month sustained change in EDSS showed similar results in favour of active treatment with a hazard ratio of 0.53 for cladribine 3.5 mg/kg and 0.68 for cladribine 5.25 mg/kg (p=0.0016 and p=0.0332, respectively).

Secondary MRI endpoints included the mean number of active T1 Gd+-enhanced 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. For all imaging endpoints, a statistically significant difference between active treatment and placebo was found (p<0.001 for all comparisons). Yet again, no relevant difference between the cladribine doses was observed. Results for the tertiary endpoints supported the findings for the primary and secondary endpoints.

CLARITY recruited a total of 32 patients older than 55 years (but less than 65 years). Recently, it was shown that natalizumab is more effective in younger patients compared to older ones (Matell et al., 2015). Given that cladribine, like natalizumab, could also be considered a potent anti-inflammatory treatment, a similar age-dependent effect could be possible. In response to a CHMP request, a subgroup analysis of patients aged ≤50 years (N=1155) compared to patients >50 years (N=171) was performed. Despite higher disease activity in younger patients, the analysis showed beneficial effects of cladribine 3.5 mg/kg and 5.25 mg/kg in both subgroups in line with the results for the overall study population. The relative risk for a qualifying relapse with cladribine 3.5mg/kg compared to placebo was 0.41 for patients ≤50 years (p<0.0001) and 0.48 for patients >50 years (p=0.0273).

With regards to high disease activity patients, treatment with cladribine was superior to placebo for all efficacy endpoints. With regards to ARR, HDA patients treated with cladribine 3.5 mg/kg had a relapse rate of 0.16-0.22 compared to 0.47-0.57 in HDA patients treated with placebo. The relative risk ranged from 0.32 to 0.38 across the 4 defined HDA subgroups. In non-HDA patients the relapse rate was 0.13-0.14 for patients receiving cladribine 3.5 mg/kg compared to 0.29-0.30 for placebo. The relative risk was within the range of 0.43-0.49. These findings support a trend for a greater benefit of cladribine in patients with high disease activity. The same pattern was seen for the 5.25 mg/kg dose. A greater effect of cladribine in HDA patients compared to non-HDA patients was observed for other endpoints including time to 3 months or 6 months disease progression, but not for MRI and NEDA endpoints, where there was no difference.

Overall, based on the disease activity in the placebo groups across the 4 HDA subgroups, all groups appear to have been reasonable defined to identify relevant patients. There were however substantial overlaps in the definition of the HDA groups and it was not possible to single out one of the HDA subgroups that improved most with cladribine. This was not considered a major issue though in light of the consistent trend of increased efficacy seen across all HDA subgroups.

Overall, the CLARITY study showed a clinically relevant effect of cladribine in the treatment of adult patients with RRMS and subgroup analyses support a trend for a greater benefit of cladribine in HDA patients. As no additional effect was observed in patients treated with a cumulative cladribine dose of 5.25 mg/kg compared to patients receiving cladribine 3.5mg/kg, the lower dose was considered a more appropriate choice for use clinical practice. Modelling of the exposure-effect relationship suggested that 3.5 mg/kg was close to the minimal effective dose (see section 2.4.3.). Modelling also supported the proposed duration between two

treatment courses including the proposition that the second dose in year 2 can be delayed up 6 months without loss of efficacy.

CLARITY EXT

Of the 1184 patients who completed CLARITY, only 883 patients were enrolled into CLARITY EXT. CLARITY EXT was not initiated immediately but only after 54% of the patients had completed CLARITY. The most frequent reasons for study discontinuation were patient's decision, loss to follow-up or AEs. The gap between the two studies could explain why not all of the patients completing CLARITY continued in CLARITY EXT and could have contributed to the recruitment of a selected patient population. However, there were only few differences in the basic demographic characteristics of patients who entered CLARITY EXT and patients who never entered the study: patients who never entered CLARITY EXT had longer disease duration and slightly higher EDSS at baseline of CLARITY. Furthermore, patients randomised to placebo in CLARITY who never entered CLARITY EXT had a higher disease burden at the end of CLARITY, thus making the placebo/low dose group appear healthier (PPLL).

Overall, the baseline demographic characteristics were similar for all treatment groups and resembled the baseline demographic characteristics in CLARITY. Notably, baseline EDSS score in the placebo treated patients had not changed at the time of entry into the CLARITY EXT study compared to enrolment in CLARITY i.e. for two years there was no worsening in disability despite absence of treatment. This again speaks for a mildly affected study population.

Overall, the efficacy results from the study should be interpreted with caution, given the exploratory nature of the analyses. However, the majority of clinical efficacy results suggested that there was no relevant added benefit of additional treatment courses beyond year 2 and that the treatment effect obtained in CLARITY was maintained. Comparison of the ARRs observed in CLARITY and CLARITY EXT as well as across the treatment groups in CLARITY EXT showed no clinically meaningful difference for any of the comparisons, with the only exception, as expected, for the group of patients switching from placebo in CLARITY to low dose cladribine in CLARITY EXT. For these patients the ARR was reduced from 0.33 (at the end of CLARITY) to 0.10, which is in the range of the effect observed for the active treatment arms in CLARITY (see above). A similar pattern was observed for the proportion of patients who were qualifying relapse free during the CLARITY EXT.

The gap-interval did not seem to influence the ARR. This adds some support to the possibility of having a six months delay in treatment between first and second treatment course, if needed (see clinical safety discussion in section 2.6.).

No clear pattern in the proportion of subjects with or without 3-month confirmed EDSS progression was observed. Numerically fewer patients in the HLPP and the LLLL treatment groups (9.8% and 11.8%, respectively) compared to patients in the LLPP treatment group (18.4%) experienced 3-month confirmed disease progression. While the comparison between LLPP and LLLL does not support a sustained effect of the lower dose of cladribine, the low proportion of patients with disability progression in the HLPP treatment group does. A similar pattern was seen for time to 6-month confirmed EDSS progression.

The MRI endpoints did not unequivocally point in one direction and the interpretation of the results was severely hampered by the fact that there were different numbers of MRI scans for the CLARITY and the CLARITY EXT studies as well as a considerable proportion of missing data for certain analyses. The mean number of T1 Gd+ lesions appeared higher in the LLPP and HLPP groups compared to LLLL, HLLL or PPLL groups. Between-group comparisons were nominally significant for the active vs placebo groups (HLLL and LLLL, and HLPP and LLPP; $p<0.001$) as well as the low-dose 192 week vs 96 week treatment groups (LLLL and LLPP; $p<0.001$). In addition, in the LLPP group, mean numbers of new T1 Gd+ lesions were higher

among subjects with gap duration >43 weeks than among subjects with gap duration between 4 and 43 weeks or subjects with gap duration ≤4 weeks. In addition, proportions of subjects with a mean of at least 1 new T1 Gd+ lesion per scan were higher among subjects with gap duration >43 weeks compared to the other subgroups. The inflammatory disease activity in the LLPP and HLPP groups reflected by higher number of T1Gd+ lesions might be an early subclinical signal of increasing risk for a relapse, even though it is not yet reflected in actual increase of the ARR. However, the need for re-treatment beyond 4 years has not been studied and no clear recommendations could be given. The applicant therefore agreed to further investigate recurrence of disease activity and the need for re-treatment as secondary objective in the planned long-term cohort post-authorisation study (see section 2.7.).

The initial increase in active T2 lesions observed in all treatment groups during the first year of CLARITY EXT can possibly be explained by the effect of the gap between studies and the dissemination in time of the disease however, even in the active treatment groups (LLLL and HLLL), the level from the CLARITY study was not reached by the end of CLARITY EXT. The Applicant suggested that the increase was driven by patients who entered CLARITY EXT as outliers in terms of disease activity as measured by MRI. While not entirely convincing as a sole explanation, the outlier hypothesis may explain the finding to some extent.

With regards to patients with high disease activity, the Applicant presented *post hoc* analyses for LLPP patients (patients receiving 3.5 mg/kg in CLARITY followed by placebo in CLARITY EXT). For LLPP patients, the ARR in the extension study remained low on average and similar to that seen on active treatment in CLARITY, whereas the mean number of active T2 lesions was as high as in the CLARITY placebo group. There were no meaningful differences in the ARR, T1 Gd+ lesions, or active T2 lesions during CLARITY EXT between LLPP patients fulfilling either HDA or non-HDA definitions.

ONWARD

In the placebo + IFN-β group, the mean (SD) number of qualifying relapses was 0.56 (0.90) compared with 0.23 (0.53) relapses in the cladribine 3.5 mg/kg + IFN-β group. The CHMP noted that the ARR in the placebo +IFN-β group was similar to ARRs reported previously for different IFN-β products. Other secondary efficacy endpoints also consistently showed superior efficacy of add-on cladribine treatment compared to IFN-β treatment alone. However, no difference in the effect on disability progression between treatment groups was observed. Given the small number of patients and events and that the study was not designed for a formal proof of efficacy, it is possible that the study was not adequately powered for the efficacy evaluations.

Although the low number of SPMS patients with superimposed relapses limits interpretation, subgroup analyses indicate a similar treatment effect in terms of relapse reduction with cladribine in both RRMS and SPMS patients with superimposed relapses. To further strengthen these results, analyses of the combined CLARITY + ONWARD patient population using baseline EDSS ≥ 3.5 as a proxy for SPMS (or high risk of transitioning to SPMS) was performed and there were no meaningful differences when comparing patients who entered the study with a baseline EDSS ≥ 3.5 and the complementary subgroup (EDSS ≤ 3). The ARR risk ratio was 0.40 in the EDSS ≤ 3 subgroup compared to 0.47 in the EDSS ≥ 3.5 subgroup. Based on these results and in order to keep consistency with recently approved MS DMDs as well as the Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, Rev. 2), which states that it is reasonable to assume that relapses in RRMS and SPMS have the same underlying inflammatory pathophysiology and therefore efficacy on relapses in RRMS patients may be extrapolated to efficacy on relapses in SPMS, the CHMP was of the view that are more appropriate target population for cladribine would be patients with highly active RMS instead of RRMS.

ORACLE

Both cladribine doses tested (3.5mg/kg and 5.25 mg/kg) demonstrated superiority over placebo in conversion from CIS to CDMS in ORACLE study. The results for secondary endpoints were consistent with the primary efficacy analysis. The results of ORACLE, including the *post-hoc* analysis for the subgroup of patients retrospectively identified to fulfil the 2010 McDonald criteria were considered supportive.

Pooled analysis

Despite the heterogeneity of the combined study population from CLARITY and ONWARD, the pooled analysis showed almost identical efficacy results for the primary and secondary endpoints as in the CLARITY study including the analysis for HDA patients.

Efficacy data were also compared for subgroups by baseline characteristics including number of relapses (no relapses versus ≥1 relapses), T1 Gd+ lesion counts (no T1 Gd+ versus ≥1 T1 Gd+), T2 lesion number (<9 T2 versus ≥ 9 T2), prior use of DMD, sex, age (≤40 versus >40 years old), EDSS (≤3 vs >3) and found no differences for most of parameters compared, except for an age effect on time to 3 month confirmed EDSS progression (worse effect in older than 40 years patients for cladribine 3.5mg/kg, interaction p=0.0422). However, the interaction of age was not reproduced in the cladribine 5.25 mg/kg versus placebo comparison. Given the multiplicity of the analyses, the observed age effect might be a chance finding.

Further, some analyses (3 month confirmed EDSS progression as well as MRI endpoints) showed a better effect in males compared to females. The applicant explained that the mean numbers of T1 Gd+ lesions per patient per scan as well as the cumulative number of active T2 lesions during the 96-weeks of CLARITY+ONWARD was higher in males compared to females on placebo, which could to some extent explain the observed interaction of gender. Overall, it was considered reassuring that in both males and females a treatment benefit of cladribine has been shown.

The analyses of efficacy for HDA subgroups were in general consistent with the analyses in CLARITY.

Additional expert consultation

During the course of the assessment of the present application, the CHMP decided to consult the scientific advisory group neurology on a number of questions related to the benefits, risks and the identification of a suitable target population for cladribine. The experts advised the following:

Question 1: What is the SAG members view on the documented effect of cladribine, including the effect in the high disease activity (HDA) patient groups as well as the potential benefit associated with the posology (2 treatment weeks/year).

All SAG members agreed that a clear beneficial effect of cladribine in the treatment of (R)RMS has been shown. The observed effect size was within the range of other disease modifying treatments (DMTs), although it was noted that the patient population recruited in the main study with cladribine (CLARITY) had overall rather low disease activity, which was in fact lower than in the patient populations in whom recently approved DMTs have been studied. Other limitations of the clinical trial program for cladribine include the lack of an active comparator and that the evidence in HDA patients was derived from a *post-hoc* subgroup analysis. Nevertheless, the experts considered the evidence convincing and some members even questioned the need for restricting the target population to HDA as cladribine could also be a treatment option in patients with mild or moderate disease. However, ultimately the majority of SAG members considered that the choice of the target population for cladribine needs to take into account the safety profile and related uncertainties

(see also question 3) and that further evidence may be needed in order to support the use in a broader population.

The oral route of administration and the need for very few treatment cycles only were considered a clear advantage for patients over most other available treatment options, many of which require frequent injections. This view was stressed by the patient representatives, who would welcome a therapeutic option with a low treatment burden.

<u>Question 2:</u> What is the SAG members view on the risk of malignancies with the use of cladribine given the observed imbalance between cladribine and placebo in the rate of malignancies and in particular solid tumours (All Exposed Cohort), and considering the mechanism of action of cladribine? The experts are invited to reflect on all relevant non-clinical, clinical and epidemiological data as well as available data for other MS products.

The SAG discussed the observed imbalance of malignancy cases observed with cladribine compared to placebo in the clinical trials program. The argument that the difference was driven by a lower than expected incidence rate in the placebo arm was not fully supported as the indirect comparisons with other DMTs and epidemiology data (GLOBOCAN) were viewed as problematic. Replication of the analyses performed and independent verification of the findings would be reassuring. However, in any event such indirect comparison was not considered suitable to fully address the uncertainty arising from a finding based on data from prospective, randomised, controlled trials. Another explanation for the low rate of cancers in patients receiving placebo could in fact be that the selected study population was generally at a low risk. One expert noted that the inclusion of older patients may have contributed to the study findings with regards to malignancies and that maybe use in younger patients e.g. aged less than 40 years could be an option. However, while among the baseline factors related to cancer risk, age was found to be of relevance, it did not explain the observed imbalance between cladribine and placebo (suggesting that cancer risk may generally be increased in elder patients). Furthermore, such age cut-off may be difficult to implement in clinical practice.

In any event, the pattern of malignancies in terms of tumour types (including the lack of clear clusters) and latency was considered reassuring as it was not in line with what would be expected with a carcinogenic substance. The fact that hairy-cell leukaemia patients treated with cladribine seem not to have an increased risk of malignancies was also reassuring. Overall, the experts considered other risks with cladribine to be equally or even more relevant, in particular the risk of infections. Furthermore, the possibility of women of childbearing potential becoming pregnant during treatment with cladribine was a concern.

<u>Question 3</u>: How do the SAG members perceive the benefits as discussed above, in light of the potential risk of malignancies in the treatment of (R)RMS? Taking into account currently available treatment options for (R)RMS, is there a suitable target population, including the applicant's proposal for HDA patients, in whom cladribine would be a useful treatment alternative?

The experts found it difficult to make a judgement where cladribine fits in the therapeutic armamentarium of MS treatments. Part of this is due to the fact that the studies were conducted several years ago and the therapeutic landscape has changed since. In this sense, the lack of an active comparator was unfortunate as it would have helped to put into context the benefits and risks of cladribine. Cladribine seems to have clear advantages over some existing treatment options such as the absence of secondary autoimmunity during the immune reconstitution phase. It also has a very low treatment and monitoring burden and could be a good addition to the range of available MS therapies.

In order to decide on an adequate patient population, the experts felt that the total safety profile including the risk of infections should be considered. There was consensus that the benefits of treatment with cladribine outweighed the risks in a restricted target population with high disease activity, such as the one defined in the post-hoc analyses and proposed by the applicant for inclusion in the SmPC (i.e. subjects with at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions, OR subjects with 2 or more relapses in the previous year regardless of previous treatment status). However, as previously mentioned (see question 1 and 2) there is only data form post-hoc subgroup analyses primarily based on a sinlgle randomised controlled trial and uncertainties with regards to safety remained.

The experts highlighted the need for further data collection in the future and thorough post-marketing surveillance, such as safety of switching between cladribine and other DMTs, should the product be approved. Clear information on the risks of malignancies and infections should be presented in the product information to allow prescribers and patients to make an informed decision.

2.5.6. Conclusions on the clinical efficacy

Overall, the available clinical efficacy data were considered adequate to support the use of cladribine in the treatment of adult patients with highly active RMS as defined by clinical or imaging features.

Results from the pivotal study CLARITY showed a clinically relevant effect of cladribine in patients with RMS in terms of reduction of relapse rate as well as MRI lesions and delay in disability progression. Subgroup analyses suggested a larger effect size in patients with high disease activity. Furthermore, data in SPMS patients with superimposed relapses, although very limited, supported a beneficial effect of cladribine on the relapse rate in this population. Based on these data and since relapses in both SPMS and RRMS patients have the same underlying inflammatory pathophysiology, patients with RMS (instead of RRMS) were considered a more suitable target population.

The data furthermore support the use of a cumulative dose of 3.5 mg/kg to be administered in 2 courses each for 2 years. Maintenance of the treatment effect in year 3 and 4 was supported by long-term data from CLARITY EXT. No clinically relevant added benefit of additional treatment cycles beyond year 2 was evident.

2.6. Clinical safety

The main support for the clinical safety assessment was derived from data of the oral cladribine clinical development program including the 4 clinical phase II/III studies CLARITY, CLARITY EXT, ONWARD and ORACLE. In addition, supportive data were provided from the ongoing PREMIERE Registry and the safety study RECORD MS. Finally, safety data from the Scripps studies with parenteral cladribine also contributed to the overall safety database.

Table 22 - Overview of the supportive observational studies performed with oral cladribine

Study No. or Study Identifier	Sponsor / Countries and Number of Sites	Study design / Description	Treatment Regimen / Treatment Duration	No. Subjects Enrolled / Evaluated Sex (M/F)
Supportive (Observational) Studies: Oral Cladribine				
PREMIERE Registry	In the USA: EMD Serono, Inc	Prospective, observational, long-term safety registry of subjects who had participated in	As per the study from which the subject originated.	As of 20 Feb 2015, 1133 subjects had been enrolled (2175

Study No. or Study Identifier	Sponsor / Countries and Number of Sites	Study design / Description	Treatment Regimen / Treatment Duration	No. Subjects Enrolled / Evaluated Sex (M/F)
	Approx. 234 sites In the ROW: Merck Serono SA	at least 1 of 5 oral cladribine clinical studies: CLARITY, CLARITY EXT, ONWARD, ORACLE MS, and pantoprazole DDI study (Protocol 27967)	No further cladribine was administered	planned) Safety set (N=1133) Lymphocyte set (N=1133)
RECORD MS study	Australia: Merck Serono Australia Pty Ltd 7 sites in Australia	Prospective, observational, post-authorization safety study of cladribine tablets in cladribine-naïve subjects in the Australian Patient Familiarization Program	Cladribine tablets administered in routine medical care	35 subjects enrolled. No further subjects to be enrolled.

F=female; M=male; MS=multiple sclerosis; ROW=rest of the world; RRMS=relapsing-remitting multiple sclerosis; USA=United States of America.

The PREMIERE registry (Prospective observational long-term safety REgistry of Multiple sclerosis patients who have participated in cladribine clinical studies PREMIERE) was ongoing at the time of this report and included subjects previously enrolled CLARITY, CLARITY EXT, ONWARD and ORACLE (as well as the pantoprazole DDI study 27967). For the purpose of this application, interim data were presented based on a data cut-off of 20 February 2015.

RECORD MS (Prospective Observational Post-Authorization Safety Study of Cladribine Tablets in Patients with Multiple Sclerosis in Australia) was a multicenter prospective single-arm cohort study of subjects diagnosed with relapsing forms of MS as per indication in Australian-approved Product Information, and initiating treatment with cladribine tablets administered in routine clinical practice. The main purpose of this study was to obtain long-term safety data on cladribine tablets in subjects with MS by estimating the frequency of serious adverse drug reactions over a period of time, extending beyond cladribine exposure, in a population of subjects who had been exposed to cladribine in a routine clinical practice setting. Notably, while cladribine was authorized for the treatment of RRMS in Australia (and Russia), the product was subsequently withdrawn from the market in these 2 countries. Enrolment in RECORD MS was stopped after a total of 35 subjects had been enrolled.

An integrated data analysis was conducted focussing on 3 analysis cohorts:

- All Exposed cohort: includes subjects from all Phase II/III studies with follow-up data (CLARITY, CLARITY EXT, ONWARD, ORACLE-MS, PREMIERE, Scripps A, Scripps B, Scripps C, MS-Scripps and MS-001) and with any formulation of cladribine. This cohort was used to identify potential safety signals for rare events and for events beyond 2 years after first treatment dose. .
- Placebo-controlled Double-blind cohort: includes safety data from the placebo-controlled double-blind period of CLARITY, ORACLE MS, Scripps-B, Scripps-C, MS-Scripps (first sequence only), and MS-001 with a monotherapy application (oral or parenteral) of cladribine.
- Monotherapy Oral cohort: includes safety data from all studies that used cladribine as oral monotherapy (CLARITY, CLARITY EXT, ORACLE MS and PREMIERE). This was the primary cohort for the safety assessment as it includes all the safety data from the target formulation and allows differentiation between the dose and the dose durations (ie, 2 years vs 4 years of therapy).

All analyses on the integrated clinical database were based on the safety analysis set, including all subjects treated at least once with cladribine, placebo, cladribine plus concomitant active therapy (IFN-β), or placebo plus concomitant active therapy (IFN-β).

Safety data were furthermore analysed in a HDA cohort comprising the HDA subgroups from the CLARITY, CLARITY EXT, and ONWARD studies. See sections 2.5.2.1. and 2.5.3. for the HDA subgroup definition (Table 9) and related efficacy analyses.

Patient exposure

Of the subjects included in the All Exposed cohort, 1976 subjects received at least one dose of cladribine and 802 received placebo. Subjects exposed to cladribine were followed over a longer period of time (on average 4.4 years) compared with placebo (on average 2.3 years), resulting in 8650 patient-years (PY) of treatment and follow-up for the cladribine-treated subjects compared to 2361 PYs of treatment and follow-up for the subjects on placebo.

Table 23 summarizes the extent of exposure within the 3 analysis cohorts.

Table 23 - Extent of Exposure in the All Exposed and Monotherapy Oral Cohorts

Cohort	Placebo	Cladribine	Cladribine 3.5 mg/kg	Cladribine 3.5 mg/kg re-exposed*	Cladribine 5.25 mg/kg	Cladribine 5.25 mg/kg re-exposed*
	(n; PY)	(n; PY)	(n; PY)	(n; PY)	(n; PY)	(n; PY)
Number of subjects exposed; Patient years						
All Exposed	802; 2361.13	1976; 8650.16	--	--	--	--
Placebo-controlled Double-blind	745; 1135.29	1458; 2400.17	--	--	--	--
Monotherapy Oral	641; 2025.97	--	923; 3432.65	195; 769.35	632; 2136.61	195; 755.20
Median time on study (Q1, Q3) [weeks]						
All Exposed	122.00 (95.14, 184.86)	230.64 (118.29, 301.07)	--	--	--	--
Placebo-controlled Double-blind	95.00 (65.14, 95.71)	95.14 (82.86, 96.14)	--	--	--	--
Monotherapy Oral	133.14 (96.29, 212.29)	--	156.14 (110.00, 272.14)	227.57 (123.00, 295.29)	148.79 (98.21, 251.50)	226.57 (121.86, 287.43)

* For the 3.5 mg and 5.25 mg/kg re-exposed arms, cumulative dose is computed from date of first treatment; these treatment groups include patient time and events from true re-exposure time.

The patient population for the proposed indication (high disease activity [HDA]) included, depending on the definition of HDA cohort, up to 250 patients (see Table 24) who were exposed to the 3.5 mg/kg dose, of which 243 were exposed for at least 6 months, 217 for at least 12 months, 150 for at least 2 years and 10 for at least 5 years.

Table 24 - Number of Subjects Exposed to Study Drug by HDA Subgroup

	Placebo	Cladribine 3.5 mg/kg	Cladribine 3.5 mg/kg re-exposed	Cladribine 5.25 mg/kg	Cladribine 5.25 mg/kg re-exposed
HDA1 subgroup	**(N=114)**	**(N=250)**	**(N=69)**	**(N=77)**	**(N=30)**
PY of exposure	249.670	531.943	97.257	229.604	66.730
HDA2 subgroup	**(N=150)**	**(N=243)**	**(N=66)**	**(N=133)**	**(N=58)**
PY of exposure	332.901	603.644	130.905	379.510	139.910
HDA3 subgroup	**(N=140)**	**(N=217)**	**(N=54)**	**(N=122)**	**(N=51)**
PY of exposure	313.517	530.543	104.851	348.679	122.746
HDA4 subgroup	**(N=197)**	**(N=377)**	**(N=103)**	**(N=154)**	**(N=65)**
PY of exposure	427.866	866.617	174.130	441.090	153.966

DMD=disease modifying drug; Gd=gadolinium; HDA=high disease activity; SD=standard deviation; PY=Patient Years.

[a] For the 5.25 mg/kg re-exposed* arm, cumulative dose is computed from date of first treatment.

In the Monotherapy Oral cohort (which was as primary data set for the presentation of the safety data) median age of subjects who received placebo and those who received cladribine were very similar: 36.6 years (range, 18 to 64) and 36.5 years (range, 18 to 65), respectively. By age category, the majority of patients belonged to the ≤40 years age group (64.7% placebo and 64.1% cladribine) and around two-thirds of the subjects were female (66.1% and 66.3%, respectively). The vast majority (96.9% placebo and 97.3% cladribine) of patients were white. Mean disease duration at baseline was 8.9(0.4- to 39.5) years for the placebo-exposed and 7.9 (0.3 to 42.3) years for the cladribine-exposed patients. Mean EDSS at baseline was 2.5 for the placebo-exposed and 2.6 for the cladribine-exposed patients. Mean number of T1 Gd+ lesions for the placebo and cladribine exposed patients was 0.8 and 1.1 respectively. Mean number of T2 lesions for the placebo and cladribine exposed patients was 27.1 and 29.6 respectively. Around 20% of the participants had taken DMDs prior to study start, of which almost all had taken first line MS-DMDs.

Demographics were overall comparable between treatment cohorts and between cladribine and placebo groups.

Adverse events

Adverse events (AEs) and medical histories in all studies were recoded into Medical Dictionary of Regulatory Activities (MedDRA) version 17.1. AE data were based on treatment-emerged adverse events (TEAEs). An AE was treatment-emerged in the period of interest (treatment period) if the AE occurred at or after day 1 of the period of interest, i.e. those events which were absent prior to treatment, but started during the treatment period or whose severity worsened during the treatment period relative to the pre-treatment state. AEs were indicated as 'related' to treatment if the investigator considered the relationship probable, probable/likely, certain, possible, very likely/certain, and missing. It was considered 'unrelated' if a relationship to study drug was judged as unlikely, doubtful, unlikely/doubtful, unrelated, not related and none.

Safety data are presented primarily for the Monotherapy Oral cohort with a focus on cladribine 3.5 mg/kg proposed for use in clinical practice. The data are supplemented by data from the other cohorts as relevant for the assessment. For the identification of adverse reactions for inclusion into the SmPC, the AEs observed in the DB Placebo-Controlled cohort have also been considered. Incidence rates were provided as

observation-adjusted incidence rates by 100PY to account for different duration of observation periods between treatment groups.

An overview of the AEs reported in the Monotherapy Oral cohort is provided in Table 25. TEAEs were generally more frequent among the cladribine-treated patients compared to the placebo-treated patients and there was a dose-dependent increase in the rate of patients with at least 1 TEAE.

Table 25 - Overall Summary of AEs (Monotherapy Oral Cohort)

Parameter	Placebo (N=641)			Cladribine Dose (mg/kg)											
				3.5 mg/kg (N=923)			3.5 mg/kg re-exposed* (N=195)			5.25 mg/kg (N=632)			5.25 mg/kg re-exposed* (N=195)		
	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	N	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY
At least 1 TEAE	515	546.3	**94.26**	773	748.4	**103.29**	157	207.9	**75.51**	548	423.3	**129.46**	165	206.5	**79.89**
At least 1 serious TEAE	67	1876.3	**3.57**	124	3096.8	**4.00**	30	699.7	**4.29**	72	2133.2	**3.38**	30	667.5	**4.49**
At least 1 serious TEAE leading to death	5	2024.7	**0.25**	9	3431.0	**0.26**	1	769.3	**0.13**	1	2316.6	**0.04**	1	755.2	**0.13**
At least 1 TEAE leading to treatment discontinuation	21	1993.7	**1.05**	67	3229.0	**2.07**	27	672.2	**4.02**	53	2174.6	**2.44**	30	656.1	**4.57**
At least 1 related TEAE	291	1162.8	**25.03**	542	1605.5	**33.76**	118	355.2	**33.22**	426	833.9	**51.09**	126	340.3	**37.03**
At least 1 severe TEAE	57	1912.5	**2.98**	115	3111.2	**3.70**	34	666.6	**5.10**	85	2052.7	**4.14**	30	670.6	**4.47**

n = number of subjects with events; T = total subject's time on study in years (if a subject has multiple events, the time to first event is considered; for a subject with no event the time is censored at the last follow-up time for that subject); Adj-AE per 100PY = the time adjusted AE incidence rate (number of events occurring in 100-patient years).

The most frequently reported TEAEs for the Monotherapy Oral Cohort are presented in Table 26.

Table 26 - Most Frequent Reported AEs - Adj-AE per 100 PY of ≥ 1.0 in Any Group (Monotherapy Oral Cohort)

System Organ Class Preferred Term	Placebo (N=641)			Cladribine Dose mg/kg											
				3.5 mg/kg (N=923)			3.5 mg/kg re-exposed* (N=195)			5.25 mg/kg (N=632)			5.25 mg/kg re-exposed* (N=195)		
	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY
At least one TEAE	**515**	**546.3**	**94.26**	**773**	**748.4**	**103.29**	**157**	**207.9**	**75.51**	**548**	**423.3**	**129.46**	**165**	**206.5**	**79.89**
Infections and Infestations	**314**	**1160.8**	**27.05**	**478**	**1917.5**	**24.93**	**99**	**460.1**	**21.52**	**352**	**1245.0**	**28.27**	**100**	**448.6**	**22.29**
Nasopharyngitis	97	1764.5	5.50	158	2951.0	5.35	24	701.9	3.42	107	2011.6	5.32	31	664.6	4.66
Upper respiratory tract infection	61	1869.1	3.26	109	3112.0	3.50	19	703.1	2.70	87	2052.5	4.24	26	675.9	3.85

System Organ Class Preferred Term	Placebo (N=641)			Cladribine Dose mg/kg											
				3.5 mg/kg (N=923)			3.5 mg/kg re-exposed* (N=195)			5.25 mg/kg (N=632)			5.25 mg/kg re-exposed* (N=195)		
	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY
Influenza	51	1898.1	2.69	87	3169.5	2.74	16	726.0	2.20	60	2141.8	2.80	25	693.4	3.61
Bronchitis	22	1964.4	1.12	55	3234.1	1.70	5	764.4	0.65	31	2219.1	1.40	12	725.0	1.66
Urinary tract infection	46	1916.8	2.40	55	3249.7	1.69	17	714.6	2.38	40	2202.7	1.82	17	709.4	2.40
Herpes zoster	4	2019.0	0.20	28	3360.2	0.83	7	749.1	0.93	19	2257.8	0.84	11	719.3	1.53
Pharyngitis	31	1961.4	1.58	27	3348.0	0.81	4	752.1	0.53	28	2238.9	1.25	2	746.8	0.27
Rhinitis	22	1962.3	1.12	24	3354.0	0.72	9	738.5	1.22	22	2247.7	0.98	1	752.4	0.13
Nervous System Disorders	**226**	**1429.5**	**15.81**	**327**	**2346.7**	**13.93**	**42**	**633.1**	**6.63**	**232**	**1576.4**	**14.72**	**58**	**587.6**	**9.87**
Headache	144	1631.9	8.82	230	2641.9	8.71	22	649.9	3.17	163	1787.7	9.12	30	652.7	4.60
Dizziness	36	1944.4	1.85	47	3268.0	1.44	4	758.1	0.53	30	2198.1	1.36	5	743.9	0.67
Multiple sclerosis relapse [a]	11	2014.0	0.55	21	3404.9	0.62	3	763.8	0.39	10	2307.0	0.43	8	744.2	1.07
Gastrointestinal Disorders	**197**	**1454.9**	**13.54**	**278**	**2482**	**11.20**	**44**	**623.0**	**7.06**	**213**	**1625.2**	**13.11**	**38**	**655.0**	**5.80**
Nausea	62	1845.6	3.36	86	3134.4	2.74	13	723.2	1.80	77	2071.6	3.72	6	743.3	0.81
Diarrhoea	44	1915.9	2.30	68	3202.0	2.12	6	747.6	0.80	50	2160.8	2.31	10	735.0	1.36
Abdominal pain upper	22	1969.2	1.12	42	3283.1	1.28	4	758.2	0.53	28	2235.7	1.25	6	734.5	0.82
Toothache	22	1957.5	1.12	35	3335.8	1.05	7	757.5	0.92	37	2199.7	1.68	3	742.0	0.40
Abdominal pain	23	1966.2	1.17	30	3346.2	0.90	3	766.1	0.39	25	2239.7	1.12	6	734.6	0.82
Constipation	22	1968.7	1.12	24	3368.3	0.71	5	754.5	0.66	19	2247.2	0.85	5	744.6	0.67
Vomiting	24	1982.6	1.21	21	3363.7	0.62	5	756.2	0.66	22	2246.7	0.98	0	0	0
Blood and Lymphatic System Disorders	**47**	**1901.6**	**2.47**	**276**	**2543.4**	**10.85**	**84**	**487.4**	**17.24**	**236**	**1519.1**	**15.54**	**89**	**466.7**	**19.07**
Lymphopenia	21	1985.0	1.06	217	2731.8	7.94	72	519.4	13.86	206	1632.1	12.62	82	492.4	16.65
Leukopenia	8	2008.4	0.40	43	3276.9	1.31	20	712.3	2.81	46	2177.5	2.11	20	693.8	2.88
Neutropenia	4	2015.0	0.20	27	3362.8	0.80	8	729.4	1.10	17	2265.0	0.75	10	722.0	1.39
Musculoskeletal and Connective Tissue Disorders	**153**	**1608.0**	**9.51**	**245**	**2654.5**	**9.23**	**46**	**615.5**	**7.47**	**182**	**1746.4**	**10.42**	**50**	**593.1**	**8.43**
Back pain	46	1890.0	2.43	102	3115.8	3.27	16	724.4	2.21	68	2109.8	3.22	18	695.1	2.59
Arthralgia	38	1938.8	1.96	63	3236.0	1.95	5	756.1	0.66	40	2191.6	1.83	8	729.3	1.10
Pain in extremity	33	1965.6	1.68	50	3283.6	1.52	10	726.9	1.38	43	2203.0	1.95	11	727.4	1.51
Myalgia	21	1966.3	1.07	28	3356.9	0.83	0	0	0	18	2261.1	0.80	6	740.8	0.81
Musculoskeletal pain	16	1989.1	0.80	19	3375.9	0.56	1	764.8	0.13	12	2287.7	0.52	10	728.5	1.37
General Disorders and Administration Site Conditions	**168**	**1558.5**	**10.78**	**213**	**2717.1**	**7.84**	**34**	**656.5**	**5.18**	**157**	**1824.0**	**8.61**	**31**	**663.7**	**4.67**
Influenza like illness	61	1857.4	3.28	75	3167.6	2.37	14	731.7	1.91	45	2186.1	2.06	11	727.3	1.51
Fatigue	47	1897.2	2.48	54	3252.1	1.66	8	734.8	1.09	44	2167.1	2.03	10	728.3	1.37
Pyrexia	20	1980.8	1.01	36	3341.5	1.08	3	761.9	0.39	27	2244.9	1.20	5	735.2	0.68

System Organ Class Preferred Term	Placebo (N=641)			Cladribine Dose mg/kg											
				3.5 mg/kg (N=923)			3.5 mg/kg re-exposed* (N=195)			5.25 mg/kg (N=632)			5.25 mg/kg re-exposed* (N=195)		
	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY
Asthenia	25	1941.8	1.29	33	3311.5	1.00	4	750.9	0.53	27	2237.2	1.21	3	746.0	0.40
Investigations	**83**	**1802.4**	**4.61**	**145**	**2939.6**	**4.93**	**27**	**692.4**	**3.90**	**96**	**2034.6**	**4.72**	**28**	**660.1**	**4.24**
Lymphocyte count decreased	2	2023.1	0.10	26	3337.4	0.78	6	756.5	0.79	30	2212.5	1.36	8	729.3	1.10
Psychiatric Disorders	**85**	**1787.8**	**4.75**	**121**	**3009.3**	**4.02**	**18**	**709.5**	**2.54**	**95**	**2014.6**	**4.72**	**19**	**695.7**	**2.73**
Insomnia	32	1938.7	1.65	46	3285.5	1.40	4	751.4	0.53	24	2245.0	1.07	4	742.2	0.54
Depression	23	1960.6	1.17	46	3298.1	1.39	9	745.8	1.21	34	2237.3	1.52	5	740.1	0.68
Anxiety	12	2002.3	0.60	37	3312.1	1.12	3	762.9	0.39	26	2225.5	1.17	5	744.5	0.67
Respiratory, Thoracic and Mediastinal Disorders	**95**	**1770.8**	**5.36**	**118**	**3065.2**	**3.85**	**16**	**711.9**	**2.25**	**104**	**1986.6**	**5.24**	**19**	**695.8**	**2.73**
Oropharyngeal pain	35	1929.2	1.81	44	3278.8	1.34	5	749.9	0.67	42	2197.1	1.91	5	738.4	0.68
Cough	27	1968.3	1.37	34	3336.6	1.02	9	738.8	1.22	31	2236.4	1.39	6	737.3	0.81
Vascular Disorders	**45**	**1909.6**	**2.36**	**72**	**3231.2**	**2.23**	**8**	**746.9**	**1.07**	**44**	**2174.3**	**2.02**	**14**	**716.4**	**1.95**
Hypertension	25	1965.3	1.27	35	3338.5	1.05	5	752.2	0.66	28	2222.4	1.26	5	743.1	0.67
Ear and Labyrinth Disorders	**35**	**1930.6**	**1.81**	**53**	**3269.0**	**1.62**	**9**	**741.0**	**1.21**	**59**	**2164.3**	**2.73**	**9**	**727.8**	**1.24**
Vertigo	22	1966.4	1.12	35	3317.9	1.05	6	750.2	0.80	28	2247.4	1.25	5	736.6	0.68
Injury, Poisoning and Procedural Complications	**81**	**1830.4**	**4.43**	**115**	**3090.3**	**3.72**	**17**	**713.5**	**2.38**	**67**	**2162.5**	**3.10**	**34**	**664.3**	**5.12**
Fall	13	1985.9	0.65	24	3371.1	0.71	2	759.4	0.26	17	2282.1	0.74	5	740.4	0.68

n = number of subjects with events; T = total subject's time on study in years (if a subject has multiple events, the time to first event is considered; for a subject with no event the time is censored at the last follow-up time for that subject); Adj-AE per 100PY = the time adjusted AE incidence rate (number of events occurring in 100-patient years).

[a] Preferred term "Multiple sclerosis relapse" was reported in PREMIERE where relapse was not an efficacy endpoint.

The most frequently occurring AEs belonged to the MedDRA system organ class (SOC) of Blood and Lymphatic System Disorders (driven by the preferred term [PT] lymphopenia) and Infections and Infestations (including herpes zoster). The most common TEAE in the Monotherapy Oral cohort was headache, which was reported in similar incidences in terms of AEs per 100PY in the cladribine 3.5 mg/kg and placebo groups (8.71 vs. 8.82, respectively). TEAEs observed more frequently for cladribine 3.5 mg/kg compared to placebo (AE rate per 100PY, difference of ≥0.50), presented by frequency in the 3.5 mg/kg cladribine group) were:

- lymphopenia (7.94 vs. 1.06)
- back pain (3.27 vs. 2.43)
- bronchitis (1.70 vs. 1.12)
- leukopenia (1.31 vs. 0.40)

- anxiety (1.12 vs. 0.60)
- herpes zoster (0.83 vs. 0.20)
- lymphocyte count decreased (0.78 vs. 0.10)
- neutropenia (0.80 vs. 0.20)

For lymphopenia a dose-response relationship was observed. The findings in this cohort were generally similar to the findings for the All Exposed and Double-blind Placebo-controlled cohorts.

AEs that were observed with a higher incidence rate on cladribine compared to placebo in the Placebo-Controlled Double-Blind cohort and that also show an apparent dose response in the Monotherapy Oral cohort included alopecia and rash. The incidence rates in the Placebo-Controlled Double-Blind cohort for alopecia were 1.84 on cladribine vs. 1.16 on placebo and in the Monotherapy Oral cohort 0.40 on placebo, 0.60 on cladribine 3.5 mg/kg, and 0.97 on cladribine 5.25 mg/kg. A similar trend was seen in the CLARITY trial (1.10 on placebo, 3.50 on cladribine 3.5 mg/kg, and 3.10 on cladribine 5.25 mg/kg). Incidence rates of 2.09 on cladribine vs. 1.34 on placebo were observed for events of rash in the Placebo-Controlled Double-Blind cohort. In the Monotherapy Oral cohort, rash occurred with an incidence of 0.45 on placebo, 0.60 on cladribine 3.5 mg/kg, and 0.75 on cladribine 5.25 mg/kg. In CLARITY, a similar trend was seen (1.1 on placebo, 2.3 on cladribine 3.5 mg/kg, and 2.4 on cladribine 5.25 mg/kg). Evaluation of the latency between first cladribine use and the first onset of the AE revealed that in approximately one third of the patients, rash occurred within the first 3 months of cladribine treatment.

High disease activity (HDA)

With regards to HDA patients, across the subgroups, lymphopenia was consistently reported at higher frequency rates (Adj-AE per 100 PY) compared to placebo.

A comparison between HDA4 and non-HDA4 patients (which constituted the largest HDA subgroup and comprised all patients of the other 3 HDA subgroups) showed no major difference in the AE profile. With regard to SAEs, the total incidence rate was higher in the HDA4 subgroup (6.63) compared with the non-HDA4 subgroup (4.22) but by PT, no particular pattern of SAEs could be identified. The incidence rate of lymphopenia was similar between the cladribine HDA4 (10.77) and non-HDA4 (11.89) subgroups. The incidence rate of the SOC Infections and Infestations was also similar between the cladribine HDA4 (31.03) and non-HDA4 (29.37) subgroups, as well as the corresponding placebo subgroups (31.53 versus 30.44). The incidence rate of the SOC Neoplasms benign, malignant and unspecified was 1.06 in cladribine HDA4 and 1.76 in the corresponding non-HDA4.

Abdominal pain upper, constipation, nausea, fall, arthralgia, back pain, musculoskeletal pain, and pain in extremity were reported at a slightly higher incidence rate in cladribine HDA4 compared to non-HDA4. However, the same trend was seen when comparing the placebo HDA4 and non-HDA4 subgroups. The incidence rate for asthenia was also slightly higher in cladribine HDA4 compared to cladribine non-HDA4, however the cladribine incidence rates as well as the placebo HDA4 incidence rate were lower than the placebo non-HDA4 incidence rate, indicating that the asthenia findings are most likely due to chance. For alopecia, a higher incidence rate was seen in cladribine HDA4 compared to non-HDA4, with the same trend being seen in the placebo groups.

AEs by severity and relatedness

The majority of TEAEs in the Monotherapy Oral cohort were mild or moderate in severity. Severe lymphopenia was the only severe AE that occurred more frequently (difference ≥0.5 AE per 100PY) on cladribine 3.5 mg/kg than on placebo (0.59 vs. 0.00).

Overall, most TEAEs that were considered to be possibly/probably related to treatment occurred at an observed Adj-AE per 100PY rate of <0.10. Of these frequently reported related TEAEs, 5 were identified as occurring with a higher observed Adj-AE per 100PY rate in the cladribine 3.5 mg/kg and 5.25 mg/kg groups compared to subjects receiving only placebo (Adj-AE per 100PY for: placebo vs 3.5 mg/kg vs 5.25 mg/kg, respectively):

- Lymphopenia: 0.65 vs 7.38 vs 12.31
- Leukopenia: 0.35 vs 1.25 vs 2.07
- Lymphocyte count decreased: 0.05 vs 0.66 vs 1.26
- Neutropenia: 0.10 vs 0.65 vs 0.71
- Herpes zoster: 0.10 vs 0.62 vs 0.66

Adverse Events of Special Interest (AESIs)

Three main categories of AESIs were defined for the clinical program: (i) Severe (≥Grade 3) sustained lymphopenia (expected event based on the mechanism of action of cladribine), (ii) infections (as a result of the impaired cell-mediated immunity), and (iii) malignancies.

- *Severe lymphopenia (Grade ≥3)*

Overall, the incidence rate of lymphopenia AEs was higher in each pooled cohort of cladribine-exposed subjects compared with placebo. Furthermore, the incidence rate of severe lymphopenia AEs in the 3.5 mg/kg cladribine group was lower than that in the 5.25 mg/kg group (Adj-AESI per 100PY of 0.72 vs 1.07 respectively, Monotherapy Oral cohort). Similarly, the incidence rate of lymphopenia AEs that led to treatment discontinuation was higher in each cohort of cladribine-exposed subjects compared with placebo and lower in the 3.5 mg/kg treatment group than that in the 5.25 mg/kg dose treatment group. Re-exposure in Years 3 and 4 was associated with an increase in the incidence rates of lymphopenia AEs (Adj-AESI per 100PY of 1.94 in the cladribine 3.5mg/kg re-exposed group and 1.82 in the cladribine 5.25 mg/kg re-exposed group).

Lymphopenia was consistently dose-dependent across the clinical program of oral cladribine: in CLARITY, Grade ≥3 lymphopenia occurred in 110 (25.6%) and 204 (44.9%) of subjects in 3.5 mg/kg and 5.25 mg/kg dose groups, respectively; in ORACLE MS, Grade ≥3 lymphopenia occurred in 46 (22.3%) and 74 (36.5%) of subjects receiving 3.5 mg/kg or 5.25 mg/kg, respectively; and in patients treated according to the original protocol of ONWARD, Grade ≥3 lymphopenia occurred in 12 (75%) and 15 (88.2%) of subjects in the 3.5 mg/kg and 5.25 mg/kg dose groups, respectively. Notably, higher incidences of Grade ≥3 lymphopenia were observed when cladribine was given with concomitant IFN-β treatment in ONWARD compared to monotherapy in CLARITY.

Grade 4 lymphopenia was infrequent throughout the clinical program. In CLARITY, Grade 4 lymphopenia occurred in only 3 subjects (0.7%) treated with oral cladribine at 3.5 mg/kg and in 13 subjects (2.9%) treated at 5.25 mg/kg. In the CLARITY EXT study in the LLPP group (cladribine 3.5 mg/kg over 2 years,

followed by no treatment in the 2 years of EXT) no subjects had Grade 4 lymphopenia and 5 (5.1%) had Grade 3 at some time during the CLARITY EXT study.

In CLARITY, median total lymphocyte counts reached a nadir at Week 16, in both the 3.5 mg/kg and 5.25 mg/kg cladribine treatment groups; and the counts were lower at the cladribine 5.25 mg/kg dose (0.7×10^9/L) than at the cladribine 3.5 mg/kg dose (1.1×10^9/L). After re-treatment at Weeks 48 and 52, the nadirs of median total lymphocyte counts were observed at Week 55 (ie, 8 weeks after restarting cladribine in Year 2) and were lower than after initial treatment (0.6×10^9/L for cladribine 5.25 mg/kg and 0.8×10^9/L for cladribine 3.5 mg/kg). At the first nadir (Week 16) following start of treatment in year 1, and the second nadir (Week 55) following start of treatment in year 2 (Week 8 after treatment at Week 48), the median lymphocyte counts decreased by 42% and 58%, respectively, from baseline pre-treatment levels in the oral cladribine 3.5 mg/kg group. The median durations of these Grade 3 or 4 lymphopenias were 23.4 weeks (5.4 months) and 24.1 weeks (5.6 months), respectively, for the cladribine 3.5 mg/kg and cladribine 5.25 mg/kg groups in CLARITY.

At the end of the CLARITY study, 8 (0.9%) subjects in the 3.5 mg/kg group and 21 (2.4%) subjects in the 5.25 mg/kg group had Grade ≥3 lymphopenia. Further follow-up of these subjects showed that all those who received the 3.5 mg/kg dose eventually recovered to a lymphocyte count Grade 0 or 1. Results from the CLARITY and CLARITY EXT trials showed that even in subjects treated for more than 4 years with cladribine (cumulative dose of 7 mg/kg) the recovery to Grade 0 or 1 by the end of each treatment year occurred in the majority of patients (aproximately 86% of subjects), provided that their baseline lymphocyte counts were Grade 0 at baseline of year 1 and Grade 0 or 1 at each of the subsequent yearly treatment courses. The incidence of Grade ≥3 lymphopenia was lower at the end of the treatment years, if subjects were treated with cladribine 3.5 mg/kg only if they had a baseline lymphocyte count of Grade 0 in year 1 and of Grade 0 to Grade 1 in year 2 (0.5% and 0.8% respectively), compared to subjects treated when lymphocyte grades were ≥1 at baseline of year 1 and Grade ≥2 at year 2 (3.6% and 12.2% respectively). No Grade 4 lymphopenia was reported at the end of the treatment years in either group.

Furthermore, in the ONWARD study (cladribine + IFN-β) after implementation of the amended protocol including the introduction of lymphocyte-based (re-)treatment guidelines (patients to have a normal ALC before initiation of cladribine treatment in year 1 and an ALC which is within the normal range or not worse than Grade 1 before treatment in year 2) and the discontinuation of the 5.25 mg/kg cladribine dose, only 2 (1.6%) subjects in the 3.5 mg/kg cladribine group had Grade 4 lymphopenia. In comparison, under the original protocol, 2 subjects (12.5%) in the 3.5 mg/kg cladribine dose group and 3 subjects (17.5%) in the 5.25 mg/kg cladribine dose group had Grade 4 lymphopenia. Furthermore, with the (re-)treatment criteria in place, at the end of year 1, only 1 (0.6%) subject had a Grade 3 lymphopenia, and at the end of year 2, only 1 (1.2%) subject had Grade 3 lymphopenia. No subjects had Grade 4 lymphopenia at the end of either year.

Post-hoc analyses performed on the lymphopenia data from the ORACLE MS study, in which treatment guidelines were applied throughout the study showed that the duration of Grade ≥3 lymphopenia in subjects treated with 3.5 mg/kg cladribine was shorter (median of 3.0 and 3.7 months, respectively, for the first and last episodes of Grade 3 or Grade 4 lymphopenia) than in CLARITY where the treatment guidelines were not applied. Furthermore, Grade 4 lymphopenia was limited to 3 subjects (1 subject [0.4%] in the cladribine 3.5 mg/kg group and 2 subjects [1.0%] in the cladribine 5.25 mg/kg group).

To support the re-treatment scheme, modeling and simulation analysis on the severity and duration of lymphopenia in cladribine-treated subjects were performed to gather further evidence on the best re-treatment strategy for cladribine (see section 2.4.3.). From the developed model, inferences about the time for return to a given lymphopenia grade from a certain ALC nadir could be made. The simulations showed

that the proposed (re-)treatment guidelines applied to the use of cladribine at a cumulative dose of 3.5 mg/kg as the proposed dosing scheme, resulted in shorter lymphopenia recovery time, a lower incidence of Grade 3 lymphopenia. Modeling and simulation analyses support the postponement of cladribine treatment in year 2 for 6 months.

No effect on ALC measurements was seen when subjects had received concomitant glucocorticoids, but measurements associated with IFN-β-1a treatment (rescue therapy, as defined by the ORACLE MS protocol, for patients converting to clinically definite MS) were found to be approximately 19% lower than in the absence of IFN-β-1a treatment ($p \leq 0.01$). No effect of HDA on the ALC time-course could be identified in the covariate analysis.

- *Infections*

Incidende rates of the most common infections were similar between the placebo and the cladribine-exposed groups with the exception of herpes zoster (adj-AE per 100PY in the Monotherapy Oral cohort was 0.83 for cladribine 3.5 mg/kg and 0.20 for placebo) including severe cases (0.09 and 0.05, respectively.) The incidence of severe infections was generally higher among the cladribine-treated patients as compared to placebo albeit the absolute numbers were low (adj-AE per 100PY: 1.25 vs. 1.08, All Exposed cohort). Serious infections also occurred more frequently in the cladribine group compared to placebo (adj-AE per 100PY: 0.94 vs. 0.64, All Exposed cohort)

Table 27 – Most Frequently Reported TEAEs (Adj-AE of ≥1.0 in Any Group): Infections and Infestations SOC (Monotherapy Oral Cohort)

Preferred Term	Placebo (N=641)			Cladribine Dose (mg/kg)											
				3.5 mg/kg (N=923)			3.5 mg/kg re-exposed* (N=195)			5.25 mg/kg (N=632)			5.25 mg/kg re-exposed* (N=195)		
	2025.974 PY			3432.654 PY			769.352 PY			2316.608 PY			755.195 PY		
	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY
Overall Infections and Infestations SOC	**314**	**1160.8**	**27.05**	**478**	**1917.5**	**24.93**	**99**	**460.1**	**21.52**	**352**	**1245.0**	**28.27**	**100**	**448.6**	**22.29**
Nasopharyngitis	97	1764.5	5.50	158	2951.0	5.35	24	701.9	3.42	107	2011.6	5.32	31	664.6	4.66
Upper respiratory tract infection	61	1869.1	3.26	109	3112.0	3.50	19	703.1	2.70	87	2052.5	4.24	26	675.9	3.85
Influenza	51	1898.1	2.69	87	3169.5	2.74	16	726.0	2.20	60	2141.8	2.80	25	693.4	3.61
Bronchitis	22	1964.4	1.12	55	3234.1	1.70	5	764.4	0.65	31	2219.1	1.40	12	725.0	1.66
Urinary tract infection	46	1916.8	2.40	55	3249.7	1.69	17	714.6	2.38	40	2202.7	1.82	17	709.4	2.40
Herpes zoster	4	2019.0	0.20	28	3360.2	0.83	7	749.1	0.93	19	2257.8	0.84	11	719.3	1.53
Pharyngitis	31	1961.4	1.58	27	3348.0	0.81	4	752.1	0.53	28	2238.9	1.25	2	746.8	0.27
Rhinitis	22	1962.3	1.12	24	3354.0	0.72	9	738.5	1.22	22	2247.7	0.98	1	752.4	0.13

n = number of subjects with events; T = total subject's time on study in years (if a subject has multiple events, the time to first event is considered; for a subject with no event the time is censored at the last follow-up time for that subject); Adj-AE per 100PY = the time adjusted AE incidence rate (number of events occurring in 100-patient years).

Overall, in subjects exposed to cladribine, the incidence of herpes zoster infections was higher in patients with Grade 3 or Grade 4 lymphopenia. In the Monotherapy Oral cohort, the AE rate for cladribine 3.5 mg/kg

group was 2.16 per 100 PY with Grade 3 or 4 lymphopenia and 0.75 without Grade 3 or 4 lymphopenia. For cladribine 5.25 mg/kg, the respectve rates were 2.01 per 100 PY (with Grade 3 or 4 lymphopenia) and 0.756 (without Grade 3 or 4 lymphopenia).

Regarding opportunistic infections, a customized MedDRA query was used including tuberculosis, and progressive multifocal leukoencephalopathy (PML). There was no evidence for an increased risk in subjects treated with cladribine, although for lymphopenic patients, the incidence was higher as compared to those without. In the Monotherapy Oral cohort, adj-AE per 100 PY were as follows: cladribine 3.5 mg/kg with lymphopenia (1.72 Adj-AE per 100PY); cladribine 3.5 mg/kg without lymphopenia (1.03 Adj-AE per 100PY); cladribine 5.25 mg/kg with lymphopenia (1.72 Adj-AE per 100PY); and cladribine 5.25 mg/kg without lymphopenia (0.86 Adj-AE per 100PY).

In clinical trials of both oral and parenteral cladribine in MS, no PML cases have been reported during a total observation period of more than 8500 PYs. However, some cases have been reported with parenteral cladribine in lymphoma patients.

Three cases of tuberculosis were reported in subjects exposed to cladribine (one case each in CLARITY [actual dose 0.84mg/kg], CLARITY EXT [assigned dose 8.75mg/kg], and PREMIERE assigned dose 3.5mg/kg]). The case in CLARITY was fatal. All cases were reported prior to the implementation of the pre-screening for tuberculosis in the study protocols.

There were two case of hepatitis B. One subject, tested negative for hepatitis B prior to study entry, was diagnosed with hepatitis B on Study Day 43 and died from hepatitis B on Study Day 49. The event was considered unrelated to study treatment.

- *Malignancies*

In general, malignancy rates were higher among the cladribine-treated patients as compared to placebo.

As Table 28 displays, after adjudication, 37 cases of malignancies reported in 35 subjects across the cladribine clinical program were reported across the cladribine clinical program. Of these, 33 occurred under cladribine treatment (in 32 patients) and 4 with placebo. The majority of subjects were between 40 and 59 years old. The types of malignancies seen in cladribine-treated subjects consisted only of solid tumors. Overall, there was no obvious pattern or cluster of specific tumour types or locations for either cladribine or placebo. There were no cases of leukemia, lymphoma or lymphoproliferative disorders.

Table 28 - Malignancies Reported in the Cladribine Development Program (All Exposed Cohort)

Organ System	Number (%) of events (N=37)	Preferred terms of reported events (number of events reported)
Skin [a]	14 (37.8%)	Basal cell carcinoma (7), squamous cell carcinoma of skin (3), malignant melanoma (3), skin cancer (1)
Reproductive tract / Breast	10 (27.0%)	Cervix carcinoma stage 0 (3), cervix carcinoma (1) breast cancer (3), ovarian cancer (2), choriocarcinoma (1)
Gastrointestinal tract	7 (18.9%)	Rectal cancer (3), colorectal cancer metastatic (1), colon cancer stage 0 (1), pancreatic carcinoma metastatic (1), bile duct adenocarcinoma (1)
Thyroid	3 (8.1%)	Papillary thyroid cancer (2), thyroid cancer (1)
Kidney/urinary tract	2 (5.4%)	Renal cell carcinoma (1), bladder transitional cell carcinoma (1)
Respiratory tract	1 (2.7%)	Nonkeratinising carcinoma, differentiated (nasopharyngeal cancer) (1)

[a] One additional case of neoplasm skin was adjudicated as an indeterminate case.

In order to compare crude numbers of malignancies in patinets treated with cladribine and placebo, data from the 2-year, Phase III, placebo-controlled studies of CLARITY and ORACLE were used. There was a total of 5 malignancies reported in 636 patients (0.79%) in the 3.5 mg/kg cladribine group (3 in CLARITY and 2 in ORACLE), 2 in 658 patients (0.30%) in the 5.25 mg/kg group (2 in CLARITY and 0 in ORACLE), and 0 in 641 patients in the placebo group.

Table 29 provides the results of the comparative analyses for incidence rate ratios (RR) and incidence rate differences (RD) comparing cladribine to placebo. The RD for cladribine treatment groups was 0.2457 events per 100PY (95%CI: -0.1803; 0.5849) in the Placebo-controlled Double-blind cohort and 0.2033 events per 100PY (95%CI: -0.0785; 0.3947) in the All Exposed cohort.

Table 29 - Comparison of Malignant Tumors (Adjudicated Cases) between Placebo and Cladribine-Incidence Rates (Placebo-controlled Double-blind and All Exposed Cohorts)

Placebo-controlled Double-blind Cohort	Placebo (N=745)	Cladribine (N=1458)
Patient-years at risk	1135.12	2397.03
Number of subjects with at least one malignant tumor	1	8
Incidence per 100 PY	0.08810	0.33375
95% CI of incidence[a]	0.0124 ; 0.6254	0.1669 ; 0.6674
Risk Difference per 100 PY		**0.2457**
95% CI of Risk Difference per 100 PY[c]		**-0.1803 ; 0.5849**
Risk Ratio		3.7884
95% CI of Risk Ratio[b]		0.4738 ; 30.2896

Placebo-controlled Double-blind Cohort	**Placebo (N=745)**	**Cladribine (N=1458)**
All Exposed Cohort	**Placebo (N=802)**	**Cladribine (N=1976)**
Patient-years at risk	2357.09	8579.39
Number of subjects with at least one malignant tumor	4	32
Incidence per 100 PY	0.16970	0.37299
95% CI of Incidence per 100 PY [a]	0.0637 ; 0.4522	0.2638 ; 0.5274
Risk Difference per 100 PY		**0.2033**
95% CI of Risk Difference per 100 PY [c]		**-0.0785 ; 0.3947**
Risk Ratio		2.1979
95% CI of Risk Ratio [b]		0.7773 ; 6.2148

CI=confidence interval; PY=patient year.

Per subject a unique event is a unique PT and date of onset. Total time at risk (T) is the total subject time on study in years. If a subject has multiple events, the time to first event is considered. For a subject with no event the time is censored at the last follow-up time for that subject.

[a] CI is computed with the exact Clopper-Pearson formula.

[b] CI is computed with the Wald method for the number of subject with events using a Poisson regression model with fixed effect for treatment group and with log of time at risk as an offset.

[c] CI is computed using the Miettinen and Nurminen method.

The risk for NMSC was not increased (RR=1.09). The risk for all skin cancers was only slightly increased (RR=1.51). However, analyses of all malignancies excluding non-melanoma skin cancer (NMSC) in the All Exposed cohort showed an RD of 0.19 (95% CI: -0.04; 0.35) and RR of 3.29 (95% CI: 0.78; 13.92). The RR of solid tumours excluding all skin cancers was 2.87 (95% CI 0.67; 12.26).

An analysis of baseline risk factors for cancer in all treatment groups of the cladribine clinical studies was perfomed. The only baseline factor showing a prominent effect for all malignancies was age. Patients developing malignancies were on average 7 years older than those who did not delvelop malignancies. Furthermore, no association between malignancy cases and prior experience of lymphopenia of Grade ≥3, was found in an analysis of subjects from the Placebo-controlled Double-blind cohort with an odds ratio of 1.01 [95% CI: 0.16, 5.19].

No dose-relationship was apparent with adj-AEs per 100 PY of 0.37 in the dose range of 0-3.5mg/kg, 0.42 in the dose range of >3.5 – 5.25mg/kg, 0.31 in the dose range of > 5.25 – 7.0mg/kg, 0.46 in the dose range of > 7.0 – 8.75mg/kg and 0.21 in the dose range of > 8.75mg/kg.

In an analysis of the cumulative incidence for malignancies over time in the All Exposed cohort, it appears as if malignancies occurred sooner among cladribine-treated patients as compared to placebo-treated. By year 2 on study, 1 malignancy had developed in the placebo group as opposed to 10 malignancies in the cladribine group. This trend continues through year 4 by which a total of 2 malignancies in the placebo group have developed as opposed to a total of 24 in the cladribine group. By year 6 this tendency is maintained. By the final observation, there was a total of 4 patients with malignancies in the placebo group. This is in contrast to the 32 patients with malignancies in the cladribine group. Overall, a constant malignancy incidence rate was observed for cladribine in Years 1 to 4 and in the period thereafter (incidence per 100PY was 0.38 for each

period), whereas the incidence rates observed for placebo increased over time (0.10 for year 1-4 and 0.57 thereafter).

Comparison with epidemiology data

To put the malignancy rates in the cladribine integrated safety database into perspective, a comparison with the GLOBOCAN (2012) database of malignancies was performed. For this, Standardized Incidence Ratio (SIRs) for the overall malignancies in the cladribine and placebo groups were calculated in relation to the GLOBOCAN reference population with matched follow-up distribution (with respect to sex, age, and country) and estimated by treatment group. NMSCs are not represented in the GLOBOCAN database and were therefore not included in this analysis.

The results of these analyses are summarized in Table 30.

Table 30 - Comparison of Malignancies Excluding NMSC with Cladribine and Placebo Compared to a GLOBOCAN Reference Population

Cohort: Monotherapy Oral	**Placebo (N=641)**	**Cladribine (N=923)**
Patient years	2025.97	3432.65
Unique observed events	2	8
Expected events	4.17	8.27
SIR (95% CI)	**0.48 (0.14-1.53)**	**0.97 (0.44-1.85)**
Placebo-controlled Double-blind Cohort	**Placebo (N=745)**	**Cladribine (N=1458)**
Patient years	1135.29	2400.17
Unique observed events	0	7
Expected events	2.34	5.05
SIR (95% CI)	**0**	**1.39 (0.59, 2.76)**
Cohort: All exposed	**Placebo (N=802)**	**Cladribine (N=1976)**
Patient years	2361.13	8650.16
Unique observed events	2	24
Expected events	5.28	22.63
SIR (95% CI)	**0.38 (0.11, 1.21)**	**1.06 (0.70, 1.55)**

CI=confidence interval; NMSC=non-melanoma skin cancer; SIR=standardized incidence ratio.
Analysis excluded NMSC and only considered adjudicated cases. SIR CI is computed using the Mid-P method.
Based on a data cut-off of 20 February 2015.

Comparison to Other MS DMDs

A recent review of the malignancy risk for DMD treatments for MS by an academic group based in the UK (Pakpoor et al., 2015) compared published data from 2-year clinical studies. The results of CLARITY, the Phase III study of cladribine in RRMS was also included in the analysis. The malignancy rates in the treatment and control groups were compared using Fisher's exact test. The authors noted that the

malignancy rate of cladribine-treated subjects in the CLARITY study (0.34%) was not significantly different from all other active treatment groups (0.67%, p=0.3669), see Figure 9.

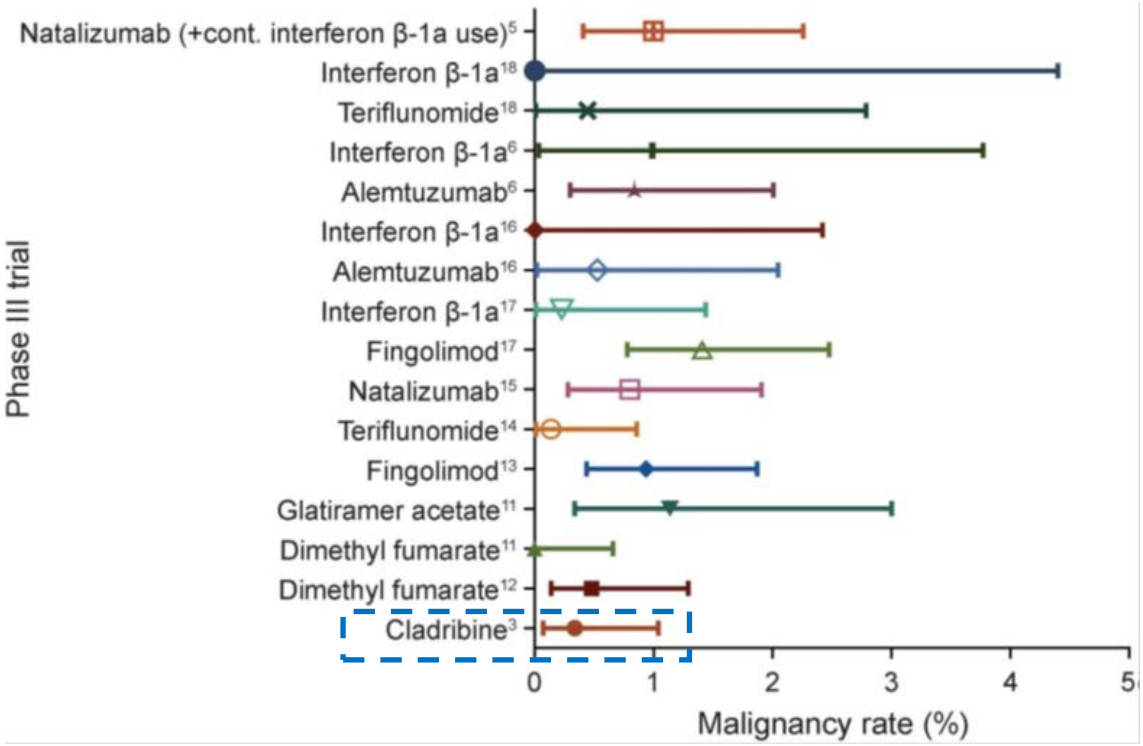


Figure 9 - Malignancy Rates for Treatment Groups of DMD MS Drugs in Phase III Trials

Source: Pakpoor et al., 2015.

DMD=disease-modifying drug; MS=multiple sclerosis.

The superscripted numbers against the drug names indicate the publications from which the data are derived. Details of these publications are available from the Pakpoor publication (2015) referenced in the source.

The malignancy rate displayed on the x axis corresponds to the proportion of subjects with relapsing multiple sclerosis in whom cancer occurred.

The fact that no malignancies were observed in the placebo group of CLARITY was unique, and was found to be significantly different to the combined cancer rate of all the other placebo groups (1.19%; p=0.0159). The authors furthermore compared the RD between cladribine and the other DMDs using random-effects pooling and found the RD to be comparable to that of other DMDs.

Safety after switching from cladribine to other DMDs

Data from 941 subjects included in the ongoing PREMIERE Registry and previously treated with cladribine were analysed. For 33.9% (319/941) of subjects, subsequent DMDs after discontinuation of cladribine treatment were recorded: The highest proportions of subjects were treated with IFN-β: 23.0% (216/941), followed by glatiramer acetate (9.7%, 91/941). Overall, no specific pattern in the reported SAEs and no unexpected safety findings were observed.

In the ORACLE study, after switching from cladribine to IFN-ß, the safety profile of subjects switching from placebo to IFN-ß was similar to that of those who switched from cladribine to IFN-ß, except for a higher rate of Grade 2 and 3 lymphopenias in the cladribine group.

In the 3.5 mg/group of the CLARITY trial, 11 subjects received rescue treatment with IFN-ß. Review of the subject data showed that the AE profiles observed in these subjects after switching from cladribine to IFN-ß did not reveal new safety findings compared to the known safety profiles of cladribine and IFN-ß.

Data from the MSBase (Multiple Sclerosis Database) Foundation included longitudinal clinical data from 90 cladribine-exposed patients from 55 Australian MS centers in February 2016. These patients had received cladribine as part of the Patient Familiarisation Program in 2011. Data were available for 62 patients (69%) who were exposed to another DMD following the commencement of the cladribine therapy. Of these, 10 (11%) experienced 12 AEs during their exposure to these DMDs (annualized rate of 0.09 events per PY) and 7/12 were evaluated as not being related to DMD.

Serious adverse events (SAEs) and deaths

Deaths

Within All Exposed cohort, there were 24 death cases: 19 were reported for the cladribine-treated subjects and 5 for the placebo subjects. All PTs were single reports, with the exception of drowning in 3 cladribine-treated subjects.

Of the 24 deaths, 4 were considered related to cladribine treatment including a case of tuberculosis (CLARITY), a case of bile duct adenocarcinoma and lymph node metastases (CLARITY EXT, PPLL group]), a case of pyrexia and herpetic encephalopathy (PREMIERE Registry, cladribine-treatment group in the ONWARD study; concurrent fatal SAEs pneumonia and pneumothorax were not considered related) and a case of rectal adenocarcinoma (PREMIERE Registry, cladribine-treatment group in the CLARITY study).

Among the 24 death cases were 4 cases in the SOC of Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps) SOC, all in cladribine-treated subjects: Rectal adenocarcinoma (related), pancreatic carcinoma metastatic (unrelated), ovarian cancer (unrelated), bile duct adenocarcinoma and metastases to lymph nodes (same subject, both related). There were furthermore 3 cases in the SOC of Infections and Infestations: Tuberculosis (cladribine subject, related), hepatitis B (cladribine subject, unrelated) and herpetic meningoencephalitis (cladribine subject, related), and 2 cases in the Psychiatric Disorders SOC: Completed suicide (placebo subject, unrelated), and intentional self-injury (cladribine subject, unrelated).

The other cases occurred in the General Disorders and Administration Site Conditions SOC (7 deaths, 6 with cladribine and 1 with placebo, all unrelated except one case of pyrexia in a cladribine treated subject), the Cardiac Disorders SOC (5 deaths, 3 with cladribine, 2 with placebo, all unrelated), the Nervous System Disorders SOC (2 deaths, one each with cladribine and placebo, all unrelated), the Injury, Poisoning and Procedural Complications SOC (2 deaths, both unrelated and with cladribine), and the Respiratory, Thoracic, and Mediastinal Disorders SOC (1 death in a cladribine subject, unrelated).

There was no difference in the incidence of TEAEs leading to death between the cladribine 3.5 mg/kg group and the placebo group: 0.26 Adj-AEs per 100PY were reported for 3.5 mg/kg cladribine-treated subjects and 0.25 Adj-AEs per 100PY for the patients on placebo. The Adj-AE per 100PY rate of death were similar in cladribine and placebo treated patients in the All Exposed cohort (0.22 versus 0.21). In the Placebo-Controlled Double-Blind Cohort, the Adj-AE per 100 PY (cladribine vs. placebo) were 0.29 versus 0.18 (corresponding to 7 versus 2 cases).

Serious Adverse Events (SAEs)

Overall, one or more SAEs were reported in 13.4% (124/923) of subjects in the 3.5 mg/kg cladribine group, 11.4% (72/632) of subjects in the 5.25 mg/kg cladribine group and 10.5% (67/641) of subjects in the placebo group (Monotherapy Oral Cohort). In addition, 30/195 (15.4%) patients each of the cladribine re-exposed cohorts experienced SAEs.

The most frequently occurring SAEs reported were Lymphopenia, Infections and Malignancies (see detailed discussion above). Reported SAEs by PT occurring with an AE rate >0.1 in either placebo or cladribine 3.5 mg/kg treated subjects were blood creatine phosphokinase increased (0.20 vs. 0.21), pneumonia (0.15 vs. 0.18), uterine leiomyoma (0.10 vs. 0.15), lymphopenia (0 vs. 0.12), and urinary tract infection (0.05 vs. 0.12). Although the observed incidence rate of serious urinary tract infections was numerically higher in the 3.5 mg/kg cladribine group when compared to placebo, the incidence rate in the 5.25 mg/kg cladribine group was approximately as high as in subjects receiving placebo (0.04 vs. 0.05 AE per 100PY). Overall, the incidence rate of urinary tract infections was not elevated in subjects treated with cladribine.

Laboratory findings

Laboratory parameters evaluated include routine haematology (haemoglobin, WBC, neutrophils, lymphocytes, and platelets), speciality haematology (lymphocyte surface markers), and clinical chemistry (creatinine, creatine kinase, bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase). The lymphocyte surface markers included: CD3+, CD4+, CD8+, CD19+, CD4+:CD8+ ratio, CD4+/CD45RO+, CD4+/CD45RA+, CD8+/CD45RO+, and CD8+/CD45RA+.

Integrated analysis based on the Monotherapy Oral cohort indicates that cladribine treatment resulted in a decrease of WBC counts, neutrophils, and lymphocytes, including CD4+ and CD8+ T-lymphocytes and CD19+ B-lymphocytes. No meaningful changes were observed in group values for hemoglobin, monocytes or eosinophils.

The median CD4+ counts decreased in the cladribine group after baseline. There was a general tendency for the CD4+ counts to recover over time although the median values remained below baseline at Week 240.

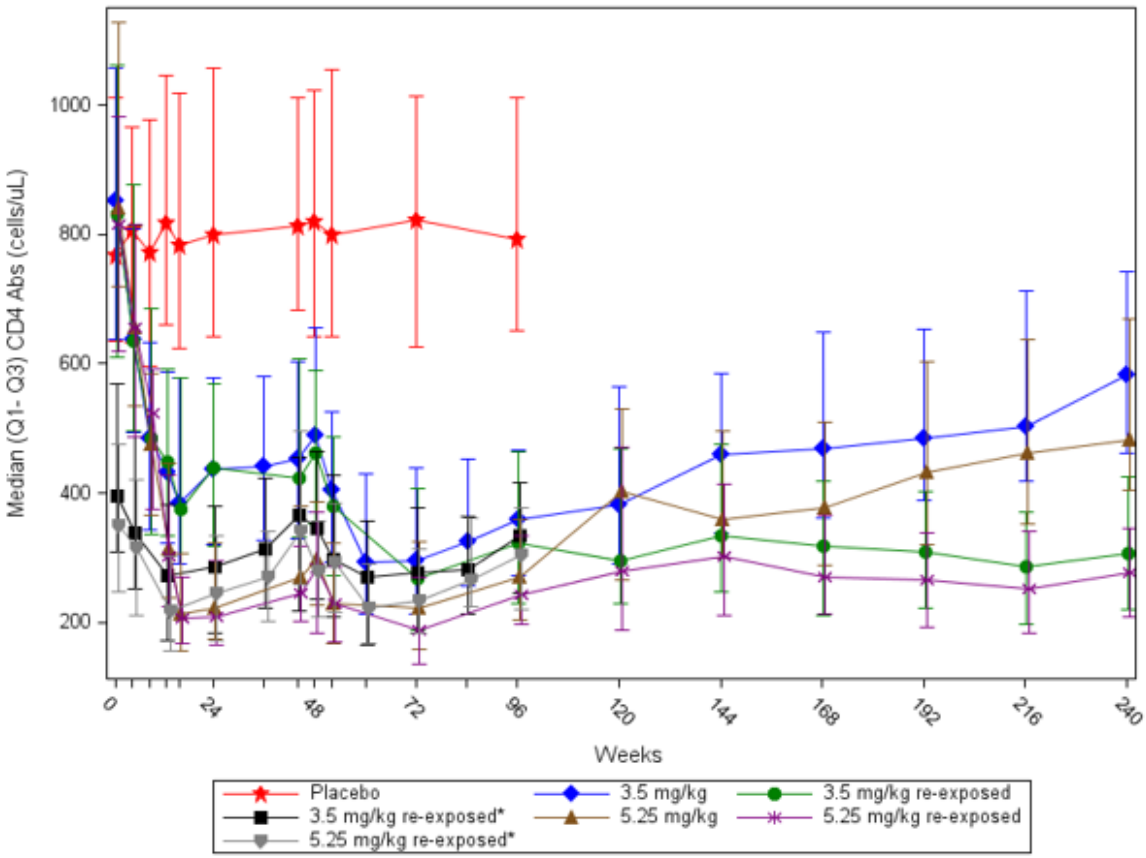


Figure 10 - Median (Interquartile Range) CD4 Abs (cells/ µL) Over Time, by Treatment (Monotherapy Oral Cohort)

The median CD8+ counts also decreased in the cladribine group after baseline. There was evidence of recovery over time. Recovery appeare dto be faster compared to CD4+.

With regards to B-cells a rapid decline of CD19+ was observed in the active groups at Week 5. The recovery continued over time with the median values at Week 240 close to baseline values.

Neutrophil count decreased even more rapid than the T cell and B cell count with a slow but recovery towards baseline. The WBC count and the platelet count decreased rapidly and did not completely recover to baseline values. However, effects on platelets and neutrophils were overall less marked compared to lymphocyte markers and most decreases were within normal ranges. Notably, platelet values remained well above levels where platelet-deficiency itself posed a haemorrhagic risk.

For other haematology parameters including red blood cell count, haematocrit values, basophils, and eosinophil values, no meaningful changes were detected.

With regard to clinical chemistry, vital signs, ECG or physical findings, there were no major findings regarded as a safety issue.

Safety in special populations

Age, Gender, Ethnicity and Weight

No patients older than 65 years were enrolled in the clinical studies in the cladribine development program. Age categories of ≤25 years, 26-45 years, 46-55 years and ≥56 years were analysed. The majority of study subjects were 26-45 years. Overall, for most AEs a tendency towards increased frequency with increasing age was evident. In particular, the rate of lymphopenia was much higher in older people and there was a consistent increase with increasing age (Adj-AE per PY in cladribine treated patients: 7.75 for ≤25 years, 10.75 for 26-45 years, 12.72 for 46-55 years and 22.53 for ≥56 years). When looking at Grade 3 or 4 lymphopenia the same pattern is observed. However, when looking at cladribine 3.5 mg/kg only (Monotherapy Oral Cohort), no difference in the incidence of lymphopenia was observed between patients ≤ 50 and patients > 50 years of age.

No studies have been conducted with cladribine in the paediatric population. A product-specific PIP waiver has been granted for MS for all subsets of the paediatric population from birth to less than 18 years of age on the grounds that the specific medicinal product is likely to be unsafe.

No major differences between female and male subjects were evident.

The majority of subjects were white in the placebo (777 out of 802, 96.8%) and cladribine (1906 out of 1976 subjects, 96.5%) groups making it difficult to draw any meaningful conclusions from the data on other ethnicities.

There were no apparent differences with regard to frequency of AEs by weight category (≤60 kg; >60 to ≤80 kg; and ≥80 kg).

Renal and hepatic impairment

No specific studies have been conducted in patients with renal or hepatic impairment.

Pregnancy and lactation

In total, 38 patients treated with cladribine experienced 44 pregnancies while 19 patients treated with placebo experienced 20 pregnancies. In the cladribine group, 41% of pregnancies resulted in live births while the corresponding proportion was 45% in the placebo group. Induced, spontaneous and medically indicated abortion accounted for 32%, 20% and 7% of pregnancies in the cladribine group and 20%, 25%, and 5% (1) of pregnancies in the placebo group. The outcome was unknown in1 case in the placebo group.

Adverse outcomes were reported for the newborns of 3 subjects treated with cladribine. In one of the three cases (asphyxia of the fetus) no further information was available. In the other two cases, he women becam pregnant more than 2 years after last administration of cladribine. No adverse outcomes were reported for the newborns of trial subjects treated with placebo.

Only 16 out of the total 38 patient who got pregnant became pregnant during administration of cladribine or within 6 months after the last dose. Three (3) of these pregnancies resulted in live births, 10 were terminated by abortion per decision of the patient, 1 was a medically induced abortion due to ectopic pregnancy, and 2 patients experienced spontaneous abortions.

In total, 11 female partners of study participants experienced 12 pregnancies. Of the study participants, 9 received cladribine and 2 received placebo. In the female partners of the 9 cladribine-treated subjects 10 pregnancies were noted. Of these, 9 resulted in live births.

Overdose and drug abuse

Events of overdose were few and no excessive toxicity was observed.

Cladribine has no known potential for drug abuse.

High Disease Activity

Across HDA groups, lymphopenia was consistently reported with high Adj-AE per 100PY rates compared to placebo. Data regarding severity of AEs, SAEs and malignancies by HDA cohort have not been provided.

Safety related to drug-drug interactions and other interactions

Drug-drug interaction studies with Refib and cladribine as well as with pantoprazole and cladribine have been conducted. These are discussed in section 2.4.

Notably, a potentiation of haematological adverse events, particularly reduction of lymphocyte count, has been observed with some concomitant DMDs. The laboratory safety data obtained in the drug-drug interaction studies with Refib suggested potential additive PD effects of the known haematological treatment-emergent adverse effects of both products, which was corroborated by ALC modeling (on ORACLE MS). Furthermore, higher incidences of severe lymphopenia were observed when cladribine was given with concomitant IFN-β treatment in ONWARD compared to monotherapy in CLARITY.

Discontinuation due to adverse events

Within the Monotherapy Oral cohort, the incidence rate of treatment discontinuation due to TEAEs was higher in the cladribine 3.5 mg/kg group than the placebo group (adj-AE per 100PY : 2.07 vs 1.05). There was evidence of a dose relationship (placebo, cladribine 3.5 mg/kg, and cladribine 5.25 mg/kg, respectively): 1.05 vs 2.07 vs 2.44.

In the cladribine-treated groups, TEAEs leading to discontinuation occurred primarily in the Blood and Lymphatic System Disorders SOC and the Investigations SOC, especially discontinuation due to lymphopenia was more pronounced upon re-exposure and differs from the placebo cohort (adj-AE per 100PY: 0.05 for placebo, 0.78 for cladribine 3.5 mg/kg, 1.30 for cladribine 5.25 mg/kg, 3.03 for cladribine 3.5 mg/kg re-exposed, and 3.24 for cladribine 5.25 mg/kg re-exposed). Notably, in the All Exposed cohort, 2 cases of hepatitis B were reported as TEAEs leading to treatment discontinuation. One of these cases was fatal.

Post-marketing experience

Cladribine is not currently marketed for the treatment of MS. While a marketing authorisation was granted in Russia and Australia previously, it was later withdrawn. Overall, 22 case report of a total of 68 AEs were received by post-approval sources (cut-off date: 29 February 2016). The sources of these cases were consumers (8 reports) and health care professionals (14 reports). The most frequent events reported from post-approval sources were oropharyngeal pain (5 events), cough, fatigue and headache (4 events reported each) and nausea (3 reports). Lymphopenia and herpes zoster were reported once each (all non-serious).

The RECORD MS Study, whose main objectives were to quantify the risk (cumulative incidence) of serious adverse drug reactions and to quantify and monitor the risk Grade 3 and Grade 4 lymphopenias, only

recruited 35 patients. Two AEs (in the same subject) were assessed by the Investigator as serious adverse drug reactions: lymphocyte count decreased and prostate cancer.

Cladribine parenteral solution is currently also approved for use in two oncology indications: hairy cell leukaemia and chronic lymphocytic leukaemia. In the EU, cladribine is approved for use in hairy cell leukaemia as (Litak® and Leustatin®). Notably, patients with hairy cell leukaemia have an inherent increase risk of secondary malignancies.

2.6.1. Discussion on clinical safety

For the integrated safety analyses, data were primarily derived from the CLARITY, CLARITY EXT, ORACLE MS, ONWARD and the PREMIERE Registry. The Scripps studies with parenteral cladribine also contributed data. Patients were analysed by three defined cohorts: All Exposed Cohort, Double-Blind Placebo-Controlled Cohort and Monotherapy Oral Cohort.

Subjects exposed to cladribine were more numerous and followed over a longer period of time compared with placebo resulting in a larger exposure in terms of patient years of treatment and follow-up for the cladribine-treated subjects: A total of 1976 subjects received at least one dose of cladribine and 802 received placebo in the integrated safety database translating into 8650 PY of exposure to cladribine (exposure and follow-up) and 2361 PY of exposure to placebo. The size of the patient population in the cladribine study program and the pooled number of PY of exposure to cladribine was considered sufficient to evaluate the overall safety profile of cladribine.

The most frequently occurring AEs belonged to the MedDRA SOC of Blood and Lymphatic System Disorders and Infections and Infestations. TEAEs were generally more frequent among the cladribine-treated patients compared to the placebo-treated patients and there was a dose-dependent increase in the rate of patients with at least 1 TEAE. The majority of events were mild or moderate in severity. Severe lymphopenia was the only severe AE that occurred more frequently in patients receiving cladribine 3.5 mg/kg compared to placebo (Adj-AE per 100PY: 0.59 vs. 0.00). Amongst the TEAEs considered related to treatment, lymphopenia, leukopenia, lymphocyte count decreased, neutropenia and herpes zoster occured with a higher rate in the active arms compared to placebo. Data presented for HDA patients gave no indication of different AE profiles by HDA groups and compared to non-HDA patients.

With regard to SAEs, the Adj-AE per 100PY rate of at least 1 SAE was 3.57 in the placebo group. Comparatively, in the 3.5 mg/kg cladribine group it was 4.00, and in the 3.5 mg/kg re-exposed cladribine group it was 4.29. Similar rates were observed in the 5.25 mg/kg and 5.25 mg/kg re-exposed groups. While the overall rate of SAEs was generally similar across treatment groups, differences between placebo and cladribine groups were observed for, among others, SAEs belonging to the SOCs of Neoplasms [Adj-AE per 100PY rate 0.50 (placebo) vs. 0.74 (cladribine 3.5 mg/kg)], Infections and Infestations [Adj-AE per 100PY rate 0.50 (placebo) vs. 0.69 (cladribine 3.5 mg/kg)], Nervous System Disorders [Adj-AE per 100PY rate 0.25 (placebo) vs. 0.32 (cladribine 3.5 mg/kg)] and Blood and Lymphatic System Disorders [Adj-AE per 100PY rate 0 (placebo) vs. 0.29 (cladribine 3.5 mg/kg)]. The latter was primarily driven by cases of serious lymphopenia. For most of the listed SOCs, an apparent dose-dependent pattern of SAEs was observed albeit the absolute number of SAEs was limited.

In the Placebo-controlled Double-blind cohort, the Adj-AE per 100PY rate of death was higher in cladribine-treated subjects (0.29),than among the placebo-treated patients (0.18) whereas there was no difference in the other cohorts. There was an apparent increased frequency of deaths due to malignancies (see discussion

on malignancies below). No increased frequency of suicide, suicide attempts, potential suicide and suicidal ideation among cladribine-treated patients has been identified.

Across the different cohorts and analyses conducted, lymphopenia consistently occurred at markedly increased rates in cladribine-treated patients compared with the placebo groups. Moreover, a dose-dependent pattern was observed, e.g. in the Monotherapy Oral Cohort the rate of adj-AE per 100PY was 12.62, 7.94 and 1.06 in the cladribine 5.25mg/kg, the cladribine 3.5mg/kg and the placebo groups, respectively. A dose-dependent increase was also observed for severe (Grade ≥3) lymphopenia. Notably, re-exposure in Years 3 and 4 was associated with an increase in the incidence rates of lymphopenia AEs (Adj-AESI per 100PY of 1.94 in the cladribine 3.5mg/kg re-exposed group and 1.82 in the cladribine 5.25 mg/kg re-exposed group). This is coupled with an increased occurrence of Herpes Zoster in patients treated with cladribine compared to placebo, which furthermore occurred at a higher rate in patients with Grade ≥3 lymphopenia. These findings were not surprising given that the mechanism of action of cladribine is based on a selective depletion of lymphocytes which in turn predispose patients to infectious diseases.

As supported by laboratory haematology parameters, cladribine treatment resulted in quite rapid and marked depletion of both T cell and B cell counts. There is evidence that particularly the T cells recover slowly, e.g. median CD4+ counts values remained below baseline at Week 240 in cladribine treatment groups including those without re-treatment in year 3 and 4. This is also supported by data from CLARITY with median durations of Grade 3 or 4 lymphopenia of 5.4 months and 5.6 months, respectively, for the cladribine 3.5 mg/kg and cladribine 5.25 mg/kg groups. In contrast, although rapid decreases are evident, the B cell counts as well as the neutrophil count slowly but gradually recover towards baseline. Decreases in red blood cell count, haematocrit, haemoglobin or platelet count compared to baseline values have also been observed but these parameters usually remained within normal limits.

During the course of the cladribine study program, risk minimization strategies involving stricter haematological criteria were implemented prior to initiation of treatment or re-treatment. Patients were to have a normal ALC before initiation of cladribine treatment in year 1 and an ALC which is within the normal range or not worse than Grade 1 (lower limt 800 cell/mm^3) before treatment in year 2. Data from ORACLE MS and ONWARD indeed support that this measure contributed to reducing the number of cases of lymphopenia, their severity and duration. Modeling data further supported postponement of the administration of cladribine in year 2 by up to 6 months in the event of prolonged lymphopenia without adversely affecting efficacy (see section 2.4.3.). However, prolonged severe lymphopenia also occurred in several patients with no apparent association with baseline haematological parameters. No indicators could be identified that were clearly predictive of prolonged severe lymphopenia. Nevertheless, as a risk minimization strategy, the proposed treatment initiation and re-treatment criteria were agreed. Furthermore, additional warnings and recommendation as regards to lymphocyte monitoring and anti-herpetic prophylaxis have been introduced in the SmPC. Further information and guidance was also agreed to be provided in a prescriber and patient guide (see section 2.7.).

With regards to infections, the incidences of the most frequently reported TEAEs were generally similar between placebo-treated and cladribine-treated groups with the exception of Herpes Zoster. A higher incidence of severe and serious infections was observed among the cladribine-treated patients as compared to placebo. However, absolute numbers were low. Further, there were 3 fatal cases of infection, all of which occurred in patients treated with cladribine.

Three cases tuberculosis in the cladribine development programme were reported. All cases occurred before tuberculosis screening was introduced in the study protocols and no cases thereafter. Therefore, it was unknown whether these events were due to reactivation of latent tuberculosis or new events. There were also

two cases of hepatitis B infection, one of which was fatal and probably acquired during the trial. No information was available to allow assessment of whether the other case was a reactivation of a latent infection. As a precautionary measure against reactivation of latent infections, the CHMP considered that cladribine should not be used in patient with active chronic infection, which was consequently added to the list of contraindications. Further, a warning was included in SmPC section 4.4 requiring screening for latent infections, in particular tuberculosis and hepatitis B and C, prior to initiation of therapy in year 1 and year 2. Vaccination of varicella zoster antibody-negative patients prior to treatment initiation as also recommended.

Overall, the Adj-AE per 100PY of opportunistic infections (excluded herpetic infections) was similar between placebo-treated and cladribine-treated patients. Many of the observed events represented diseases that can also be observed in normal, non-immunocompromised patients. During periods of Grade 3 or 4 lymphopenia in patients treated with cladribine, more opportunistic infections were reported as compared to patients without severe lymphopenia (adj-AE per 1—PY 2.23 versus 0.93 in the All Exposed Cohort; 1.73 versus 1.03 in the Monotherapy Oral Cohort). However, the overall incidence of opportunistic infections during severe lymphopenia was low and, with the exception of two events, of mild severity. Severe and opportunistic infections are considered an important potential risk of cladribine and risk mitigation measures include contraindications for immunocompromised patients and patients with human immunodeficiency virus infection.

No cases of PML have been observed in over 8500 PYs of exposure to cladribine in the development program for MS. However, as PML has been observed in patients using cladribine for the treatment of hairy cell leukaemia, baseline MRI were recommended before initiating MAVENCLAD and PML should continue to be monitored as part of pharmacovigilance activities.

With regards to malignancies, incidence rates were higher among the cladribine-treated patients as compared to placebo. In particular, there was the 3 fold higher incidence of solid tumours excluding NMSC in the cladibine group as compared to placebo (RR of 3.29 in the All Exposed cohort). Among the baseline factors related to cancer risk only age was convincingly demonstrated to be important but it did not explain the observed imbalance in incidence of malignancy.

There was no evidence of an increased incidence of cervical dysplasia in the cladribine group compared to the placebo group and the cases with cervical dysplasia or cervix carcinoma did not show any relation to grade ≥ 3 lymphopenia.

Theoretically, the immunosuppressive properties, in particular the suppression of CD8+ and CD4+ T cells, may contribute to increased malignancy rates. As CD8+ T cells were suppressed for 2 years and CD4+ T cells were suppressed for 4 years following cladribine treatment, there is biological plausible mechanism that can explain the higher frequency of malignancies. Furthermore, it is striking that by year 2 on study, 1 malignancy has developed in the placebo group as opposed to 10 malignancies in the cladribine group. This trend continues through year 4 by which a total of 2 malignancies in the placebo group have developed as opposed to a total of 24 in the cladribine group. By year 6 this tendency is maintained. By the final observation, a total of 4 malignancies have occurred in the placebo group. This is in contrast to the 32 malignancies in the cladribine group.

However, the Applicant has presented data regarding the CD4+ and CD8+ counts and associated malignancies and a causal relationship could not be established. A lower level of immune surveillance due to a reduction in CD4+ and CD8+ lymphocytes would result in virus-induced cancer or skin cancer. However, virus-induced cancer was not seen after cladribine treatment and skin cancer was not increased compared to placebo. In addition, the clinical program did not show malignancies of cell types which are mostly affected

by cladribine's mechanism of action (ie, lymphocytes). Further, the pattern of the malignancies with cladribine showed a high variety of tumour types and no clustering of specific tumour types has been seen.

In addition, clinical data support an overall latency period, from the initiation of the neoplastic event to the actual clinical detection of a solid tumour commonly in the range of 10 to 20 years (Hill & Tannock, 1998). Time from exposure to cancer diagnosis thus would seem shorter than would have been expected in case of true solid cancer induction by cladribine. The pattern regarding time to occurrence and types of malignancies may be compatible with unspecific promotion of already induced malignancies.

The Applicant also argued that the imbalance in the rate of malignancies between cladribine treated patients and those receiving placebo was driven by the low incidence rate under placebo. This was supported by a comparison with epidemiological data from the GLOBOCAN database as well as a cross-study comparison after 2-years of exposure with other DMDs. Nevertheless, uncertainties remained and the CHMP considered that any explanation regarding the observed imbalance in the incidence of malignancies remained largely speculative. Cladribine should therefore not be used in patients with active malignancies and standard cancer screening guidelines should be followed in patients treated with MAVENCLAD. Furthermore, a large, prospective, comparative Post Authorization Safety Study (PASS) will be performed to further monitor and characterize the potential malignancy risk with cladribine (category 3 in the RMP).

For the AEs alopecia, rash, and neutrophil count decrease, higher incidence rates have been observed on cladribine compared to placebo in the Placebo-Controlled Double-Blind cohort, and an apparent dose relationship was seen in the Monotherapy Oral cohort. Therefore, these events were included in the list of adverse reactions in SmPC section 4.8.

A number of special populations, such as patients with renal impairment, hepatic impairment, elderly and paediatric patients have not been studied and this is considered justified. Some experience with pregnancies and partner pregnancies was, however, available from the clinical trials program, despite pregnant or lactating women being excluded from all studies. No malformations or adverse pregnancy outcomes were observed that were attributable to cladribine exposure. However, the majority of pregnancies occurred some time after cladribine was administered and there is very limited from pregnancies carried through under actual exposure to cladribine. In light of the mechanism of action of cladribine and the non-clinical safety findings (see section 2.3.), teratogenicity was considered a potential risk of cladribine treatment and the current recommendation to avoid pregnancy in the 6 months following the last dose of cladribine was considered appropriate. Furthermore, use in pregnant women is contraindicated. A pregnancy PASS will be conducted to gather additional data on the risk of adverse pregnancy outcomes in pregnant women exposed to oral cladribine and in pregnancies fathered by male partner exposed to oral cladribine (category 3 in the RMP). Furthermore, additional information will be provided in the prescriber and patient guide including advice for use of effective contraception.

No significant PK interactions have been identified but PD interactions following simultaneous administration of immunosuppressive agents suggest a potential additive effect on the immune system caused by other immunosuppressants. Initiation of cladribine treatment in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy is therefore contraindicated. Care should be taken when using cladribine in patients who have previously been treated with immunomodulatory or immunosuppressive medicinal products and also when such medicinal products are used after treatment with MAVENCLAD. Furthermore, a higher incidence of lymphopenia was observed when cladribine was given with concomitant IFN-β treatment. While no experience of concomitant use with other DMDs was available, concomitant treatment is not recommended. Furthermore, sequential use of cladribine and other DMDs will be evaluated in the long-term PASS.

No immunological events have been observed. As cladribine is a small molecule, immunological events are not expected to be associated with cladribine.

Post-marketing data have contributed knowledge regarding cladribine used concomitantly or preceding/following other DMDs and reports of secondary malignancies have also been obtained through pharmacovigilance activities. With the exception of the possible malignancy signal (see above), post-marketing reporting has not identified unexpected safety issues. Additional safety data will be gather post-authorisation through routine Pharmacovigilance measures as well as via the PREMIERE registry, which includes subjects previously enrolled CLARITY, CLARITY EXT, ONWARD and ORACLE (category 3 PASS in the RMP) and other PASS as described above.

Additional expert consultations

During the course of the assessment of the present application, the CHMP decided to consult the Scientific Advisory Group Neurology on a number of questions related to the benefits, risks and the identification of a suitable target population for cladribine. See section 2.5.5. for the answers of the experts.

2.6.2. Conclusions on the clinical safety

Overall, the CHMP was of the view that the available clinical safety data were adequate for the purpose of assessing the safety of cladribine for the use as treatment of adult patients with highly active RMS. The main safety issues were related to the risks of prolonged severe lymphopenia, infections including reactivation of latent infections and opportunistic infections as well as malignancies. For the latter, uncertainties due to the observed imbalance of cases occurring in patients treated with cladribine compared to placebo as well as the low number of events remained, although supportive analyses did not support a causal association. Overall, the risk minimisation measures including the safety information in the product information as well as the prescriber and patient guide were considered adequate to address the risks with cladribine treatment, while further data are gathered in the post-marketing setting.

2.7. Risk Management Plan

Safety concerns

Table 31 - Summary of the Safety Concerns

Important Identified Risks	• Severe (Grade ≥ 3) lymphopenia • Herpes zoster infection • Tuberculosis
Important Potential Risks	• Severe infections • Progressive Multifocal Leukoencephalopathy (PML) • Opportunistic infections (other than tuberculosis and PML) • Malignancies • Teratogenicity/adverse pregnancy outcomes
Missing Information	• Use in patients with moderate to severe hepatic impairment • Use in elderly patients • Sequential use of other immunosuppressive or immunomodulatory agents after cladribine treatment • Impact of exposure to prior immunomodulatory/immunosuppressive agents on subsequent risks following cladribine exposure • Long-term safety data in particular for malignancy risk

Pharmacovigilance plan

Table 32 - Table of Ongoing and Planned Additional PhV Studies/Activities in the PV Plan

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns addressed	Status (planned, started)	Date for Submission of Interim or Final Reports (planned or actual)
PREMIERE Registry, (Category 3)	Long-term safety follow-up of patients who have participated in cladribine clinical trials.	To assess the frequency of serious adverse drug reactions, including malignancies and serious infections, to assess the time to resolution of lymphopenia among patients with persistent lymphopenia, to quantify and characterize the risk of AE in the 'Blood and Lymphatic System Disorders' and 'Neoplasms Benign, Malignant, and Unspecified' System Organ Classes (SOCs), and to assess pregnancy outcomes in this population	Ongoing	Study progress updates presenting the course of enrolment along with safety data from the pharmacovigilance database to be submitted with each PSUR/PBRER Registry duration: until 2018, or 8 years after the patient's first enrolment into a cladribine clinical trial, whichever occurs first Clinical Study Report (CSR) planned for 2Q2019
Long-term PASS (Category 3)	Long term, prospective, observational cohort study evaluating the safety profile, in terms of incidence of adverse events of special interest, in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine. The study will also assess the impact of prior use of immunomodulatory/ immunosuppressive agents on the incidence of adverse events of special interest.	To further characterize the safety profile of cladribine in terms of adverse events of special interest (severe lymphopenia, severe infection, herpes zoster infections, tuberculosis, PML and other opportunistic infections, and malignancies). To address the missing information regarding the impact of the prior use of immunomodulatory/ immunosuppressive agents on the incidence of adverse events of special interest.	Planned	Protocol submission within 3 months from the EC decision Study progress updates presenting the course of enrolment along with safety data from the pharmacovigilance database to be submitted with each PSUR/PBRER. Interim results reports planned after 3, 6, 9, and 12 years after start of data collection i.e. anticipated in Q2 2021, Q2 2024, Q2 2027, and Q2 2030, respectively). Final study report planned 1 year at the latest after end of data collection (Q2 2034; taking into account the duration of enrolment and of follow-up).

Study / Activity Type, Title and Category **(1-3)**	**Objectives**	**Safety Concerns addressed**	**Status (planned, started)**	**Date for Submission of Interim or Final Reports (planned or actual)**
Pregnancy PASS (Category 3)	The objectives of the study include the assessment of the occurrence of major congenital abnormalities (MCA), estimation of proportions of pregnancy outcomes, estimation of proportions of alterations in fetal growth and pre-term births in pregnant women exposed to oral cladribine and in pregnancies fathered by male partner exposed to oral cladribine, and comparison of study outcomes with pregnant women with MS not exposed to any DMDs.	Teratogenic potential of cladribine either in pregnant women with multiple sclerosis exposed to oral cladribine or in pregnancies fathered by male partner exposed to oral cladribine. Effects of *in utero* exposure to cladribine on the early life development.	Planned	Protocol submission within 3 months from the EC decision *Note: Biannual feasibility checks will be performed to assess the number of pregnant women captured in each of the selected databases, bi-annually during the first two years after launch and then annually.* Start of data collection (date of the first data analysis): for a specific database: as soon as data on at least 25 pregnant women will be available, the first analysis will be performed. In addition, the analysis will be repeated each time at least 25 additional pregnant women would have been captured End of data collection (date of the last data analysis): once the study has included 150 pregnant women overall in the selected databases or 5 years after the first feasibility check in each of the databases, if the targeted sample size cannot be reached, whichever occurs first. Final study report: planned at the latest one year after the date of the last data analysis (anticipated in Q1 2028).

Risk minimisation measures

Table 33 - Summary Table of the Risk Minimisation Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Severe (Grade ≥ 3) lymphopenia	Wording in EU SmPC section 4.2, 4.4, 4.5, 4.8; PL section 2, 4	Educational material to be provided to prescribers and to patients to ensure compliance to hematological testing and treatment requirements with respect to lymphopenia
Herpes zoster infections	Wording in EU SmPC section 4.3, 4.4, 4.8; PL section 2, 4	Educational material to be provided to prescribers and to patients to ensure awareness of signs and symptoms suggestive for a herpes zoster infection.
Tuberculosis	Wording in EU SmPC section 4.2, 4.3, 4.4; PL section 2	Educational material to be provided to prescribers and to patients to ensure awareness of the risk of tuberculosis.
Important Potential Risks		
Severe infections	Wording in EU SmPC section 4.3, 4.4; PL section 2	Educational material to be provided to prescribers and to patients to ensure awareness of signs and symptoms suggestive for severe infections.
Progressive Multifocal Leukoencephalopathy (PML)	Wording in EU SmPC section 4.2, 4.3; 4.4, PL section 2	Educational material to be provided to prescribers and to patients to ensure awareness of signs and symptoms suggestive PML.
Opportunistic infections (other than PML and tuberculosis)	Wording in EU SmPC section 4.2, 4.3, 4.4; PL section 2	Educational material to be provided to prescribers and to patients to ensure awareness of signs and symptoms suggestive for opportunistic infections
Malignancies	Wording in EU SmPC section 4.3, 4.4; 4.8; PL section 2	Educational material to be provided to prescribers and to patients to ensure awareness on the potential risk of malignancies; to ensure that risk minimization measures s such as standard cancer screening are applied.
Teratogenicity/adverse pregnancy outcomes	Wording in EU SmPC section 4.3, 4.4, 4.6, 5.3; PL section 2	Educational material to be provided to prescribers and to patients to emphasize the need for effective contraception due to the potential risk of teratogenicity.
Missing Information		

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Use in patients with moderate to severe hepatic impairment	Wording in EU SmPC section 4.2 4.4; PL section 2	Not applicable
Use in elderly patients	Wording in EU SmPC section 4.2	Not applicable
Sequential use of other immunosuppressive or immunomodulatory agents after cladribine treatment	Wording in EU SmPC section 4.4; PL section 2	Not applicable
Impact of prior exposure to immunomodulatory/immunosuppressive agents on subsequent risks following cladribine exposure	Wording in EU SmPC section 4.4 ; PL section 2	Not applicable
Long-term safety data in particular for malignancy risk	Not applicable	Not applicable

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 (dated 18 June 2017) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on the difference in the patient population compared to approved cladribine products (hairy cell leukaemia) and in light of the risks of severe prolonged lymphopenia and infections, the CHMP is of the opinion that a separate entry in the EURD list for MAVENCLAD is needed, as it cannot follow the already existing entry for cladribine. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 8 July 2010. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Quick Response (QR) code

A request to include a QR code in the labelling for the purpose of providing a link to a website as a resource for patients to access relevant information has been submitted by the applicant and has been found acceptable. The following elements have been agreed to be provided through a QR code: Package leaflet, and educational material and link to additional patient support services.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

MAVENCLAD was initially proposed for the treatment of adult patients with highly active RRMS as defined by clinical or imaging features. During the course of the procedure the indication was revised to adult patients with highly active RMS. High disease activity (HDA) patients were defined taking into account clinical and MRI criteria as previously used for DMDs approved in MS patients with HDA (fingolimod and natalizumab) and included patients with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other DMDs or patients with 2 or more relapses in the previous year, whether on DMD treatment or not.

MS is an inflammatory neurodegenerative disorder of the CNS which involves demyelination and neuronal loss resulting in neurological impairment and severe disability. In approximately 85% of patients, the disease initially presents as a relapsing, episodic disorder with gradual complete or incomplete recovery (RRMS). The aim of the treatment is to suppress relapses and delay disease progression.

3.1.2. Available therapies and unmet medical need

In addition to treatments for MS symptoms as well as acute relapses, there were 12 approved DMDs for the treatment of patients with RRMS and/or other forms of RMS in the EU at the time of this report. Therapy of patients with active disease is usually initiated with treatments with modest effect and more benign safety profile (e.g. IFN-ß, glatiramer acetate, or teriflunomide). If the treatment response is unsatisfactory, treatment alternatives with high efficacy and more unfavourable safety profile can be used such as

natalizumab, alemtuzumab or fingolimod. The latter treatments are also authorised and used to initiate treatment in patients with HDA.

Despite available treatment alternatives for RRMS patients there is a need for additional highly effective treatments with improved safety profile and convenient administration regimen in order to increase treatment compliance.

3.1.3. Main clinical studies

Four randomized, double-blind, placebo-controlled phase II/III studies have been provided in support of the present application for cladribine.

The pivotal Phase III study CLARITY along with its 2-year extension CLARITY EXT were randomized, double-blind, placebo-controlled trials evaluating the efficacy and safety of cladribine in patients with RRMS over a period of 2 years (96 weeks). A total of 1,326 patients were randomized in CLARITY and assigned to one of three treatment arms (low cumulative cladribine dose 3.5mg/kg, high cumulative cladribine dose 5.25mg/kg or placebo). Of these, 806 patients continued into CLARITY EXT to receive either placebo or low dose cladribine (3.5mg/kg) over an additional period of 2 years. Five treatment groups were investigated: LLPP (3.5 mg/kg during CLARITY, placebo in CLARITY EXT), HLPP (5.25 mg/kg during CLARITY, placebo in CLARITY EXT), LLLL (3.5 mg/kg during CLARITY, 3.5 mg/kg in CLARITY EXT), HLLL (5.25 mg/kg during CLARITY, 3.5 mg/kg in CLARITY EXT) and PPLL (placebo during CLARITY, 3.5 mg/kg in CLARITY EXT). Efficacy was evaluated based on both clinical and imaging parameters. The primary endpoint in CLARITY was ARR at 96 weeks. Secondary endpoints included time to sustained change (pre-defined at 3 months) in EDSS score over the course of the study as well as various MRI measures. Efficacy was an exploratory objective in CLARITY EXT; the main purpose of the extension study was to investigate long-term safety of cladribine.

Additional supportive data were available from the Phase II, multicenter, double-blind, randomized study ONWARD which aimed at evaluating the safety, tolerability, and efficacy of oral cladribine as an add-on to IFN-β treatment in subjects with RMS (RRMS and SPMS with relapses) who had experienced a sub-optimal treatment response to IFN-β monotherapy. Furthermore, data were presented from ORACLE MS, a 96 week Phase III, multicenter, double-blind, randomized, placebo controlled study to evaluate the efficacy and safety of oral cladribine in subjects with early disease who had experienced a first clinical demyelinating event and were at high risk of converting to definite MS.

3.2. Favourable effects

In the pivotal CLARITY study, the primary endpoint was met for both doses of cladribine. The ARRs were 0.15 (95% CI: 0.12, 0.17) for cladribine 5.25 mg/kg, 0.14 (95% CI: 0.12, 0.17) for cladribine 3.5 mg/kg, and 0.33 (95% CI: 0.29, 0.38) for placebo. The difference between both active arms and placebo were statistically significant ($p<0.001$). For the secondary endpoint, 3-month sustained change in EDSS score over 96 weeks, the hazard ratios (HR) were 0.67 (95% CI: 0.48, 0.93, $p = 0.018$) and 0.69 (95% CI: 0.49, 0.96, $p=0.026$) for cladribine 3.5 mg/kg and 5.25 mg/kg, respectively, compared to placebo. *Post-hoc* analysis defining the timeframe of sustained disease progression at 6-months in line with the MS Guideline resulted in HRs compared with placebo of 0.53 (95% CI: 0.36, 0.79, $p=0.0016$) and 0.68 (95% CI: 0.47, 0.97, $p=0.0332$) for cladribine 3.5 mg/kg and 5.25 mg/kg respectively. Secondary MRI-related endpoints included the mean number of active T1 Gd+-enhanced 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 (all measured at 96 weeks). For all

imaging endpoints, a statistically significant difference between active treatment (both doses) and placebo was found (p<0.001 for all comparisons). There were no differences between the cladribine doses.

Post hoc analyses in high disease activity (HDA) patients were conducted using 4 different, although overlapping subgroup definitions (HDA1-4). Across all subgroups, HDA patients had more pronounced effects than non-HDA patients for both ARR and time to disability progression, but not for MRI and NEDA endpoints where there was no difference. For the primary endpoint ARR, HDA patients treated with cladribine 3.5 mg/kg had a relapse rate of 0.16-0.22 versus 0.47-0.57 in HDA patients treated with placebo. The relative risk ranged from 0.32 to 0.38. In the non-HDA subgroups treated with cladribine 3.5 mg/kg, the relapse rate was 0.13-0.14 versus 0.29-0.30 in the non-HDA placebo groups. The relative risk was 0.43-0.49. While there was a trend of a larger effect size with cladribine 3.5mg/kg in HDA patients compared non-HDA patients throughout all 4 subgroups, the differences did not reach statistical significance.

With regards to disability progression, patients treated with cladribine 3.5 mg/kg and having high disease activity defined by at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions, OR 2 or more relapses in the previous year regardless of previous treatment status (subgroup HDA4) had lower HRs (HR = 0.28; 95%CI: 0.15, 0.54) compared to the HR in the non-HDA4 patients (HR = 0.8; 95% CI: 0.55, 1,17) for time to 3 months confirmed EDSS disability progression. The difference was statistically significant (p=0.0079). For time to 6-months confirmed disease progression, the HR was 0.18 (95%CI: 0.07; 0.43) for HDA4 patients and 0.82 (95% CI: 0.51, 1.30) for non-HDA4 patients (p=0.0037).

In the extension study CLARITY EXT, exploratory efficacy analyses were conducted including ARR: LLPP 0.15 (97.5% CI: 0.09, 0.21), HLPP 0.13 (97.5% CI: 0.08; 0.19), LLLL 0.10 (97.5% CI: 0.06; 0.13), HLLL 0.12 (97.5% CI: 0.08; 0.16) and PPLL 0.10 (97.5% CI: 0.07; 0.13). Comparison of the ARRs observed in CLARITY and CLARITY EXT as well as across the treatment groups in CLARITY EXT showed no clinically meaningful difference for any of the comparisons, with the only exception, as expected, for the group of patients switching from placebo in CLARITY to low dose cladribine in CLARITY EXT. For these patients the ARR was reduced from 0.33 (at the end of CLARITY) to 0.10, which is in the range of the effect observed for the active treatment arms in CLARITY (see above). No clear pattern in the proportion of subjects with or without 3-month confirmed EDSS progression was observed.

In the ONWARD study, the rate of relapses was 0.12 in the cladribine 3.5 mg/kg + IFN-β group and 0.32 in the placebo + IFN-β group. The relative risk was 0.37 (95% CI: 0.22, 0.63; p<0.001). Subgroup analyses in patients with SPMS and superimposed relapses showed a statistically significant reduction in ARR with cladribine 3.5mg/kg (ARR=0.03) compared to placebo (ARR=0.30) with a risk ratio of 0.11 (95% CI: 0.01; 0.94). Furthermore, an analyses of the combined CLARITY + ONWARD patient population using baseline EDSS ≥ 3.5 as a proxy for SPMS (or high risk of transitioning to SPMS) showed no meaningful differences when comparing patients who entered the study with a baseline EDSS ≥ 3.5 and the complementary subgroup having a baseline EDSS ≤ 3.

In the ORACLE study, the estimated HR for CDMS conversion was 0.354 (95% CI: 0.226, 0.555; p<0.0001) for the cladribine 3.5 mg/kg group vs the placebo group. The estimated HR for the time to CDMS conversion was 0.414 (95% CI: 0.269, 0.639; p<0.0001) for the cladribine 5.25 mg/kg group versus the placebo group.

3.3. Uncertainties and limitations about favourable effects

The evaluation of the efficacy of cladribine in patients with high disease activity mainly relied on *post hoc*

subgroup analyses in the CLARITY study. Patients recruited into CLARITY appeared to have generally mild disease, which is reflected in the low ARR in the placebo group (0.33), which was somewhat lower compared to the ARR in the placebo group of clinical trials with recently approved DMDs. As a consequence, the proportion of patients fulfilling the 4 HDA definitions was limited with the largest number patients (n=437, 33%) fulfilling the criteria of subgroup HDA4 (patients with at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions, OR 2 or more relapses in the previous year regardless of previous treatment status). However, despite this limitation, a trend for an increased effect in patients with HDA was observed both for reduction in ARR as well as for time to confirmed EDSS progression as compared to non-HDA patients.

Experts consulted during the course of the procedure pointed out that some of the shortcomings in the clinical trial program of CLARITY may be due to the fact that the pivotal study was initiated several years ago, whereby in the meantime the therapeutic landscape has changed. For example an active comparator would have been desirable to put into perspective the benefits of cladribine. Furthermore, since the conception of CLARITY, guideline requirements have changed including the assessment of sustained disability progression over a period of 6 months rather than 3 months (as pre-defined in CLARITY).

The CHMP also noted that results from CLARITY EXT were only exploratory and should thus be interpreted with caution. However, the results suggest that there was no added benefit with retreatment in years 3 and 4. In addition, for the MRI endpoints the interpretation of the results is hampered by the fact that there were different numbers of MRI scans for CLARITY and the CLARITY EXT studies as well as a considerable proportion of missing data for certain analyses. The results of the MRI endpoint are, however, not pivotal for the benefit/risk assessment. It is currently not clear how the treating physicians would handle reoccurrence of disease activity. The applicant agreed to further investigate recurrence of disease activity and how this is handled post-authorisation as part of the planned long-term cohort PASS.

Only a limited number of patients older than 55 years (n=32) was included in the clinical development program of cladribine. Given that recently, it was demonstrated that natalizumab is more effective in younger patients compared to the older ones (Matell et al., 2015), the question arose if a similar age effect was present for cladribine. However, subgroup analyses in patients aged ≤50 years (n=1155) compared to patients >50 years (n=171) showed beneficial effects of cladribine 3.5 mg/kg and 5.25 mg/kg in both age groups in line with the results for the overall study population.

With regards to the ONWARD study, the study was not designed for a formal proof of efficacy and therefore likely not adequately powered for efficacy evaluation. In particular, subgroup analyses in SPMS patients with superimposed relapses were based on very low numbers of patients. The small number of patients and events may explain to some extent that no difference in the effect on disability progression between treatment groups was observed.

3.4. Unfavourable effects

Overall, the integrated safety database comprised a total of 8650 PY of exposure to cladribine (exposure and follow-up) and 2361 PY of exposure to placebo.

The most frequently occurring AEs belonged to the MedDRA SOC of Blood and Lymphatic System Disorders and Infections and Infestations. TEAEs were generally more frequent among the cladribine-treated patients compared to the placebo-treated patients and there was a dose-depended increase in the rate of patients

with at least 1 TEAE. No major difference in the AE profiles of HDA compared to non-HDA patients was observed.

Cladribine induced a 42% reduction of median lymphocyte counts during treatment year 1. Lymphopenia developed within weeks (nadir at Week 16 after start of treatment in year 1) and persisted for a prolonged period of time (mean duration of Grade ≥3 Lymphopenia in the cladribine 3.5mg/kg group in CLARITY was 5.4 weeks) with signs of gradual recovery in most patients. In a small subset of patients, however, values remained well below baseline even after 240 weeks of follow-up. Patients treated with cladribine generally had more severe lymphopenia compared to placebo. Lymphopenia was consistently dose-dependent across the clinical programme of cladribine and re-exposure in years 3 and 4 was associated with an increase in the incidence rates of lymphopenia (Adj-AESI per 100PY of 1.94 in the cladribine 3.5mg/kg re-exposed group and 1.82 in the cladribine 5.25 mg/kg re-exposed group, Monotherapy Oral chohort).

The overall incidence of infections was approximately about 25 events per 100 patient-years in the 3.5 mg/kg group and was not more frequent in the cladribine group compared to placebo. However, both severe and serious infections per 100 PY were observed more frequently in cladribine treated patients compared to placebo; adj-SAE per 100 PY in the All Exposed Cohort was 0.64 (placebo) vs. 0.94 (cladribine). Furthermore, herpes zoster occurred more frequently in patients treated with cladribine compared to placebo (adj-AE per 100PY of 0.20, 0.83, 0.84 for placebo, cladribine 3.5mg/kg, and cladribine 5.25mg/kg). Overall, Grade 3-4 lymphopenia has been associated with about a two-fold increased risk for infections, e.g. for opportunistic infections and herpes zoster, the rates were 1.72 and 2.16 per 100 PY in patients receiving cladribine 3.5mg/kg with severe lymphopenia and 1.03 and 0.75 in patients receiving cladribine 3.5mg/kg without severe lymphopenia.

Overall, 3 cases of tuberculosis (1 fatal tuberculosis, 2 non-fatal pulmonary tuberculosis) have been seen in endemic areas before the introduction of tuberculosis screening and no cases thereafter. Furthermore, two cases of hepatitis B (one fatal, which was newly acquired during the study, one non-fatal) were seen. Based on these data, a possible role of cladribine in the potential reactivation of pre-existing latent infections cannot be ruled out. There were furthermore three deaths due to infections among cladribine treated patients vs. zero in the placebo groups, including one case of herpetic meningoencephalitis. So far, no cases of PML have been seen in MS patients.

To address the risk of severe prolonged lymphopenia and associated infectious diseases, the applicant has introduced (re)-treatment guidelines for lymphopenia in the clinical programme and since their introduction, the duration of grade 3-4 lymphopenia has been reduced from a mean of 5.4 months to 3.0 months and the incidence of grade 4 lymphopenia was reduced to 0.4% (ORACLE MS). Furthermore, educational material in form of a prescribers and patient guide was agreed.

There was furthermore a numerical imbalance for malignancies throughout the cladribine development programme, including 33 adjudicated malignant events in 32 patients in the cladribine group versus 4 in the placebo group in the All Exposed cohort. The comparison of malignant adjudicated tumours based on patient-years at risk for cladribine versus placebo yields a risk ratio of 2.2 (95% CI 0.78-6.22). The risk was increased 3-fold when only considering solid tumours excluding NMSC in the cladribine group as compared to placebo (RR of 3.3 95% CI 0.78; 13.92).

3.5. Uncertainties and limitations about unfavourable effects

Cladribine has clear immunosuppressive effects and acts as an antimetabolite. In this context the numerical

imbalance for malignancies caused concerns. In particular, the RR for solid tumours excluding NMSC (3.29) and solid tumours excluding all skin cancers (2.87) disfavoured cladribine.

Based on experience e.g. from solid organ transplantation, profound immunosuppression over long term is expected to give rise to a major increase in NMSC (x20-40) and a modest increase in solid tumours (x2-4). Furthermore, certain adaptive immune cells, specifically CD8+ T cells and Th1-polarized CD4+ T cells, both of which are suppressed by cladribine, have been shown to exert antitumor effects, particularly in relation to solid tumours. Virus-related tumours, such as cervical cancer, are also expected to be more common in this setting. Cladribine data however only showed a slight increase in the risk for all skin cancers (RR 1.51) and NMSC was not increased (risk ratio 1.09). There was a 3-fold increase in the risk of solid tumours, but no increase in virus related tumours and any clear clustering of specific tumour types. In addition, no association between malignancy cases and prior experience of lymphopenia of Grade ≥3 was seen. The pattern thus clearly deviates from what is expected for an immunosuppressive compound. Furthermore, there were no malignancies of cell types which are mostly affected by cladribine's mechanism of action (ie, lymphocytes).

With regards to solid tumours, epidemiological data seem to indicate that the incidence in the placebo control is lower than expected, while the number of malignancies seen with cladribine was as expected. Furthermore, the majority of the cancers observed occurred within the first 4-5 years after treatment. A constant malignancy incidence rate was observed for cladribine in Years 1 to 4 and in the period thereafter. In contrast, the incidence rates observed for placebo increased over time. After year 4, the incidence of cancer was 0.38 per 100 PY in the cladrbine group vs. 0.57 per 100 PY in the placebo group. However, the duration of follow up in the placebo group is limited. Overall, it was considered reassuring that the incidence of malignancies in the cladribine group does not increase over time.

Time from exposure to cancer diagnosis seems shorter than would have been expected from a true cancer induction by cladribine and the pattern regarding time to occurrence and types of malignancies with a high variety and mostly single cases may be more compatible with unspecific promotion of already induced malignancies.

Taking all the available evidence into account, the CHMP was of the view that it was not possible to rule out an increased risk of malignancies with cladribine. In light of the uncertainties, the CHMP considered that additional data would be needed post-authorisation. To enable the generation of conclusive data on the long-term cancer risk of cladribine, an additional study should be conducted where long-term treatment with cladribine is compared to an active comparator. This was agreed by the applicant who will conduct a post-authorisation safety study, where cladribine will be compared to fingolimod over a period of 15 years.

Furthermore, in the cladribine development programme, only about 25% of subjects were exposed to other MS-DMDs, of which the vast majority was exposed to IFN-β or glaritamer acetate and very few to other immunosuppressants or immunomodulators, prior to treatment with cladribine. Likewise, subsequent to cladribine treatment, most patients received the same types of first-line MS-DMDs. Thus, there is limited experience from sequential treatment with various types of MS-DMDs including those that act primarily via immunosuppression or immunomodulation, such as natalizumab, fingolimod, dimethyl fumarate, or alemtuzumab. Sequential use of various MS-DMDs may substantially increase the risk for development of malignancies and opportunistic infections such as PML. Therefore, sequential use of cladribine and other immunosuppressive or immunomodulatory agents is further studied after approval as part of the long-term PASS. This was supported by neurology experts consulted in the course of the procedure.

Finally, there were 38 patients treated with cladribine experienced 44 pregnancies despite pregnant or lactating women being excluded from all studies. No malformations or adverse pregnancy outcomes were

observed that were attributable to cladribine exposure. However, only very limited data were available for pregnancies during cladribine treatment up until 6 months thereafter. Given the teratogenic effect observed in non-clinical trials with mice and rabbits and in light of cladribine's mechanism of action, teratogenicity was considered a potential risk and use in pregnant women is contraindicated. A pregnancy registry will be established to gather additional data in the post-authorisation phase. Furthermore, the prescriber and patient guide will advise on the risks and recommend use effective contraception.

3.6. Effects Table

Table 34 Effects Table for MAVENCLAD for the treatment of patients with highly active relapsing multiple sclerosis

Effect	Short Description	Unit	Cladribine 3.5mg/kg (low dose)	Cladribine ≥5.25mg/kg[1] (high dose)	Placebo	Uncertainties / Strength of evidence
Favourable Effects						
Annualised Qualifying Relapse Rate	Frequency of relapses observed over 96 Weeks, corrected for time (i.e. yearly)	Mean rate Overall[2] HDA1-4 population [2, 3] Long-term data[4]	0.14 0.16-0.22 LLPP: 0.15 PPLL: 0.10	0.15 0.14-0.19 HLPP: 0.13 LLLL: 0.10 HLLL: 0.12	0.33 0.47-0.57 N/A	*Overall RR (SE) vs. placebo:* • 3.5 mg/kg: 0.43 (0.12), p<0.001 • 5.25 mg/kg: 0.43 (0.11), p<0.001 *HDA1-4 RR - range of point estimates (SE) vs. placebo:* • 3.5 mg/kg: 0.32 - 0.38, p<0.0001 • 5.25 mg/kg: 0.25 – 0.39, p<0.0001 Results from CLARITY EXT (long-term data) are only exploratory. *RR for SPMS subgroup in ONWARD (3.5mg/kg vs placebo)*: 0.11 (95% CI: 0.01; 0.94)

Effect	Short Description	Unit	Cladribine 3.5mg/kg (low dose)	Cladribine ≥5.25mg/kg[1] (high dose)	Placebo	Uncertainties / Strength of evidence
Disability progression[2]	Time to sustained change in EDSS ≥ 1 point, or ≥ 1.5 points if baseline EDSS was 0, over a period of	% of patients (10th percentile, days)				*3 months HR (SE) vs. placebo:* 3.5 mg/kg: 0.67 (0.17), p=0.018 5.25 mg/kg: 0.69 (0.17), p=0.026
	- at least 3 months		13.4% (414)	13.6% (414)	18.8% (330)	*6 months HR (95%CI) vs. placebo:*
	-at least 6 months		9.0% (NE)	11.6% (433)	15.8% (245)	3.5 mg/kg: 0.53 (0.36;0.79), p=0.0016 5,25 mg/kg: 0.68 (0.47;0.97), p=0.0332
MRI brain lesions[2]	Mean Number of Active T2 Lesions per Subject per Scan at 96 weeks	Mean (SD)	0.35 (0.66)	0.29 (0.56)	1.38 (2.11)	*Treatment differences (SE) vs. placebo:* 3.5 mg/kg: -1.05 (0.09), p<0.001 5.25 mg/kg: -1.10 (0.09), p<0.001
Unfavourable Effects[5]						
Lymphopenia	- All events	Adj-AE per 100PY %	12.6	7.9	1.1	
	- Grade 3-4 events		25.4	45.1	1.2	
	- Serious events		0.1	0.12	0	
Infections	- All events		28.3	24.9	27.1	Serious events in All-Exposed Cohort 0.94 (3 pts with reactivation of latent infections with fatal outcome); Placebo 0.64 (0 pts with reactivation of latent infections with fatal outcome)
	- Serious events		0.7	0.7	0.5	
Herpes zoster	- All events		0.83	0.84	0.20	
	- with lymphopenia Grade 3-4		2.16	2.01	0	
	- without lymphopenia Grade 3-4		0.75	0.76	0.20	

Effect	Short Description	Unit	Cladribine 3.5mg/kg (low dose)	Cladribine ≥5.25mg/kg[1] (high dose)	Placebo	Uncertainties/ Strength of evidence
Opportunistic infections	- All events		0.84	1.08	1.17	
	- with lymphopenia Grade 3-4		1.72	1.72	0	
	- without lymphopenia Grade 3-4		0.86	1.03	1.14	
Malignancies[6]	All events		0.37		0.17	Risk ratios RR (95% CI)
	Solid tumours excluding NMSC		0.28		0.08	- All cancers: 2.20 (0.78; 6.21) - Solid tumours excl NMSC : 3.29 (0.78; 13.92)

Abbreviations: Adj AE = Time adjusted adverse event incidence rate; DMD = Disease Modifying Drug; HDA = High Disease Activity; HR = Hazard Ratio; MRI = Magnet Resonance Imaging; N/A = not applicable; NE = not estimable; NMSC = Non-melanoma skin cancer; SD = Standard Deviation; PY = Patient Years; RR = Relative Risk.

[1] In addition to 3.5mg/kg, a cumulative dose of 5.25mg/kg was investigated in study 25643 (CLARITY). Study 27820 (CLARITY EXT Study) furthermore investigated cumulative doses up to 8.75mg/kg. Data in this column refer to a cumulative dose of 5.25mg/kg with the exception of the results from CLARITY EXT for the annualised relapse rate (dosing groups HLPP, LLLL and HLLL, see definition below).

[2] Based on results from study 25643 (CLARITY).

[3] The range of point estimates and relative risks is provided across the 4 HDA subgroups analysed(see below).

[4] Based on results from study 27820 (CLARITY EXT Study); see definition of study groups below.

[5] Integrated safety analysis based on Monotherapy Oral Cohort unless stated otherwise.

[6] Integrated safety analysis based on All Exposed Cohort.

Definitions:

HDA subgroups in CLARITY:

HDA1= Subjects with at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions, OR subjects with 2 or more relapses in the previous year (no prior use of DMD at any time in patient history or duration of previous DMD therapy less than 1 year) and at least 1 T1 Gd+ lesion.

HDA2= Subjects with 2 or more relapses in previous year (regardless of previous treatment status).

HDA3= Subjects with 2 or more relapses in previous year (regardless of previous treatment status), AND at least: 1 T1 Gd+ lesion OR 9 T2 lesions.

HDA4= Subjects with at least 1 relapse in the previous year while on DMD therapy and at least 1 T1 Gd+ lesion or 9 T2 lesions, OR Subjects with 2 or more relapses in the previous year (regardless of previous treatment status).

Dosing groups in CLARITY EXT:

HLPP (high dose during Study 25643 and placebo during Study 27820); LLPP (low dose during Study 25643 and placebo during Study 27820); HLLL (high dose during Study 25643 and low dose during Study 27820); LLLL (low dose during Study 25643 and low dose during Study 27820); PPLL (placebo during Study 25643 and low dose during Study 27820)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For patient with RRMS, a clinically relevant benefit has been shown with cladribine. This was evident from the pivotal CLARITY study where a statistically significant and clinically relevant effect on ARR and time to 3 months and 6 months confirmed EDSS progression (e.g. HR of 0.53 for 6-months sustained change in EDSS score with cladribine 3.5mg/kg) over placebo was shown. The observed reduction in ARR by 57% with cladribine 3.5mg/kg compared to placebo is similar to efficacy results of some other drugs used for treatment of RRMS patients including those indicated for active or highly active disease (e.g. alemtuzumab and fingolimod) with the exception of natalizumab which offers approximately 70% reduction of ARR. It is acknowledged though that the indirect comparison of observed results in different studies is confounded by the limitations associated with cross-study comparisons. The *post hoc* analysis in patients with high disease activity also showed a clear and clinically relevant difference in relapse rate and disease progression compared to patients who did not have high disease activity, although cladribine is also effective in the latter population, which is reassuring. The observed reduction in ARR (62-68%) in high disease activity patients was larger than in the overall study population.

The findings in CLARITY are to some degree supported by the data from CLARITY EXT, although the results from this study should be interpreted with caution, as efficacy was only an exploratory objective. Even if the efficacy data from the CLARITY EXTENSION study from a methodological point of view are not strong, the clinical efficacy data, in general, point in the same direction and show that the effect of cladribine treatment at the beginning of year 1 and 2 is sustained for at least an additional 2 years without any further treatment. The data showed that additional treatment cycles do not provide additional benefit but instead add significant toxicity in term of prolonged severe lymphopenia, more serious infection as well as a higher risk of developing malignancies compared to patients treated only in year 1 and 2.

An effect on relapses was furthermore shown in a *post hoc* subgroup analysis in patients with SPMS to a similar extent as in RRMS patients. This finding was supported by analyses in patients with baseline EDSS ≥ 3.5 as a proxy for SPMS (or high risk of transitioning to SPMS). These data support a benefit in patients with RMS and thus a broadening of the originally proposed indication in RRMS.

Despite available treatment alternatives for RMS patients, there is a need for additional highly effective treatments with improved safety profile and convenient administration regimen in order to increase treatment compliance. In this context, the oral administration of cladribine in two courses separated by 12 months, requiring no further treatment at least for a period of 4 years, was considered an advantage. This was supported by experts and patient representatives consulted during the course of this procedure.

With respect to the safety profile, cladribine causes prolonged and severe lymphopenia coupled with an increase in the rate of serious and severe infections including opportunistic infections associated with lymphopenia. However, there were no deaths after implementation of the retreatment guidance. In addition, there was a numerical imbalance with regards to deaths caused by infections. These findings were not surprising given the mechanism of action of cladribine. Overall, the risk was considered manageable based on the implementation of haematological criteria for (re-)treatment and with screening for latent infections, and instigation of anti-herpes prophylaxis in case of Grade 4 lymphopenia.

There was also an imbalance in the rate of malignancies with a 2-3 fold increased risk observed for cladribine compared to placebo. This imbalance creates an uncertainty, although the number of cases was overall small

in particular in light of the large safety database. However, the strength of this signal is questioned based on pattern regarding time to occurrence (with the majority of the cancers occurring within the first 4-5 years after treatment and with the magnitude of the risk not increasing over time) and types of malignancies, which seemed to be more compatible with unspecific promotion of already induced malignancies. However, firm conclusion regarding the observed imbalance in the incidence of malignancies remained largely speculative and an increased cancer risk with cladribine could not be excluded at the time of this report. A post-authorisation safety study will be conducted to provide data for cladribine versus fingolimod and this may shed more light on the malignancy risk of cladribine.

3.7.2. Balance of benefits and risks

A clinically relevant benefit of cladribine treatment has been demonstrated in RMS patients both in terms of reducing the relapse rates and delaying disease progression. A trend towards a greater treatment benefit has been observed in a population with high disease activity and for this population the benefits of treatment were considered to outweigh the risks of severe prolonged lymphopenia and infections, as well as remaining uncertainties pertaining to the increased rate of malignancies seen with cladribine. This also took into account the benefits of an oral treatment only requiring two short (4-5 days) courses of treatment separated by 12 months and with a maintained effect of 4 years. A Scientific Advisory Group consulted during the course of the procedure supported this position.

Overall, the benefit/risk balance of cladribine in the treatment of adult patients with highly active relapsing multiple sclerosis as defined by clinical or imaging features was considered favourable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of MAVENCLAD is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of MAVENCLAD is favourable in the following indication:

MAVENCLAD is indicated for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of MAVENCLAD (cladribine) in each Member State (MS) the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials (EM), including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each MS where MAVENCLAD is marketed, all prescribers and patients who are expected to prescribe / use MAVENCLAD are provided with:

- The Prescriber Guide
- The Patient Guide

The **Prescriber Guide** should include:

- An introduction to MAVENCLAD, reminding the prescriber to consider the Patient Guide while discussing MAVENCLAD treatment with the patient, to support the early identification of sign and symptoms of adverse reactions and their timely treatment;
- The treatment regimens;
- A reminder to carefully consider data on blood count monitoring and screening for latent infections before starting the treatment;
- Guidance for patient's monitoring during the treatment;
- Information on pregnancy prevention

The **Patient Guide** should include an introduction to MAVENCLAD treatment, its side effects, potential risks and information on pregnancy prevention.

The **prescriber / patient guide** should include information about the following safety concerns:

- Important identified risks
    1. Severe (Grade ≥ 3) lymphopenia, to ensure compliance to haematological testing and treatment requirements;
    2. Herpes zoster infections, to ensure awareness of signs and symptoms suggestive for these infections;
    3. Tuberculosis, to raise awareness about this risk;

- Important potential risks
    1. Progressive multifocal leukoencephalopathy (PML), opportunistic infections (other than PML and tuberculosis) and severe infections, to ensure awareness of signs and symptoms suggestive of these risks;
    2. Malignancies, to raise awareness on this risk because:
        a. Patients with current active malignancies must not receive MAVENCLAD treatment;
        b. Patients should be advised to undertake standard cancer screening after MAVENCLAD treatment;
    3. Teratogenicity/adverse pregnancy outcomes, to ensure that female patients of child bearing potential / partners of male patients receiving MAVENCLAD:
        a. Receive counselling before starting the treatment (consisting of two treatment courses administered at the beginning of two consecutive years) both in year 1 and 2;
        b. Use effective contraception during the treatment and for at least 6 months after the last dose

It is currently unknown whether MAVENCLAD may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore women of child bearing potential, using systemically acting hormonal contraceptives, should add a barrier method during Cladribine treatment and up to 4 weeks after the last dose.