EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

WITHDRAWAL ASSESSMENT REPORT
FOR
Movectro

International Nonproprietary Name:

cladribine

Procedure No. EMEA/H/C/001197

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

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application.

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Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Serono Europe Limited submitted on 6 July 2009 an application for Marketing Authorisation to the European Medicines Agency for Movectro, 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 Agency/CHMP on 26 January 2009. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of therapeutic innovation.

The applicant initially sought an approval for the use of oral cladribine tablets in the treatment of relapsing forms of multiple sclerosis. During the evaluation, the applicant proposed the following restricted indication:

MOVECTRO is indicated as disease-modifying therapy in relapsing-remitting multiple sclerosis (MS) for the following subjects:

- Patients with high disease activity and/or risk of disease progression defined as those with 2 or more relapses in the previous year and one or more T1 gadolinium-enhancing lesions.

or

- Patients who are intolerant to beta-interferon or glatiramer acetate therapies.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

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.

1.1.1. Information on paediatric requirements

Pursuant to Article 7, of Regulation (EC) No 1901/2006 the application included an Agency Decision P/101/2009 (EMEA-000383-PIP01-08) for the following condition:

- Multiple sclerosis

on the granting of a product-specific waiver,

1.1.2. Information relating to orphan market exclusivity

Not applicable.

1.1.3. CHMP Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.1.4. Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 6 July 2009.
- The procedure started on 22 July 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 October 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 October 2009.
- During the meeting on 16-19 November 2009, 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 20 November 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 March 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 May 2010.
- During the CHMP meeting on 17-20 May 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of outstanding issues on 22 June 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 5 July 2010.
- During the meeting on 19-22 July 2010, the CHMP agreed on the second consolidated List of Outstanding Issues to be sent to the applicant. The final consolidated List of Outstanding Issues was sent to the applicant on 22 July 2010.
- The applicant submitted the responses to the CHMP final consolidated 2nd List of Outstanding Issues on 20 August 2010. As part of the responses, the applicant requested a Conditional Marketing Authorisation in accordance with Article 3(1) of Regulation (EC) No 507/2006.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of outstanding issues to all CHMP members on 7 September 2010.
- During the CHMP meeting on 20-23 September 2010, the list of outstanding issues was addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20-23 September 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Movectro on 23 September 2010.

1.3. Steps taken for the re-examination procedure

- The applicant submitted written notice to the EMA on 8 October 2010 to request a re-examination of Movectro CHMP opinion of 23 September 2010.
- During its meeting on 23 October 2010, the CHMP appointed Rapporteur and Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 23 November 2010. The re-examination procedure started on 24 November 2010.
- During its meeting on 13-16 December 2010, the CHMP adopted the List of Questions to the SAG on Neurology to be held on 12 January 2011. A list of experts for the SAG Neurology meeting was adopted by written procedure on 10 January 2011.
- The Rapporteur's re-examination Assessment Report was circulated to all CHMP members on 22 December 2010. The Co-Rapporteur's re-examination Assessment Report was circulated to all CHMP members on 24 December 2010.
- During a meeting of the SAG on 12 January 2011, experts were convened to consider the grounds for re-examination. During this meeting the applicant presented an oral explanation. A report of this meeting was forwarded to the CHMP.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 14 January 2011.
- During the CHMP meeting on 18 January 2011, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20 January 2011, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the conditional marketing authorisation.

2. Scientific discussion

2.1. Introduction

Movectro is an oral (tablet) formulation of cladribine. Cladribine is a 'purine analogue', a cytotoxic substance belonging to the group of 'antimetabolites'. In the body cladribine is converted within lymphocytes into a chemical called CdATP, which interferes with the production of new DNA. CdATP is incorporated into DNA strands, thereby blocking DNA chain elongation and inhibiting DNA repair and it will inhibit ribonucleotide reductase. Cell death then occurs from energy depletion and apoptosis. Apart from lymphocytes CdATP can also affect other cells, particularly other types of blood cells.

Parenteral cladribine is approved in several countries for the treatment of hairy cell leukaemia (HCL) under various trade names. It has also been approved in some countries for the treatment of chronic lymphoid leukemia (CLL).

Currently, no oral medication is approved for the treatment of relapsing-remitting multiple sclerosis (RRMS); all presently available disease modifying drugs (DMDs) for the management of MS are administered subcutaneously (s.c.), intramuscularly (i.m.), or intravenously (i.v.). An oral formulation of cladribine was developed for evaluation as a disease modifying therapy for MS to avoid the disadvantages associated with the use of parenteral disease-modifying therapies. The applicant initially sought an approval for the use of oral cladribine tablets in the treatment of relapsing forms of MS. During the evaluation, the applicant proposed the following restricted indication:

"MOVECTRO is indicated as disease-modifying therapy in relapsing-remitting multiple sclerosis (MS) for the following subjects:

- Patients with high disease activity and/or risk of disease progression defined as those with 2 or more relapses in the previous year and one or more T1 gadolinium-enhancing lesions.

or

- Patients who are intolerant to beta-interferon or glatiramer acetate therapies."

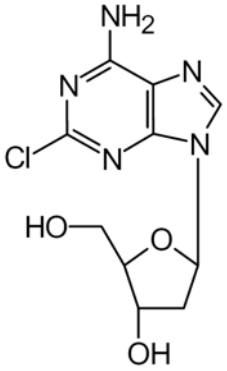
2.2. Quality aspects

2.2.1. Introduction

The product is presented as tablets for oral use containing 10 mg of cladribine as active substance. Other ingredients are defined in section 6.1 of the SPC.
The tablets are packed in Alu/Alu blisters inserted in a child-resistant plastic tablet holder.

2.2.2. Active substance

Cladribine is the common name of chemical substance -Chloro-9-(2-deoxy-β-D-erythro-pentofuranosyl) 9H-purine-6-amine. The molecular formula is C10H12ClN5O3, with a relative molecular mass of 285.69 and the following structural formula:



Cladribine is a synthetic analogue of the purine nucleoside adenosine. It is a known active substance, which is described in an European Pharmacopoeia monograph. Cladribine is a white, non-hydroscopic, crystalline powder. It is slightly soluble in distilled water (5 mg/ml at 20 °C) and in a variety of organic solvents that possess hydrogen bonding capability. Cladribine is stable at high temperatures (85 °C). Cladribine is a molecule with three stereogenic centres. The stereogenic centres in 3´- and 4´-position are given from the deoxyribose (chiral pool), they are definite. For the third stereogenic centre two stereo isomers, 9- α and 9- β stereoisomer, are possible. Cladribine is the 9- β stereoisomer. Cladribine is sufficiently characterised by numerous analytical techniques, its structure is adequately elucidated. It is known that cladribine shows polymorphism. Satisfactory supportive information is provided to support the non-conversion of the polymorphic form after synthesis.

Information on the active substance cladribine is presented in form of an Active Substance Master File.

2.2.2.1. Manufacture

Cladribine is manufactured by a proprietary process. A detailed description of the manufacturing process, including process flow diagram and in-process controls are provided. Sufficient batch analysis data of commercial scale batches of cladribine are presented. The batch analysis data show that the manufacturing process proposed in the ASMF produces batches of drug substance consistently with same quality.

2.2.2.2. Specification

A suitable specification for the drug substance is proposed taking into account the Ph.Eur. monograph for cladribine. Acceptable limits are set based on an adequate number of batch results. Adequate validation data was presented for the in-house analytical methods.

2.2.2.3. Stability

ICH compliant stability studies have been performed in accelerated, intermediate and long-term storage conditions. The following parameters were investigated: appearance, water content, dissolution, assay, related substances and microbiological purity. The stability data provided support the proposed re-test period of 24 months without special storage conditions.
In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

2.2.2.4. Comparability exercise for "Active Substance"

Not applicable

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.2.3. Finished Medicinal Product

2.2.3.1. Pharmaceutical Development

The product is presented as white round, biconvex tablets for oral use containing 10 mg of cladribine as active substance.
The formulation development has been adequately described. Minor modifications of the formulation intended for market have been made in order to get a more robust production process at industrial scale. The comparability of the optimised commercial formulation and the clinical formulation has been reviewed in detail by the applicant.
There are no novel excipients used in the drug product formulation. All the excipients are controlled to the requirements of their current Ph. Eur. monographs.

2.2.3.2. Adventitious agents

The active substance, cladribine, and all excipients are absent of BSE/TSE risk.

2.2.3.3. Manufacture of the product

A detailed description of the manufacture of cladribine 10 mg tablets is provided. The critical steps in the manufacture were identified and adequate in-process control and testing procedures were established. Process validation has been performed on a satisfactory number of batches. Process validation data indicate that the manufacturing process of cladribine 10 mg tablets is capable of consistently producing tablets of suitable quality which meet the release specification.

2.2.3.4. Product specification

The finished product specification includes tests for appearance, description, identification by two independent methods, water content, dissolution, uniformity of dosage units, related substances, assay, and microbiological purity. The proposed specifications include all of the required tests relevant to this dosage form. The limits set are acceptable.
All analytical procedures and test methods have been adequately described and validated.
Batch analysis results are provided for a satisfactory number of commercial scale and pilot scale batches. All batch results are acceptable. All data are well within the proposed specifications.

2.2.3.5. Stability of the product

Stability studies on the drug product were carried out on batches of the clinical formulation and of the optimised formulation intended for market. The blistered tablets were stored at long-term and accelerated storage conditions according to ICH guidelines. No significant tendencies in any of the parameters tested are observed. The proposed shelf-life of 3 years is justified by stability data presented. No labelled storage condition is required.
In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

2.2.3.6. Comparability Exercise for Finished Medicinal Drug Product

Not applicable

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Movectro is adequately established. In general, satisfactory chemical and pharmaceutical documentation have been submitted for the marketing authorisation. There are no major deviations from EU and ICH requirements.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the medicinal product is acceptable. There were no quality outstanding issues on the quality of the active substance or finished medicinal product at the time of Opinion.

2.3. Non-clinical aspects

2.3.1. Introduction

Cladribine is a well-known drug with a proven efficacy in patients with leukemia, especially hairy cell leukemia. As it has been shown that cladribine is able to preferentially deplete lymphocytes, especially T cells it has been suggested to be of potential benefit in the treatment of multiple sclerosis (MS). This has been confirmed in some phase II/III studies, where cladribine was applied parenterally.

The applicant developed an oral formulation with a specific dosage regimen of cladribine for patients with relapsing-remitting MS (RRMS). The pivotal phase III study was conducted using the oral formulation. Safety pharmacology, toxicology and toxicokinetic studies conducted were done in accordance with GLP.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

In the preclinical documentation provided by the applicant the experimental autoimmune encephalomyelitis (EAE) model was chosen as a rodent model for MS in order to assess the potential of cladribine to minimize clinical symptoms of MS. Although this model is often used to assess drugs of potential therapeutic value in MS, no preclinical validated model of MS exists. 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 ip. injections (1mg/kg/day) after induction of EAE. Mice were evaluated daily for clinical signs 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. As clinical symptoms of EAE emerged within ten days after sensitization, immunological and histological samples were collected at day eight ("preclinical phase") and at day fourteen during "clinical phase". Additionally, all mice were evaluated for clinical signs of EAE. In neither of the studies cladribine exerted measurable effects on clinical signs of EAE. It is speculated that this might be due to pharmacogenetic differences affecting PK and PD between rodents and humans. It is hypothesized that the levels of cladribine necessary to suppress the immune response was either not achieved or not sustained for sufficient time to have an effect.

2.3.2.2. Secondary pharmacodynamic studies

Cladribine is structurally related to the endogeneous ligand adenosine. Therefore, the affinity of cladribine for adenosine receptors A1, A2,and A3 as well as the effects on adenosine uptake were investigated under in vitro conditions. Compared to selective ligands for these receptor sites cladribine showed weak affinities to both central adenosine receptors and the adenosine uptake site. Only at a concentration of 10 µM inhibition between 24% - 75% was found. This is well above plasma concentrations seen clinically at 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 hemolytic effects were studied using blood of rabbits. At concentrations between 0.1 – 100 µM the drug was devoid of any effect.

2.3.2.3. Safety pharmacology programme

The package of studies presented in the section safety pharmacology is compliant with ICH S7A and ICH S7B. All safety pharmacology studies conducted were GLP compliant. The tests included the assessment of effects on cardiovascular, respiratory and central nervous system and were supplemented by in gastrointestinal and renal in vivo studies. Generally, both the selected species and the doses/concentrations of cladribine are appropriate to characterize the safety profile of cladribine. The drug does not block the channel current of the hERG channel and did not affect action potential duration at concentrations below 10-4 M. It was found that cladribine administered to monkeys (oral or sc. route) did not affect the duration of the heart rate-corrected QT interval. Therefore, it is concluded that the potential of cladribine to elicit cardiotoxic effects under therapeutic conditions seems negligible. The respiration rate and volume were increased with doses at and above 0.5 mg/kg. Cladribine did not affect various parameters addressing the function of the CNS. Additionally, no effects on gastrointestinal and renal function were seen up to 10 mg/kg iv. The results of the safety pharmacological studies demonstrate that cladribine has an acceptable pharmacological safety profile in animals and has a considerable safety margin compared to doses and exposures intended for human use.

2.3.2.4. Pharmacodynamic drug interactions

Since cladribine is intended as monotherapy no pre-clinical pharmacodynamic drug interaction studies has been performed.

2.3.3. Pharmacokinetics

The pharmacokinetic profile of cladribine was evaluated in vitro as well as in vivo. In vivo PK / TK 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 in PK / TK studies for determination of plasma (mice, rats, rabbit, dog, monkey) urine (monkeys) concentration of cladribine and its major metabolites were validated and main parameters of these methods were assessed. The analysis of the plasma samples from the repeated oral dose toxicity studies (mice and monkeys) were performed in compliance with GLP.

Absorption studies have been done with different formulations of cladribine (cladribine in HPβCD water solution, HPβCD-tablets or capsules, cladribine dissolved in isotonic saline). Absorption was rapid in all species but the absolute bioavailability was clearly different among the species: Moderate values were found in rats (27%) and dogs (45%) and low in monkeys (11%). It should be noted that rapid absorption as well as moderate oral bioavailability has also been found in humans after administration of HPβCD tablets. In the studies it has been shown that after oral, iv. and sc. dosing linear absorption and exposition took place. After repeated administration no accumulation of the parent compound was found. Although cladribine is neither substrate nor inhibitor of the ABC-transporter molecule P-glycoprotein, membrane permeation of cladribine seems to be affected by the nucleoside transporter ABCG2.

After administration of 3H-cladribine, tissue distribution was rapid and large, with a predominance of well-perfused organs and subsequently excretion organs (gastrointestinal tract, kidney and bladder). Drug-drug interactions due to displacement from plasma proteins are not expected. It should be noted that cladribine was able to enter the CSF. Neither in the PK studies nor in the TK studies placental passage has been investigated.

Metabolism studies revealed that cladribine is metabolized only to a small extent by phase I and II enzymes and neither induction nor inhibition of the phase I CYP450 enzymes has been found. Therefore, drug – drug interactions at the level of metabolism are unlikely to occur. The elimination of cladribine after iv. administration was rather slow in dogs and monkeys with a half-life of about 10.3 and 5.7 hours respectively. Half-lives measured after oral administration in dogs and monkeys (13.7 h and 3.6 h respectively) were roughly similar with the ones determined after i.v. administration. Similarly to dogs and monkeys, in humans the terminal half-life for cladribine was found to be comparable after oral dosing (19.7 h) and iv. (18.4 h) administration. The mean systemic clearance after parenteral administration was moderate to high in monkeys (21.5

ml/min/kg; ~50% of liver blood flow); while it was high in rats and dogs with a systemic clearance between 50 and 90 % of the liver blood flow (48.6 and 24.4 ml/min/kg respectively). From the results obtained in mice and humans it becomes clear that urinary excretion is the primary route of elimination with the parent compound being the main substance in urine. A biliar excretion study was not performed.

Studies related to possible drug – drug interactions has been done at the level of absorption and metabolism, respectively. Whereas there is clear evidence neglecting interactions at the level of metabolism the data seem to indicate a possible pharmacokinetic interaction of cladribine with drugs which are substrate of the nucleoside transporter ABCG2. By comparing the oral exposures in mice and monkeys in the repeat dose toxicity studies to human exposure after 10 mg tablet/day safety margins were calculated. It has been found that cladribine exposure in mice at the NOAEL is more than 120 times (Cmax) or 27 times (AUC) higher than that of humans. For monkeys the respective values were 4 (Cmax) and 5 (AUC).

Overall, pharmacokinetic properties of cladribine meet the requirements to support this application.

2.3.4. Toxicology

The non-clinical safety profile of cladribine was evaluated in single and multiple dose studies in both rodent (mice, rats) and non rodent species (dog, cynomolgus monkey). All studies meet the requirements of Good Laboratory Practice (GLP).

2.3.4.1. Single dose toxicity

Single dose toxicity studies have been done with cladribine administered by i.v. 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 96 and 100 mg/kg by iv. and sc. routes, respectively. The main clinical signs observed at these doses consisted of prostration, decrease in activity and pilo-erection. In dogs, no lethality was seen after a single iv. dose of 25 mg/kg (the highest feasible dose). However, foamy emesis occurred in most dogs dosed at 25 mg/kg.

2.3.4.2. Repeat dose toxicity (with toxicokinetics)

Toxicokinetic investigations were performed in repeated dose toxicity studies in mice and cynomolgus monkey after both parenteral and oral administration. These animal species were considered appropriate for the non-clinical safety evaluation of this compound due to similarities in plasma deoxycytidine levels compared to humans. Generally, the toxic effects observed in mice and monkeys are dose-dependent and reversible. The main symptoms were anemia, leucopoenia, 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 effect on the kidney (kariomegaly 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, nervous system 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 NOAEL versus the projected human exposure at the anticipated oral clinical dose in MS indication (i.e. 10 mg tablet/day corresponding to 0.175 mg/kg/day for a person of around 55-60 kg). Since the toxicity of cladribine in humans appears to be related to the total cumulative dose (i.e. about 200 mg/year corresponding to about 3.5 mg/kg/year for a person of around 55-60 kg), safety margins were also evaluated based on cumulative exposure ratios. In conclusion, submitted repeat dose toxicological evaluation of cladribine is considered sufficient.

2.3.4.3. Genotoxicity

The genotoxic potential of cladribine was tested in standard in vitro and in vivo tests. Cladribine effectively inhibits DNA repair and causes DNA double strand breaks. It therefore is considered to

be mutagenic which is reflected in the in vivo micronucleus assay and has also to be considered a potentially germ cell mutagen.

2.3.4.4. Carcinogenicity

Cladribine was tested for its carcinogenic potential in a single 22 month study in mice only due to the differences in toxicokinetic and pharmacological parameters in rats compared to other species including humans. Additionally a transgenic bioassay in TgrasH2 was conducted. A significant increase in Harderian gland tumours was observed in the long term mouse study. Although the majority of the tumours were benign adenomas there were also three adenocarcinomas in the high dose group. 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). The negative transgenic bioassay in TgrasH2 mice without any sign of harderian gland alteration further added to the conclusion that the harderian gland tumors are considered clinically irrelevant. The complete report of the TgrasH2 bioassay showed no evidence for a carcinogenic potential of cladribine in mice. Preliminary tumour findings of the range finder study are not confirmed and are considered as having occurred by chance. This study was performed with the intended oral route of application and included a ßcyclodextrin arm as well. Therefore it is concluded that overall the mice studies did not reveal evidence for a clinically relevant carcinogenic potential of cladribine.

2.3.4.5. 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.

No effects on female fertility were seen at any dose tested. In treated males testes weights and the percentage of motile sperms were significantly decreased. Testicular effects (marked testicular atrophy and the complete absence of spermatogenesis) had also been observed in one out of two monkeys in a repeated dose study. 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 in the lower and upper mid dose groups as well as in the high dose group. Based on a detailed discussion on possible mechanisms for male-mediated teratogenicity provided by the applicant it can be agreed that if spermatogonial cells were involved damage would have occurred in the differentiating spermatogonial cells rather than in primitive stem cells. This would imply a minimal risk of inheritable genetic damage after discontinuation of cladribine treatment for a period long enough for a new spermatogenetic cycle to achieve completion. Furthermore as the applicant could show that in the male fertility study the incidence in the affected treated groups was in the same range as the spontaneous incidence of amelia and phocomelia in CD1 mice (Szabo, 1989), the relevance of these findings is further attenuated. Cladribine has been approved originally for the treatment of hairy-cell leukaemia (Litak).

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

2.3.4.6. Local Tolerance

Local tolerability studies were done using Syrian golden hamster treated in the cheek pouch, single dose subcutaneous irritation in mouse, intra-and paravenous 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.

2.3.4.7. Other toxicity studies

Antigenicity of cladribine was studied in guinea pigs. Based on the results of both the ASA test and the PCA test, cladribine does not seem to have antigenic potential.

2.3.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment according to guideline EMEA/CHMP/4447/00 was provided. The calculated PECSURFACE WATER refined based on published data on the prevalence of all forms of the disease multiple sclerosis in total is 0.008µg/L and thus below the threshold of 0.01µg/L. The value of Log Kow is 0.0595 (pH 7) and does not indicate a risk for bioaccumulation. Therefore, it is assumed that cladribine is unlikely to represent a risk for the environment following its prescribed usage in patients.

2.3.6. Discussion on non-clinical aspects

Cladribine has been used in patients with hairy cell leukaemia for many years. The drug requires phosphorylation to 2-CdATP to become biologically active. The main mechanism of lymphotoxicity in cells exposed to cladribine is the interference of 2-CdATP with normal DNA synthesis (DNA strand breaks and repair inhibition) which leads to blockade of cellular energy metabolism and normal proliferative cell cycling. Based on this mode of action selective lymphocyte depletion, especially of T cells occurs. Cladribine, given as an oral formulation was extensively evaluated in a variety of non-clinical studies aimed to characterize the pharmacodynamic and pharmacokinetic profile as well as the safety pharmacology and toxicology. Safety pharmacology, toxicology and toxicokinetic studies conducted were done in accordance with GLP.

The experimental autoimmune encephalomyelitis (EAE) model was chosen as a rodent model for MS. In neither of the two studies conducted cladribine exerted measurable effects on clinical symptoms of EAE. The safety pharmacology profile of cladribine was assessed according the respective guidelines. Generally, both the selected species and the dose/concentrations of the drug are appropriate to characterize the safety profile of cladribine. The results of these studies demonstrate that cladribine has an acceptable pharmacological safety profile in animals and has a considerable safety margin compared to doses and exposures intended for human use.

Data pertaining to the absorption, distribution, metabolism and excretion (ADME) of cladribine have been gathered in a series of studies conducted in mice, rats, rabbits, dogs and monkeys via three routes of administration, i.v., s.c., and oral. Bioanalytical methods were validated for the quantification of cladribine and its metabolites in mouse, rat, rabbit, dog, monkey and human plasma as well as in cerebrospinal fluid of dogs and monkeys. 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. It should be noted that cladribine was able to enter the CSF. Metabolism studies revealed that cladribine is metabolized only to a small extent by phase I and II enzymes and neither induction nor inhibition of the phase I CYP450 enzymes has been found. Studies related to possible drug – drug interactions has been done at the level of absorption and metabolism, respectively. Whereas there is clear evidence neglecting interactions at the level of metabolism the data seem to indicate a possible pharmacokinetic interaction of cladribine with drugs which are substrate of the nucleoside transporter ABCG2.

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). The pivotal toxicity studies were performed in compliance with GLP. Most toxicology studies were performed by s.c. or i.v. routes, which, based on exposure were considered relevant also for the oral administration. The pivotal studies designed to evaluate the repeated dose toxicity of cladribine were conducted in mice and cynomolgus monkeys. These animal species were considered appropriate for the non-clinical safety evaluation of this compound due to similarities in plasma deoxycytidine levels compared to humans. The heart and the liver were the primary target organs of toxicity in the rat, whereas rapidly dividing tissues (e.g. bone marrow, lymphoid tissue of spleen, thymus and lymph nodes) were shown to be the primary target organs in the other species, including human. These clearly different profiles of toxicity are most likely related to the differences

in cellular exposure to phosphorylated cladribine because of the dissimilar deoxycytidine levels. A chronic toxicity study was performed in mice by the oral route (gavage) to evaluate possible effects related to the intended route of administration in humans and to assess the reversibility of these effects. The results obtained in this study showed that cladribine administered by the oral route to mice for up to 7 monthly cycles was well tolerated, inducing no relevant signs of toxicity or any histopathological lesions. In conclusion, as expected from the pharmacological mechanism of action of the compound, the primary target organs following repeated administration with cladribine were the lymphoid tissues/organs (e.g. spleen, thymus and lymph nodes) and the bone marrow. Cladribine was shown to be genotoxic, causing chromosomal damage in the bone marrow of mice in vivo and in CHO-WBL cells in vitro.

The carcinogenic potential of cladribine was assessed in a 22-month s.c. study in mice using an intermittent dosing schedule of seven days of treatment followed by a 3-week drug free period. Additionally a transgenic bioassay in TgrasH2 was conducted. Although some benign adenomas (harderian gland) and three adenocarinomas were found in the long term mouse study no evidence for carcinogenic potential was found in the transgenic bioassay. The harderian gland tumours were considered clinically irrelevant as humans do not have a comparable anatomical structure. Based on these results cladribine is not considered to pose a carcinogenic risk to humans. Reprotoxocity studies revealed clear embryolethal as well as teratogenic effects in mice and rabbits. The observed embryolethal and teratogenic effects are consistent with the pharmacologic mechanisms of cladribine.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical properties of Movectro have been adequately documented and meet the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

Movectro is an oral (tablet) formulation of cladribine. Cladribine is a 'purine analogue', a cytotoxic substance belonging to the group of 'antimetabolites'. In the body cladribine is converted within lymphocytes into a chemical called CdATP, which interferes with the production of new DNA. CdATP is incorporated into DNA strands, thereby blocking DNA chain elongation and inhibiting DNA repair and it will inhibit ribonucleotide reductase. Cell death then occurs from energy depletion and apoptosis. Apart from lymphocytes CdATP can also affect other cells, particularly other types of blood cells.

Parenteral cladribine is approved in several countries for the treatment of hairy cell leukaemia (HCL) under various trade names. It has also been approved in some countries for the treatment of chronic lymphoid leukemia (CLL). Currently, no oral medication is approved for the treatment of relapsing-remitting multiple sclerosis (RRMS); all presently available disease modifying drugs (DMDs) for the management of MS are administered subcutaneously (s.c.), intramuscularly (i.m.), or intravenously (i.v.). An oral formulation of cladribine was developed for evaluation as a disease modifying therapy for MS to avoid the disadvantages associated with the use of parenteral disease-modifying therapies. The applicant initially sought an approval for the use of oral cladribine tablets in the treatment of relapsing forms of MS. During the evaluation, the applicant proposed the following restricted indication in a rapidly evolving and severe:

"MOVECTRO is indicated as disease-modifying therapy in relapsing-remitting multiple sclerosis (MS) for the following subjects:

- Patients with high disease activity and/or risk of disease progression defined as those with 2 or more relapses in the previous year and one or more T1 gadolinium-enhancing lesions.

or

- Patients who are intolerant to beta-interferon or glatiramer acetate therapies."

Based on the existing data from the Phase II and Phase III trials in MS with parenteral cladribine, an oral tablet formulation of cladribine was developed employing a short course dosing regimen. The tablet formulation was tested in two randomized, open-label cross-over studies to evaluate the bioavailability of cladribine following oral administration in comparison to the s.c. and i.v. administration of cladribine (IXR-101-09-186. and IXR-102-09-186),. These studies allowed the determination of an oral dose of cladribine that provides comparable exposure to that achieved using the parenteral product.

The efficacy and safety of oral cladribine as a disease modifying therapy for RRMS was studied in one pivotal trial, supported by the data from the Scripps-C trial. The pivotal trial 25643 (CLARITY) is a Phase III randomized, double-blind, three-arm, placebo-controlled, multi-center clinical trial. A total of 1326 patients have been included in the phase III study. Overall, 437 patients with RRMS received placebo, 433 patients received a cumulative dose of cladribine 3.5 mg/kg, and 456 patients received a cumulative dose of 5.25 mg/kg.

Other placebo controlled clinical trials have been conducted in the treatment of other forms of MS (2-CdA-MS-SCRIPB "Scripps-B", 2-CdA-MS-001 "MS-001", and 2-CdA-MSSCRIPP "MS-Scripps"). Subjects in these trials were diagnosed with progressive forms of MS, whereas subjects enrolled in the CLARITY and Scripps-C trials were diagnosed with RRMS. For this reason, results from the Scripps-B, MS-001, and MS-Scripps trials are not included in the analysis of efficacy. However, the relevant safety data from these trials are included in the integrated safety database.

In addition to the completed studies, the following studies are ongoing:

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

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

Trial 28821 (ORACLE MS): a Phase III, randomized, double-blind, placebo-controlled, multicenter, 3-treatment group trial to evaluate the safety and efficacy of oral cladribine in subjects with early disease who have experienced a first clinical demyelinating event and who are at high risk of converting to MS. The trial will include three treatment periods, each lasting up to 2 years. The primary objective, which will be addressed during the initial treatment period, is to evaluate the effect of 2 dosage regimens of oral cladribine versus placebo on the time to conversion to Clinical Definite Multiple Sclerosis (from randomization) according to the Poser criteria, defined by either a second attack or a sustained increase in EDSS score in subjects in subjects with a first clinical demyelinating event at high risk of converting to MS.

As the occurrence of MS is very low in the paediatric population the Applicant sought a product specific waiver from the requirement to develop Movectro for the treatment of children and young adolescents. The Paediatric Committee (PDCO) at EMA agreed on the request for waiver in the paediatric population from birth to less than 18 years of age for Movectro based on the ground that the specific medicinal product is likely to be unsafe in part or all of the paediatric population.

2.4.2. GCP

The Clinical trials were performed in accordance with GCP 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.
According to the information received by the Applicant, sites from the CLARITY study have been inspected by the Austrian Agency, under the national inspection programme. These inspections showed no indication for GCP non-compliance.

2.4.3. Pharmacokinetics

Due to the long lasting selective reduction in lymphocyte numbers mediated by cladribine all clinical pharmacology studies were designed and conducted in patients.

2.4.3.1. Methods

Two analytical methods, HPLC –Fl and HPLC/MS/MS were used in the determination of cladribine and its main metabolite 2-chloroadenine in human plasma and urine. Both methods have been developed and used for the assay of samples in patients from clinical phase I and II trials. The performance of calibration standards and QC samples in regard to the accuracy and precision has been shown to meet international standards.

2.4.3.2. Absorption and bioavailability

- **Study IXR 101-09-186:**

This is an Open-Label, Randomized, Four-Way Crossover Study on the Relative Bioavailability of Cladribine (2-Chloro-2'-Deoxy- Adenosine, 2-CdA) Administered in Tablet and Hard Shell Capsule Formulations and as Subcutaneous Injection in Patients with Multiple Sclerosis-A Pilot Study.

The main objective of the study is to assess the systemic availability of cladribine after oral administration of two different tablet formulations and a hard shell capsule formulation in comparison with a s.c. administration (reference formulation) in subjects with MS. Subjects received cladribine Tablet 1 HPβCD complex formulation 3 mg (Lot number N0120), cladribine Tablet 2 (muco-adhesive formulation) 3 mg (Lot number N0121), cladribine capsule (hard shell) 3 mg (Lot number RD03030) and Leustatin® (cladribine) Injection. The four treatment periods were separated by a drug-free interval of at least five days between periods to allow wash-out of the drug before next dose. Drug administration was under fasting conditions following an overnight fast of at least ten hours. After drug administration patients continued to fast for another four hours post dose. PK plasma samples were collected within 30 to 5 minutes before administration, and at 15 and 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours post-dose. CdA was determined using a validated method involving the use of HPLC/MS/MS. The LOQ was 100 pg/mL. The pharmacokinetic parameters estimated were, tmax, Cmax, t1/2, AUC(0-24) and AUC(0-∞).

- **Study IXR 102-09-186:**

This is an open-Label randomised, Three-Way Crossover Study on the Absolute Oral Bioavailability of cladribine administered in a Tablet Formulation and as an IV Injection in Patients with Multiple Sclerosis.

The main objective is to assess the absolute systemic bioavailability of cladribine after oral administration of two different fixed oral doses in subjects with MS, and to evaluate the safety and tolerability of cladribine. Treatments administered were cladribine Tablet 1 HPβCD complex formulation 3 mg (Lot number N0120B), cladribine Tablet 1 HPβCD complex formulation 10 mg (Lot number N0126B) and Leustatin® (cladribine) Injection. The subjects received, on three separate occasions, with at least a 5 days washout period in-between, the two different fixed oral doses (3 mg and 10 mg) of the tablet and the i.v. dose of 3 mg (administered as a 1 h infusion). Drug administration was under fasting conditions (at least 10 hours over night). After the administrations, the patients remained in the semi-supine position for one (1) hour. PK plasma samples were collected within 30 to 5 minutes before administration, and at 15 and 30 minutes, and 1, 2, 4, 6, 8, 12, 16, and 24 hours post-dose. Cladribine was determined using a validated method involving the use of HPLC/MS/MS. The LOQ was 100 pg/mL. The pharmacokinetic parameters estimated were, tmax, Cmax, t1/2, AUC(0-24) and AUC(0-∞).

Of the different oral formulations investigated, a cladribine/cyclodextrin tablet formulation (HPβCD/betadex cladribine) was selected because it showed the largest bioavailability and lowest variability in pharmacokinetic parameters of different oral formulations studied. The absolute bioavailability of oral tablets of HPβCD cladribine is approximately 40% and is mainly determined by the absorption process. The variability in AUC and Cmax is acceptable, with coefficients of variation of about 30% and 25%, respectively. Following oral administration of tablets absorption was rapid, with a time to maximum concentration (tmax) in the range of 0.5-1.5 hours. The effect

of food on the pharmacokinetics of cladribine administered orally to subjects with multiple sclerosis was studied in a randomised, two-way cross-over study to assess the effects of food. A high fat breakfast resulted in a statistically significant (p=0.0091) 29% reduction in cladribine maximum exposure (Cmax, geometric mean). This was associated with a delay in the occurrence of the median tmax from 0.5 h in the fasted state to 1.5 h in the fed state. The effect of the high fat breakfast on the extent of absorption (AUC(0-∞)) of cladribine did not reach statistical significance. Overall, the outcome of the study indicates cladribine can be administered without regard to food.

2.4.3.3. Distribution

The applicant performed two in vitro studies to assess protein binding and blood/plasma distribution. In spiked human plasma, the plasma protein binding of cladribine was low (20%) and independent of concentration. The volume of distribution is large with a mean of 482 L and complex, with specific accumulation of the phosphorylated forms of cladribine in lymphocytes.

2.4.3.4. Elimination

The metabolic profiles of cladribine were investigated in urine and plasma after i.v. 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 adenine-deoxyribose bond, oxidation at the adenine or the deoxyribose moiety, and conjugation. Following both oral and i.v. administration, the parent compound cladribine was the main component present in plasma and urine. By definition, 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. 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. The elimination of cladribine is equally dependent on renal and non-renal routes (23.1 L/h for renal clearance and 22.7 L/h for non-renal clearance), where the non-renal elimination consists predominantly of intracellular metabolism and elimination of cladribine and phosphorylated forms of cladribine. Hepatic metabolism of cladribine plays only a minor role (i.e. < 10% of the total cladribine clearance). The terminal elimination half-life after oral administration was almost equal to that after intravenous administration (i.v.:18.4 ± 6.6 h; oral: 19.7 ± 5.0 h).

2.4.3.5. Dose proportionality and time dependencies

In patients with different indications (humoral malignancies, cancer) i.v. administered cladribine showed linear PK. However dose proportionality was not adequately demonstrated for the proposed dosage form. The PK of cladribine appears to be time-independent. There was no significant accumulation of cladribine in plasma after repeated oral dosing.

2.4.3.6. Special populations

Gender and race
No dedicated clinical pharmacology trial has been performed to investigate the potential differences in between plasma from male or female donors. No specific study or population PK analysis comparing cladribine PK in different ethnic groups has been provided.

Paediatric population
The Paediatric Committee (PDCO) at EMA agreed on the request for waiver in the paediatric population from birth to less than 18 years of age for Movectro based on the ground that the specific medicinal product is likely to be unsafe in part or all of the paediatric population.

Elderly
Clinical studies of cladribine did not include elderly subjects above 65 years. Therefore, it cannot be determined whether patients > 65 years may have different PK of cladribine than younger subjects. In general, for an elderly patient caution is advised, reflecting the greater frequency of decreased

renal, cardiac or hepatic function, and of concomitant diseases or concomitantly administered drugs.

Impaired renal function
The renal clearance of cladribine exceeds the glomerular filtration rate, indicating the drug undergoes net tubular secretion in addition to glomerular filtration. This was a consistent observation in the performed studies. In the population PK analysis in subjects with MS it was concluded that approximately half of the elimination of cladribine is related to renal elimination (CLR: 23.1 L/h, CLNR: 22.7 L/h). The patients included in the pop PK analysis had a median (range) CLCR of 107.9 (49.6 -244.4) mL/min.

In the pop PK analysis it could be concluded that total clearance of cladribine is dependent on the CLCR in the individual patient. The predicted decrease in total clearance for a typical patient with typical creatinine clearance representing the different degrees of renal function was predicted to 18% in mild impairment (CLCR = 65 ml/min), 30% in moderate renal impairment (CLCR = 40 ml/min), and 40% in severe renal impairment (CLCR = 20ml/min). Caution is recommended when used in this group of patients. Experience in patients with moderate to severe renal impairment is limited.

Impaired liver function
Cladribine is excreted unchanged in the urine in the range 20 – 60% of an i.v. dose. Low amounts of metabolites have been found in plasma and in urine. Therefore, hepatic impairment was not expected to have any substantial impact on the elimination of cladribine by the applicant and a dedicated hepatic impairment study has not been performed in subjects with MS.

2.4.3.7. Pharmacokinetic interaction studies

In Vitro assessment of the potential for induction of human hepatic enzymes showed no evidence for either inhibition or induction of CYP450 enzymes. The most plausible concomitant medication is interferon-β1a. Thus an open label, multiple dose, three period, single centre study was performed to assess the effect of oral cladribine on the PK of interferon (IFN)-β1a and vice versa in subjects with MS. Seventeen (15 analyzed) Caucasian subjects with MS, 6 males and 11 females in the mean (SD) age of 46.5 (7.2) years, and mean (SD) body weight of 68.5 (12.6) kg participated to the study. With regards to PK, results led to the conclusion that IFN-beta-1a does not alter the disposition of co-administered cladribine to a clinically relevant extent. The data also indicate that cladribine does not alter the disposition of co-administered IFN-beta-1a. However, due to incomplete serum concentration-time curves for IFN-beta-1a, the results must be interpreted with some caution.

2.4.4. Pharmacodynamics

2.4.4.1. Mechanism of action

Cladribine has been shown to exert long-lasting anti-inflammatory effects by selectively suppressing lymphocytes and the autoimmune processes involved in the pathophysiology of multiple sclerosis. Intracellular phosphorylation of cladribine is specifically mediated by the enzyme deoxycytidine kinase (DCK), which is highly expressed in lymphocytes. At the same time, the levels of the 5'-nucleotidases (5'NTases) responsible for degradation of cladribine triphosphate (CdATP) are low in lymphocytes. CdATP represents the active principle, causing a disruption of cellular metabolism, DNA damage and impairment of DNA synthesis, thereby causing subsequent cell death of both dividing and quiescent cells.

2.4.4.2. Primary and Secondary pharmacology

The mechanism of action for Cladribine is well established. Thus, no new data on primary pharmacology were provided.

Pharmacology studies in human healthy volunteers are limited by the toxicity of the product. All the data collected was as ancillary studies, piggybacked in main clinical trials. In particular, the cardiac safety of Movectro was assessed in a sub-population of RRMS patients (N=135) from the

pivotal Phase III CLARITY trial. This ECG sub-study in the target population of RRMS subjects was designed to evaluate potential acute and/or accumulative effects of cladribine on the ECG time-intervals (RR, PR, QRS, QT, QTcB, and QTcF) and T-wave morphology, with a particular emphasis on the heart rate-corrected QT interval (QTcF primary; QTcB supportive). Moreover, subjects included in this sub-study underwent PK sampling in order to allow for concentration/QT analysis. The ECG evaluation did not indicate any effect of Movectro on heart rate, AV conduction, or cardiac depolarization as measured by the PR and QRS interval durations. The morphological changes showed no clinically important signal of cladribine effect. In addition, the data showed no clear evidence of an acute cladribine concentration-dependent effect on cardiac repolarization. Considering the limitations of the relatively small sample size, the long duration of the trial, and the possible contribution of the subjects' underlying condition, the consistency of the QTcF measurements over time was quite good. The results are overall reassuring form the safety point of view. There is no sign that cladribine is associated with an increase in QTc prolongation.

2.4.5. Discussion on clinical pharmacology

Due to the long lasting reduction in lymphocyte numbers mediated by cladribine, 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. For this very reason, it is also acknowledged that not all otherwise typical elements of clinical pharmacology programs for non-cytotoxic new molecular entities could be conducted with cladribine.

A cladribine/cyclodextrin tablet formulation (HPβCD/betadex cladribine) was selected as it showed the largest bioavailability and lowest variability in pharmacokinetic parameters of different oral formulations studied. 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 AUC and Cmax is acceptable. Following oral administration of tablets absorption was rapid, with a time to maximum concentration (tmax) in the range of 0.5-1.5 hours. Food delayed cladribine absorption and decreases maximum plasma level whereas the extent of absorption (AUC(0-∞)) of cladribine was similar.

The PK of cladribine appears to be time-independent. In patients with different indications (humoral malignancies, cancer) cladribine i.v. showed linear PK. However dose proportionality was not adequately demonstrated for the proposed oral dosage form. There was no significant accumulation of cladribine in plasma after repeated oral dosing over 5 days. The volume of distribution is large and complex with specific accumulation of the phosphorylated forms of cladribine in lymphocytes. Intracellular concentrations of cladribine nucleotide in leukaemic cells were found to be several hundred-fold higher than the corresponding plasma concentrations of cladribine. Plasma/serum protein binding of cladribine is overall low and concentration independent. The elimination of cladribine is equally dependent on renal and non-renal routes, where the non-renal elimination consists predominantly of intracellular metabolism, and only to a minor extent hepatic metabolism. The evidence on the dependence of total cladribine clearance on creatinine clearance is mostly based on population PK analysis. 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. A dedicated hepatic impairment study has not been performed in subjects with MS. There is no evidence of gender-related differences in the PK of cladribine.

No in vitro evidence for either inhibition or induction of CYP450 enzymes has been observed. This is confirmed by in vivo interaction studies with IFN-β-1a and cladribine showing that concomitant administration of these drugs does not lead to relevant pharmacokinetic interactions.

The mechanism of action for Cladribine is well established. Thus, no new data on primary pharmacology were provided. The results of a cardiological ancillary study conducted within the CLARITY are reassuring as it did not suggest that cladribine is related with an increase in QTc prolongation.

2.4.6. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data submitted are considered satisfactory.

2.4.7. Clinical efficacy

2.4.7.1. Dose response studies

The applicant based his knowledge on findings derived from phase I and phase II studies, in which cladribine was parenterally administered and which included two different forms of MS patients, PRMS and SPMS, as well as the approved leukemia indication. The cladribine tablet 5.25 mg/kg treatment regimen, used in the CLARITY pivotal study was developed to provide the equivalent of the parenteral cladribine exposure of 2.1 mg/kg, used in the phase II Scripps-C trial. The applicant claimed equivalence of cladribine tablets to the parenteral formulation that is based on a 40% plasma bioavailability. The cladribine tablet 3.5 mg/kg treatment regimen, used in the pivotal CLARITY study provided a lower dose at two-thirds of the total cladribine tablet 5.25 mg/kg exposure.

Therefore, no adequate dose-finding studies in the intended target RRMS population, and with the intended oral formulation were performed. Insufficient scientific rationale for the dose used in the pivotal study per cycle of oral cladribine, for the interval between the cycles and the number of cycles was provided. In addition, there was no clear dose-dependent effect in the CLARITY trial. For a cytotoxic agent with a narrow therapeutic window, the minimal effective dose should be clearly defined.

2.4.7.2. Main studies

The efficacy and safety of oral cladribine as a disease modifying therapy for RRMS was studied in one pivotal trial, supported by the data from the Scripps-C trial.

Study ID	**No. of study centres locations No of subjects**	**Design/ objective**	**Study Posology**	**Primary Endpoint**	**Key Secondary Endpoints**
2CdA-MS-SCRIPC ("Scripps-C")	1 (US) 52 subjects (49 consented to the use of their data)	Randomized, phase II, double-blind, placebo-controlled, parallel group	Parenteral (subcutaneous)cladribine 2.1 mg/kg or placebo	Presence/absence of T1 brain lesions at final evaluation assessed by Gd-enhanced MRI	Annualized exacerbation rates Change from baseline in number and volume of T1 enhanced and volume of T2 lesions Changes from baseline in EDSS and SNRS scores
25643 ("CLARITY")	155 (North/South America, Eastern/Western Europe, Russia, Middle East/Northern Africa)	Randomized, phase III, double-blind, placebo-controlled, 3 parallel group	Oral cladribine 3.5 mg/kg or 5.25 mg/kg or placebo	Qualifying relapse rate at 96 week	Mean number of T1 Gd-enhanced lesions Mean number of active T2 lesions Mean number of combined unique lesions

	1326 subjects				Relapse-free status Time to 3-month sustained change in EDSS score

Pivotal Phase III study 25643 (Clarity study)

2.4.7.2.1. Methods

This was a phase III, randomized, double-blind, three-arm, placebo-controlled, multi-center, 96-week study of oral cladribine in subjects with RRMS.

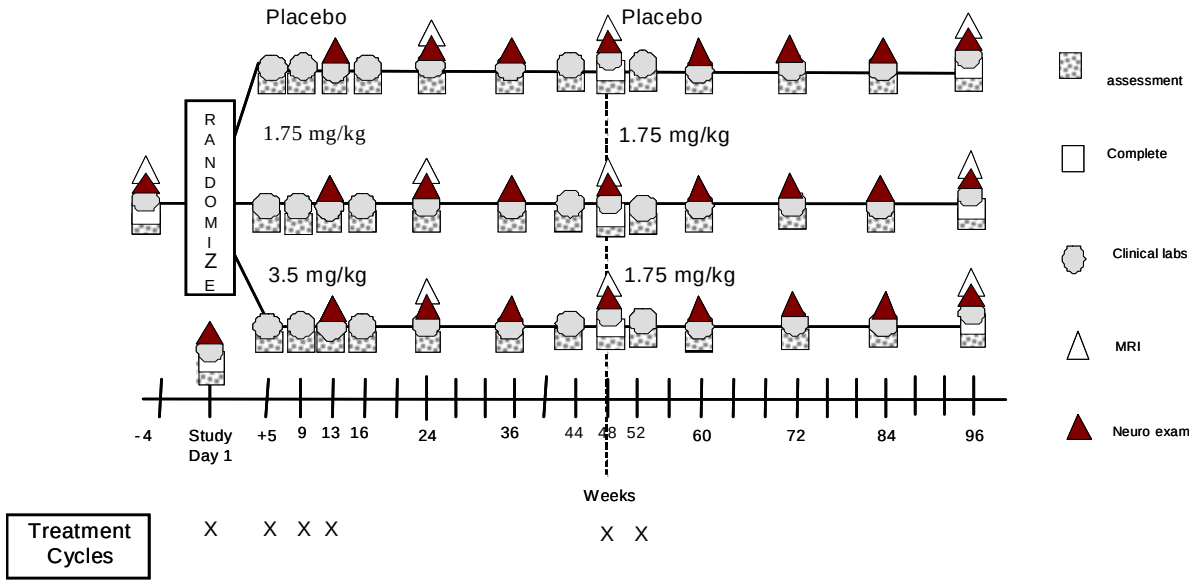
2.4.7.2.1.1. Study Participants

Key inclusion criteria were: Male or female, between 18 and 65 years of age; Had definite MS according to the McDonald criteria; Had RRMS with one or more relapses within twelve months prior to Trial Day 1; Been clinically stable and not have had a relapse within 28 days prior to Trial Day 1; Had an EDSS from 0-5.5, inclusive;

Key exclusion criteria were: 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 received cladribine, mitoxantrone, total lymphoid irradiation, myelosuppressive therapy, campath-1h, cyclophosphamide, azathioprine, methotrexate or natalizumab; Had prior or current history of malignancy, had a history of persistent anemia, leukopenia, neutropenia, or thrombocytopenia after immunosuppressive therapy, had compromised immune function or infection; Had platelet and absolute neutrophil counts below the lower limit of normal range within 28 days prior to Trial Day 1, had significant leukopenia within 28 days prior to Trial Day 1; Had systemic disease that, might interfere with subject safety, compliance or evaluation of the condition under trial.

2.4.7.2.1.2. Treatments

The trial included a pre-trial evaluation period (up to 28 days prior to the start of treatment); an initial treatment period during the first 48 weeks in the trial; and a re-treatment period during the second 48 weeks in the trial. The overall trial design is displayed in the table below:



Selection and Timing of Dose for Each Treatment

Subjects participating in the CLARITY trial received either:

i) cladribine tablets 3.5 mg/kg, administered p.o. as 0.875 mg/kg/course for the first two consecutive courses followed by placebo tablets p.o. for two additional consecutive courses during the beginning of the first 48 weeks and 0.875 mg/kg/course for two consecutive courses during the beginning of the second 48 weeks of the trial,

or

ii) cladribine tablets 5.25 mg/kg, administered p.o. as 0.875 mg/kg/course for four consecutive courses during the beginning of the first 48 weeks and 0.875 mg/kg/course for two consecutive courses during the beginning of the second 48 weeks of the trial,

or

iii) matching placebo tablets p.o. for four courses during the first 48 weeks and for two courses during the second 48 weeks of the trial.

The different treatment regimens are illustrated in the table below.

Arm	Cycle 1 Day 1	Cycle 2 Wk5	Cycle 3 Wk9	Cycle 4 Wk13	Yearly cumulative dose (Year One)	Cycle 5 Wk48	Cycle 6 Wk52	Yearly cumulative dose (Year Two)	Total Cumulative Dose
Placebo	Placebo	Placebo	Placebo	Placebo	0 mg/kg	Placebo	Placebo	0 mg/kg	0 mg/kg
Low Dose	Active	Active	Placebo	Placebo	1.75 mg/kg	Active	Active	1.75 mg/kg	3.5 mg/kg
High Dose	Active	Active	Active	Active	3.5 mg/kg	Active	Active	1.75 mg/kg	5.25 mg/kg

Cladribine was administered orally in 10 mg tablets. The number of tablets administered was standardized based on weight, using 10 kg weight ranges. The lowest weight range was 40–49.9 kg and the uppermost weight range was 110-120 kg. All subjects within a specific weight range received the same number of tablets per course.

Prior and Concomitant Therapy
Corticosteroids were permitted for the treatment of acute relapses at the discretion of the Treating Physician. The use of any of the following therapies concomitantly with cladribine was not permitted: Immunomodulatory therapy (including glatiramer acetate, interferons, natalizumab; with the exception of Rebif®, to be given as rescue medication); Immunosuppressive therapy (including cyclophosphamide, mitoxantrone, cyclosporin, methotrexate, and azathioprine); Cladribine (outside of the current trial protocol), total lymphoid irradiation, myelosuppressive therapy, campath-1h, IVIG and plasmapheresis; Cytokine or anti-cytokine therapy. The concomitant usage of medications that could affect GI motility and absorption of cladribine, including proton pump inhibitors, H2 antagonists, etc., were strongly discouraged and were to be discussed with the Sponsor Medical Responsible prior to use.

Rescue Medication:
The lymphocyte reduction targeted with cladribine at the proposed doses was expected to be achieved by 24 weeks of the treatment. As such, the rescue option applied after the first 24 weeks of treatment when subjects would have experienced the full effects of cladribine. For all randomized subjects, a rescue option of treatment was available, if the subject experienced more than one qualifying relapse and/or experienced a sustained increase in their expanded disability status score (EDSS) of ≥ 1 point (or ≥1.5 points, if baseline EDSS was 0), over a period of three months or greater during a calendar year beginning at Week 24. Rebif®, supplied by Sponsor, was the preferred rescue medication in the trial (interferon-beta-1a, 44 mcg three times a week).

2.4.7.2.1.3. Objectives

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 subjects with RRMS.

The secondary objectives were to assess the effect of cladribine on progression of disability in subjects with RRMS; the effect of cladribine in reducing lesion activity compared to placebo as measured by MRI in subjects with RRMS; the safety of cladribine in subjects with RRMS; population pharmacokinetics in subjects with RRMS; Identify DNA polymorphisms or gene expression profiles associated with certain traits (i.e. response, adverse events) of cladribine used in the treatment of multiple sclerosis as well as potential susceptibility loci for multiple sclerosis.

2.4.7.2.1.4. Outcomes/endpoints

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

Secondary endpoints included the proportion of subjects 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 three months); the 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 "combined unique lesions") per subject per scan at 96 weeks; the mean number of active T2 lesions per subject per scan at 96 weeks; the mean number of active T1 gadolinium-enhanced lesions per subject per scan at 96 weeks.

Tertiary endpoints included the time to first qualifying relapse at 96 weeks, mean changes in brain atrophy, the assessment of the potential impact of treatment with cladribine on patients health related quality of life (HRQL); the proportion of subjects receiving rescue therapy with interferon-beta-1a.

2.4.7.2.1.5. 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 assuming 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.

2.4.7.2.1.6. Randomisation

The randomization was stratified by clinical trial centre and was determined using a centralized randomization system. In the submitted application patients with RRMS from the following regions were randomized: East European countries (n=512), West European countries (n=256), American countries (n=131, included Brasil, Canada, USA), Russia (n=300), Others (n=127, included Israel, Lebanon, Morocco, Saudi Arabia, Tunisia And Turkey). As it is known that MS is an autoimmune disease with an unknown aetiology, triggered by a combination of genetic and environmental risk factors, the applicant was asked to justify the generalisability of study results for the intended target population, the European population. In this context the applicant provided subgroup analyses stratified for the four European regions that provided no significant differences.

2.4.7.2.1.7. Blinding (masking)

At each centre, two physicians, a treating physician and a separate evaluating physician were responsible for the treatment and evaluation of each subject throughout the entire trial. Generally, the modality of blinding is considered acceptable.

2.4.7.2.1.8. Statistical methods

The analysis sets consisted of intent-to-treat (ITT), evaluable, and safety populations. The ITT population included all subjects who were randomized into the trial. Subjects who completed

treatment without a major protocol deviation with 96-week data were included in the evaluable population. The Rescued population included all subjects who qualified and received rescue therapy. 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.

All tests were two-sided and performed at the 5% significance level for evaluation of efficacy. For the Primary Efficacy Endpoint, the qualifying relapse rate was analyzed using a Poisson regression model with fixed effects for treatment group and region with log of time on trial 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. Annualized qualifying relapse rate and its associated 95% CI (97.5% CI) were estimated for each treatment group. Summary statistics for the number of qualifying relapses during the 96 weeks of the trial (i.e., without the standardization over time) included mean, standard deviation, maximum, minimum and median, and was descriptively tabulated by treatment group.

2.4.7.2.2. Results

A total of 1326 subjects were enrolled and randomized (1:1:1) into the trial from 155 investigative sites in 32 countries worldwide and comprised the ITT population for the primary analyses: 456 were randomized to cladribine 5.25 mg/kg, 433 were randomized to cladribine 3.5 mg/kg and 437 were randomized to placebo).

A major proportion of subjects completed the trial and the percentages were similar across cladribine 5.25 mg/kg, cladribine 3.5 mg/kg, and placebo groups (89.0%, 91.9% and 87.0%, respectively), as detailed in the table below.

Study 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 Study	Yes	406 (89.0)	398 (91.9)	380 (87.0)	1184 (89.3)
	No	50 (11.0)	35 (8.1)	57 (13.0)	142 (10.7)
Reasons for Withdrawing from Study Prematurely	Adverse event	9 (2.0)	5 (1.2)	5 (1.1)	19 (1.4)
	Lost to follow-up	11 (2.4)	8 (1.8)	4 (0.9)	23 (1.7)
	Protocol violation	4 (0.9)	4 (0.9)	10 (2.3)	18 (1.4)
	Death	1 (0.2)	1 (0.2)	2 (0.5)	4 (0.3)
	Disease progression	4 (0.9)	5 (1.2)	21 (4.8)	30 (2.3)
	Other	21 (4.6)	12 (2.8)	15 (3.4)	48 (3.6)

Similarly, a major proportion of subjects completed treatment and the percentages were similar across cladribine 5.25 mg/kg, cladribine 3.5 mg/kg and placebo groups (86.2%, 91.2% and 86.3%, respectively), as details in the table below.

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)

Subjects in the ITT population with major protocol deviations were excluded from what the applicant refers to as the "evaluable" population. The major protocol deviations were established prior to database lock. The proportion of subjects with major protocol deviations leading to exclusion from the evaluable population were evenly distributed across the cladribine 5.25 mg/kg, cladribine 3.5 mg/kg, and placebo groups (5.9%, 4.2% and 6.2%, respectively).

2.4.7.2.2.1. Recruitment

The date of first subject first visit is: 20 Apr 2005. The date of last subject last visit is: 12 Nov 2008.

2.4.7.2.2.2. Conduct of the study

There were nine protocol amendments. Adequate explanations were provided by the applicant. Most of amendments related to local consideration, thus not affecting the external validity of study.

2.4.7.2.2.3. Baseline data

Baseline Patient Demographics and Disease Characteristics (ITT Population) are summarised in the table below.

	Placebo (N=437)	**Cladribine 3.5 mg/kg (N=433)**	**Cladribine 5.25 mg/kg (N=456)**	**All Patients (N=1326)**
Age (yr)				
Mean ± SD	38.7 ± 9.9	37.9 ± 10.3	39.1 ± 9.9	38.6 ± 10.0
Range	18–64	18–65	18–65	18-65
Prior treatment with any disease-modifying drug*, N (%)	142 (32.5)	113 (26.1)	147 (32.2)	402 (30.3)
Disease duration from first attack, years				
Median	7.1	5.8	7.2	6.7
Mean ± SD	8.9 ± 7.4	7.9 ± 7.2	9.3 ± 7.6	8.7 ± 7.4
Range	0.4–39.5	0.3–42.3	0.4–35.2	0.3-42.3
EDSS category, N (%)				
0	13 (3.0)	12 (2.8)	11 (2.4)	36 (2.7)
1.0 – 1.5	70 (16.0)	75 (17.3)	80 (17.5)	225 (17.0)
2.0 – 2.5	127 (29.1)	133 (30.7)	119 (26.1)	379 (28.6)
3.0 – 3.5	96 (22.0)	108 (24.9)	108 (23.7)	312 (23.5)
4.0 – 4.5	83 (19.0)	71 (16.4)	84 (18.4)	238 (17.9)
≥5.0	48 (11.0)	34 (7.9)	54 (11.8)	136 (10.3)
Mean ± SD	2.9 ± 1.3	2.8 ± 1.2	3.0 ± 1.4	2.9 ± 1.3

	Placebo (N=437)	Cladribine 3.5 mg/kg (N=433)	Cladribine 5.25 mg/kg (N=456)	All Patients (N=1326)
Median T1 gadolinium-enhancing lesions	3.0	2.5	3.0	3.0
Patients with lesions, N (%)	128 (29.3)	138 (31.9)	147 (32.2)	413 (31.1)
Number of lesions, mean ± SD	0.8 ± 2.1	1.0 ± 2.7	1.0 ± 2.3	0.9 ± 2.4
Range	0.0 - 27.0	0.0 - 32.0	0.0 - 20.0	0.0 - 32.0
T2 lesion volume, mm3				
Median	10140.5	9659.0	11106.0	10140.5
Mean ± SD	14287.6 ± 13104.8	14828.0 ± 16266.8	17202.1 ± 17467.7	15466.3 ± 15785.7
Range	150.0 - 76770.0	106.0 - 128747.0	236.0 - 103645.0	106.0- 128747.0

EDSS=Expanded Disability Status Scale; SD=standard deviation

*Most commonly: intramuscular interferon beta-1a (Avonex, 11.2%), subcutaneous interferon beta-1b (Betaseron, 10.6%), subcutaneous interferon beta-1a (Rebif, 9.4%) and subcutaneous glatiramer acetate (Copaxone, 6.5%)

Subjects randomized were well balanced across treatment groups with regard to baseline disease characteristics. However, there was a statistically significant shorter disease duration (time since first attack to trial enrolment) in the cladribine 3.5 mg/kg treatment group compared to the other two groups (p = 0.005). The majority of subjects experienced one or two relapses within the 12 months prior to SD1. Most patients showed a baseline EDSS about 2-3 points, representing mild to moderate neurological impairment. A greater proportion of subjects in cladribine 3.5 mg/kg were naïve to disease modifying drugs compared to cladribine 5.25 mg/kg and placebo (73.9%, 67.8%, and 67.5%, respectively). Based on the data provided, patients included in the 3.5 mg/kg treatment group might be considered in a less advanced stage of MS when compared to the 5.2 mg/kg group and the placebo group as they had shorter disease duration and took less DMD agents. To assess the effects of the baseline characteristics on the primary efficacy endpoint, annualized relapse rate, the applicant performed sensitivity analyses including these covariates. These analyses with additional covariate adjustment had no impact on the primary outcome.

2.4.7.2.2.4. Outcomes and estimation

Primary endpoint

The qualifying relapse rate at 96 weeks was reduced in a statistically significant difference for both active treatment groups (p<0.001) as detailed in the table below. The CHMP noted the low relapse rate in the placebo group.

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	

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; 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 endpoints

Proportion of Qualifying Relapse-Free Subjects

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, indicating a difference of about 18.8% for the 5.25 mg/kg group, and a difference about 18% for the 3.5 mg/kg group, when compared to placebo.

Disability progression at 96 weeks

Time to disability progression is considered as a clinically highly relevant endpoint. It was measured in terms of a 3-month sustained change in EDSS score of at least one point, if baseline EDSS score was between 0.5 and 4.5 inclusively, or at least 1.5 points if the baseline EDSS score was 0, or at least 0.5 point if the baseline EDSS score was at least 5.

The applicant provided a post-hoc analysis to assess disability progression in terms of a 6 month sustained change in EDSS as requested by the CHMP. There was a 41% relative reduction in risk of having disability progression regarding the time to 6-month sustained change in EDSS score for the 3.5 mg/kg group when compared to placebo. However, in the placebo group 56/437 patients had a sustained 6 month change in EDSS score, while in the 3.5 mg/kg treatment group 35/433 patients had a change. .

Mean Number of Active T1 gadolinium-enhanced lesions per subject per scan at 96 weeks

The adjusted mean number of active T1 gadolinium-enhancing 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. This represented a significantly lower mean number of active T1 Gd+ lesions per subject per scan in both active groups compared to placebo.

Given the number of active T1 Gadolinium enhancing lesions at week 96 compared to those at week 48, the possibility of a rebound effect after a one-year treatment period is not excluded (see table below). Of note, there was also a significant decrease of gadolinium enhancing lesions in the placebo group.

Mean number of active T1 gadolinium-enhancing lesions by assessment time and treatment group

	Baseline	Week 24	Week 48	Week 96
Placebo	0.8	0.97	0.69	0.38
Cladribine 3.5 mg/kg	1.0	0.07	0.11	0.06

Cladribine 5.25 mg/kg	1.0	0.07	0.04	0.07

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. This represented a significantly lower mean number of active T2 lesions per subject per scan in both active groups compared to placebo.

Tertiary endpoints

Time to First Qualifying Relapse at Week 96
Treatment with cladribine 5.25 mg/kg and cladribine 3.5 mg/kg tablets demonstrated treatment benefit by significantly forestalling the time to first qualifying relapse compared to placebo ($p<0.001$, HR=0.46, and $p<0.001$, HR=0.44, respectively).

Proportion of Subjects receiving rescue therapy with interferon-beta-1a at Week 96
There was a rather small number of patients across treatment groups, that accessed interferon-beta-1a for rescue medication. A greater proportion of subjects in the placebo group (6.2%) were rescued up to Week 96 compared to the cladribine 5.25 mg/kg and cladribine 3.5 mg/kg groups (2.0%, and 2.5%, respectively). This small numbers of cladribine treated subjects that accessed interferon-beta-1a rescue medication indirectly reflect a clinical benefit given on relapse rate in the active treatment groups but also points out the generally low number of relapse rate in the overall study population.
From the data presented it can be seen, that only 6.1% of the relapses in the placebo group required more corticosteroids than those in the active treatment group. These results again question the clinical relevance of the efficacy outcomes in the examined study population.

Proportion of subjects free of sustained disability progression at the end of 96 weeks
This proportion was 79.4% in the placebo group, 85.7% in the cladribine tablets 3.5 mg/kg treatment group and 84.9% in the cladribine tablets 5.25 mg/kg treatment group. There is a difference of only 6.3% and 5.5% when comparing active treatment to placebo. The proportion of subjects free of sustained disability progression at the end of 96 weeks was 79.4% in the placebo group, but only 85.7% in the cladribine tablets 3.5 mg/kg treatment group and 84.9% in the cladribine tablets 5.25 mg/kg treatment group.

Number of Active T1 gadolinium-enhancing (Gd+) lesions by Assessment Time and Treatment Group
The mean number of active T1 Gd+ lesions was consistently lower for active cladribine treatment compared to placebo for each timepoint. The mean number of active T1 Gd+ lesions at Week 24 was 0.07 for the cladribine 5.25 mg/kg and for the cladribine 3.5 mg/kg groups, and 0.97 for the placebo group. The mean number of active T1 Gd+ lesions at Week 48 was 0.04 for the cladribine 5.25 mg/kg group, 0.11 for cladribine 3.5 mg/kg, and 0.69 for placebo. The mean number of active T1 Gd+ lesions at Week 96 was 0.07 for the cladribine 5.25 mg/kg group, 0.06 for the cladribine 3.5 mg/kg, and 0.38 for the placebo group.

2.4.7.2.2.5. Ancillary analyses

Gender: cladribine tablet-treated subgroups were both statistically significantly superior to the placebo subgroup (male vs. female). However, considering the female population, there was a smaller effect in the higher dose compared to 3.5 mg/kg; regarding the male population, there was a smaller effect in the 3.5 mg/kg treatment group.

Age Group: Subjects were stratified according to the following 5 age ranges at trial entry: ≤ 20 years (n=33), which identifies a very late adolescent/early adult RRMS cohort, 21 - 34 (n=428), 35 - 44 (n=474), 45 - 54 (n=309), and ≥ 55 (n=82) years of age. Both cladribine 3.5 mg/kg and 5.25 tablet treatment subgroups were significantly superior to the placebo treatment subgroup for the age ranges 21–34, 35-44 and 45 -54 years of age, achieving relative reductions in ARR ranging from 43.3% to 73.3%. No statistically significant treatment effects were received in the ≤ 20 years of age subgroup and in the ≥ 55 years of age subgroup. Numerically, the observed treatment effects were comparable and point into the same direction. Given the rather small subgroup of

older patients, from an efficacy point of view, results for the ≥55 years of age subgroup are considered acceptable.

Prior disease modifying drug (DMD) Therapy: MS patients who have received prior therapeutic treatment with a DMD and who have failed treatment may represent a population of subjects relatively more resistant to treatment intervention. The ARR for the DMD treatment-experienced placebo subjects was greater than that of the DMD treatment-naïve placebo group (0.40 vs. 0.31, respectively). However, it should also be taken into account, that only around 30% of the patients included in the CLARITY trial received prior therapeutic treatment with a DMD.

Sensitivity Analyses – All Relapses
A sensitivity analysis was undertaken to determine if the treatment effect of cladribine tablets on the primary endpoint, qualifying relapse rate at 96 weeks, was comparable to the treatment effect when all relapses, qualifying and non-qualifying, were considered.

Persistence of Efficacy and /or Tolerance Effects
The annualized qualifying relapse rate from Weeks 72 to Week 96 is comparable to the rate observed from Weeks 24 to Week 48. The descend rate in the placebo group is noted. The persistence of efficacy of cladribine tablets treatment in RRMS is being further investigated in the CLARITY Extension trial

Table: Annualized Relapse Rate [1] by Time Period in the CLARITY Trial

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

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

Rescue medication
Subjects enrolled in the CLARITY study, who either experienced more than one qualifying relapse, and/or experienced a sustained increase in their EDSS of ≥ one point, or ≥1.5 points if baseline EDSS was 0, (over a period of three months or greater), during a calendar year beginning at Week 24, were eligible to receive rescue medication. Rebif (44 mcg tiw) was the preferred rescue medication in the study. Subjects who used Rebif were only considered protocol deviations if they did not abide by these criteria. A total of 48 subjects used Rebif medication. Ten (of 456) cladribine 5.25 mg/kg subjects, 12 (of 433) cladribine 3.5 mg/kg subjects and 26 (of 437) placebo subjects received Rebif rescue. The CHMP asked the applicant to provide efficacy analyses without patients having used Rebif, independent of the dose. The applicant provided a side-by-side comparison of the full ITT population and the ITT population less the 48 subjects who used Rebif accordingly which showed comparable comparable results in both groups.

Stratification according to relapse History in 12 Months Prior to Trial Entry: Subjects were stratified according to the following baseline relapse count converted to ARR at trial entry: ARR ≤ 1 (n=934, 70.4%), ARR = 2 (n=328, 24.7%), ARR ≥ 3 (n=64, 4.8%). Both cladribine tablet treatment groups were significantly superior to the placebo subjects across all baseline Annualised Qualifying Relapse Rate (ARR) ranges. Subjects in the cladribine tablets 3.5 mg/kg and 5.25 mg/kg treatment groups experienced treatment responses as follows:
- 48.2% and 51.9% relative reductions in ARR compared to placebo treatment for subjects in the baseline ARR ≤ 1 category (0.14 and 0.13 vs. 0.27, respectively; both p-values < 0.001);
- 68.9% and 57.8% relative reductions in ARR compared to placebo treatment for subjects in the baseline ARR = 2 category (0.14 and 0.19 vs. 0.45, respectively; both p-values < 0.001);
- 65.7% and 76.1% relative reductions in ARR compared to placebo treatment for subjects in the baseline ARR ≥ 3 category (0.23 vs. 0.67, p = 0.006 and 0.16 vs. 0.67, respectively; p=0.004).

2.4.7.2.2.6. Ancillary analyses in the high disease activity subgroups

Patients with high disease activity and/or risk of disease progression defined as those with 2 or more relapses in the previous year and one or more T1 gadolinium-enhancing lesions.

This is one of the two populations for which the applicant is seeking an indication. Only just 41 patients in the placebo group and 50 patients in the cladribine 3.5 mg/kg group represent a high disease activity subgroup meet this definition. As shown below.

	Placebo	**Cladribine 3.5 mg/kg**	**All Subjects**
	(N=437)	**(N=433)**	**(N=1326)**
Annualized Relapse Rate ≥ 2 Plus Presence of T1 Gd+ Lesions	41 (9.4)	50 (11.6)	138 (10.4)

* The High Disease Activity subgroup is defined as having two or more relapses and having one or more T1 Gd+ lesions at baseline or having two or more relapses and ≥ 9 T2 lesions at baseline.

Efficacy results in the individual components of the high disease activity subgroup are presented in the table below.

≥2 Relapses Plus ≥1 T1 Gd+ lesions	**Placebo (n= 41)**	**Cladribine 3.5 mg/kg (n=50)**	
Annualized Relapse Rate	0.67	0.22	Both p < 0.001
Relative Reduction ARR (Cladribine vs. PBO)		67.2%	
Proportion of Subjects Relapse-Free	46.3%	70.0%	P=0.024 (Clad 3.5 mg/kg) p=0.002 (Clad 5.25 mg/kg)
Time to 3-month Sustained Disability Progression, months	5.4	13.5	P=0.509 (Clad 3.5 mg/kg) p=0.024 (Clad 5.25 mg/kg)
Proportion of Subjects Sustained Disability-Free	75.6%	78.0%	p=0.788 (Clad 3.5 mg/kg) p=0.026 (Clad 5.25 mg/kg)
T1-Gd+ Lesions	2.50 (2.96)	0.25 (0.52)	Both p < 0.001
Active T2 Lesions	2.97 (2.76)	0.59 (0.82)	Both p < 0.001
CU Lesions	3.73 (3.41)	0.69 (0.93)	Both p < 0.001

Supportive analyses in otherwise defined high disease activity subgroups

An indication is not sought for those subgroups. Results are presented in the table below.

	Placebo	**Cladribine 3.5 mg/kg**
High Disease Activity Defined by Baseline Neurological Disability ≥3.5 on EDSS		
	n=174	n=161
Annualized Relapse Rate	0.35	0.15 p<0.001
Relative Reduction ARR (Cladribine vs. PBO)		57.1%

Proportion of Subjects Relapse-Free	60.3%	77.0% p=0.001
Time to 3-month Sustained Disability Progression, months	8.1	13.6 p=0.069
Proportion of Subjects Sustained Disability-Free	76.4%	83.9% p=0.092
T1-Gd+ Lesions	0.99 (2.12)	0.07 (0.26) p<0.001
Active T2 Lesions	1.39 (2.17)	0.28 (0.54) p<0.001
CU Lesions	1.73 (2.82)	0.32 (0.60) p<0.001
High Disease Activity Defined by ≥2 Relapses		
	n=131	n=130
Annualized Relapse Rate	0.48	0.16 p<0.001
Relative Reduction ARR (Cladribine vs. PBO)		66.7%
Proportion of Subjects Relapse-Free	52.7%	76.9% p<0.001
Time to 3-month Sustained Disability Progression, months	5.42	13.62 p<0.001
Proportion of Subjects Sustained Disability-Free	75.6%	90.8% p=0.002
T1-Gd+ Lesions	1.20 (2.06)	0.12 (0.37) p<0.001
Active T2 Lesions	1.75 (2.33)	0.41 (0.77) p <0.001
CU Lesions	2.14 (2.82)	0.46 (0.83) p <0.001

2.4.7.2.2.7. Ancillary analyses in patients intolerant to prior beta-interferon or glatiramer acetate therapies

This is the second population for which the applicant is seeking an indication for. Only a small number of patients had taken any disease modifying drug pre-treatment, around 30% in each treatment group. Patients who had previously failed treatment with two or more DMDs on basis of efficacy had been excluded from the study. Only 44 intolerants were included in the placebo group, 45 intolerants in the 3.5mg/kg active treatment group, patients were pre-treated around 19 month (see table below).

	Placebo (n=437)	**Cladribine 3.5 mg/kg (n=433)**	**All Subjects (n=1326)**
All Intolerants Only	44 (10.1)	45 (10.4)	152 (11.5)

Efficacy results in all subjects with a prior history of beta-Interferon or glatiramer acetate treatment failure are presented in the table below. Time to disability progression failed to reach statistical significance when compared to placebo, probably with respect to the small number of patients.

	Intolerants subgroup		**Whole study population**	
	placebo N= 44	cladribine 3.5 mg/kg N= 45	placebo N = 437	cladribine3.5 mg/kg N = 433

Annualized relapse rate	0.77	0.42	0.56	0.25
Proportion of subjects relapse-free	43.2%	64.4%	60.9%	79.7%

2.4.7.2.2.8. Ancillary efficacy analyses according to revised re-treatment guidelines in the high disease activity patient subgroup

This analysis was performed at the request of the CHMP to assess the impact of the re-treatment guidelines on the efficacy of cladribine in the sought HDA population. Only 37 patients were included in the placebo group, 33 patients in the 3.5 mg/kg active treatment group. As shown in the table below, results were generally consistent with those obtained for the HDA population without revised re-treatment guidelines. No statistically significant differences were achieved for the secondary endpoint, time to disability progression.

	High Disease Activity Patients with Re-treatment Guidelines		**High Disease Activity Patients defined by ≥ 2 Relapses PLUS Presence of T1 Gd+ Lesions**	
	Placebo	Cladribine 3.5 mg/kg	Placebo	Cladribine 3.5 mg/kg
	n=37	n=33	n=41	n=50
Annualized Relapse Rate	0.64	0.15 p<0.001	0.67	0.22 p<0.001
Relative Reduction ARR (Cladribine vs. PBO)		76.6%		67.2%
Proportion of Subjects Relapse-Free	45.9%	75.8% p=0.013	46.3%	70.0% p=0.024
Annualized All Relapse Rate	1.11	0.40 p<0.001	1.15	0.50 p<0.001
Relative Reduction ARR (Cladribine vs. PBO)		64.0%		56.5%
Time to 3-month Sustained Disability Progression, months	5.4	13.6 p=0.207	5.4	13.5 p=0.509
Proportion of Subjects Sustained Disability-Free	75.7%	84.8% p=0.342	75.6%	78.0 p=0.788
T1-Gd+ Lesions	2.41 (2.86)	0.33 (0.58) p<0.001	2.50 (2.96)	0.25 (0.52) p<0.001
Active T2 Lesions	2.90 (2.53)	0.72 (0.86) p<0.001	2.97 (2.76)	0.59 (0.82) p<0.001
CU Lesions	3.66 (3.21)	0.84 (0.99) p<0.001	3.73 (3.41)	0.69 (0.93) p<0.001

2.4.7.2.2.9. Summary of main studies

The following table summarises the efficacy results from the single pivotal trial 25643 – the CLARITY trial supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: the "CLARITY" Trial: 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	Phase 3, Randomized, double-blind, three-arm, placebo-controlled, multi-center, 96-week study conducted in 32 countries: cladribine vs. placebo.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		20.04.2005 (FPFV) – 12.11.2008 (LPLV) Initial treatment phase: 48 weeks Re-treatment phase: 48 weeks
Hypothesis	Superiority		
Treatments groups	Cladribine tablets 3.5 mg/kg		Administered p.o. as 0.875 mg/kg/course [i.e. cycle] 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.
	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.
	Matching Placebo		Administered p.o. for four courses during the first 48 weeks and two courses during the second 48 weeks.
Endpoints and definitions	Primary endpoint		Reduction of qualifying relapse rate during 96 weeks of treatment in subjects with RRMS.
	Secondary Endpoint		Proportion of Qualifying Relapse-Free Subjects at week 96
	Secondary Endpoint		Disability progression at 96 weeks (time to sustained change in EDSS ≥one point if baseline was 0.5-4.5, or ≥1.5 points if baseline EDSS was 0, or ≥0.5 point if baseline was ≥5, over a period of at least three months).
	Secondary Endpoint		Mean number of Active T1 GD enhanced lesions per subject per scan at 96 weeks
	Secondary Endpoint		Mean number of Active T2 lesions per subject per scan at 96 weeks

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Primary endpoint Descriptive statistics and estimate variability	Treatment group	Cladribine 3.5 mg/kg	Cladribine 5.25 mg/kg	Placebo
	Number of subject	456	433	437
	Relapse rate (Annualized)	0.15	0.14	0.33
	95% CI	(0.12, 0.17)	(0.11,0.17)	(0.29,0.38)
	Relative reduction % (Cladribine vs. placebo)	54.5	57.6	
Effect estimate per comparison	Primary endpoint	Comparison groups	Cladribine 3.5 mg/kg vs. placebo	
		Relative Risk, point estimate (SE[1])	0.43 (0.12)	
		95% CI	(0.34,0.54)	
		P-value[2]	<0.001	

	Primary endpoint	Comparison groups	Cladribine 5.25 mg/kg vs. placebo	
		Relative Risk, point estimate (SE[1])	0.43 (0.11)	
		95% CI	(0.35,0.54)	
		P-value[2]	<0.001	
Notes	[1] SE is presented on log scale. [2] 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 endpoint *(Proportion of Qualifying Relapse-Free Subjects at week 96)* Descriptive statistics and estimate variability	Treatment group	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Number of subject	456	433	437
	Relapse-Free status	YES: 360 NO: 96	YES: 345 NO: 88	YES: 266 NO: 171
Effect estimate per comparison	Secondary endpoint	Comparison groups	Cladribine 3.5 mg/kg vs. placebo	
		Odds ratio (Cladribine/placebo Point Estimate (SE)	2.53 (0.15)	
		95% CI	(1.87,3.43)	
		P-value	<0.001	
	Secondary endpoint	Comparison groups	Cladribine 5.25 mg/kg vs. placebo	
		Odds ratio (Cladribine/placebo Point Estimate (SE)	2.43 (0.15)	
		95% CI	(1.81,3.27)	
		P-value	<0.001	
Secondary endpoint *(Disability progression at 96 weeks)* Descriptive statistics and estimate variability	Treatment group	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Number of subject	456	433	437
	Time to 3-Month Sustained change in EDSS Score	n (missing): 456 n (Events): 62 n (Censored): 394	n (missing): 433 n (Events): 58 n (Censored): 375	n (missing): 437 n (Events): 82 n (Censored): 355
Effect estimate per comparison	Secondary endpoint	Comparison groups	Cladribine 3.5 mg/kg vs. placebo	
		Hazards ratio (Cladribine/placebo Point Estimate (SE)	0.67 (0.17)	
		95% CI	(0.48, 0.93)	
		P-value	0.018	
	Secondary endpoint	Comparison groups	Cladribine 5.25 mg/kg vs. placebo	
		Hazards ratio (Cladribine/placebo Point Estimate (SE)	0.69 (0.17)	
		95% CI	(0.49, 0.96)	
		P-value	0.026	

Secondary endpoint *(Mean Number of Active T1 gadolinium-enhanced lesions per subject per scan at 96 weeks)* Descriptive statistics and estimate variability	Treatment group	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Number of subject	456	433	437
	Mean Number of Active T1 gadolinium-enhanced lesions per subject per scan at 96 weeks	Mean (SD): 0.07 (0.37)	Mean (SD): 0.09 (0.30)	Mean (SD): 0.86 (1.78)

Effect estimate per comparison	Secondary endpoint	Comparison groups	Cladribine 3.5 mg/kg vs. placebo
		Treatment Difference (Cladribine/placebo Point Estimate (SE)	-0.78 (0.07)
		95% CI	(-0.92, -0.65)
		P-value	<0.001
	Secondary endpoint	Comparison groups	Cladribine 5.25 mg/kg vs. placebo
		Treatment Difference (Cladribine/placebo Point Estimate (SE)	-0.80 (0.07)
		95% CI	(-0.94, -0.66)
		P-value	<0.001

Secondary endpoint *(Mean number of Active T2 lesions per subject per scan at 96 weeks)* Descriptive statistics and estimate variability	Treatment group	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Number of subject	456	433	437
	Mean number of Active T2 lesions per subject per scan	Mean (SD): 0.29 (0.56)	Mean (SD): 0.35 (0.66)	Mean (SD): 1.38 (2.11)

Effect estimate per comparison	Secondary endpoint	Comparison groups	Cladribine 3.5 mg/kg vs. placebo
		Treatment Difference (Cladribine/placebo Point Estimate (SE)	-1.05 (0.09)
		95% CI	(-1.22, -0.87)
		P-value	<0.001
	Secondary endpoint	Comparison groups	Cladribine 5.25 mg/kg vs. placebo
		Treatment Difference (Cladribine/placebo Point Estimate (SE)	-1.10 (0.09)
		95% CI	(-1.27, -0.94)
		P-value	<0.001

2.4.7.3. Supportive study: Study 2CdA-MS-SCRIPC (Scripps-C)

Methods
This is a phase II, randomized, parallel group, double-blind, placebo-controlled, single-center, study of subcutaneously administered cladribine in subjects with RRMS. The presented efficacy results were derived from retrospective analyses. The total duration was 18 months. The study was designed to serve as a proof of concept study.

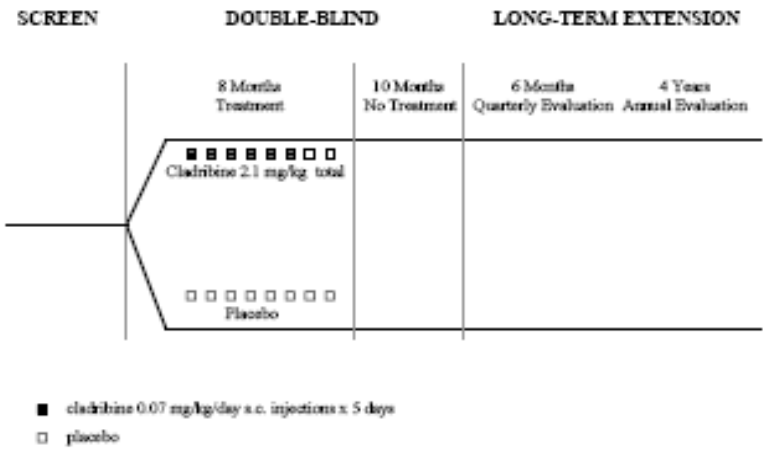
Participants and treatments
Subjects participating in the Scripps-C trial received either:

- 5 daily subcutaneous injections of parenteral cladribine (0.07 mg/kg/day) for 6 courses for a total dosage of 2.1 mg/kg (one 5-day course per month for six months) and two placebo courses

or

- eight placebo courses.

Subjects were to be followed in a double-blind manner for a total of 18 months, including the dosing period. After the conclusion of the double-blind period, subjects were eligible to receive a course of treatment with cladribine in an open-label fashion. This included retreatment (former cladribine 2.1 mg/kg subjects) and new treatment (former placebo subjects). The study design is illustrated in the figure below.



Endpoints
The original protocol designated the co-primary endpoints of mean number of active lesions per subject per year as determined by MRI and an index based on the SNRS score and, as a secondary endpoint, annualized relapse rate. However, in a meeting with representatives of the FDA, March 1998, MRI results were considered to be an important endpoint that could serve as the basis for the evaluation of efficacy. Therefore, in the final clinical trial report, the primary efficacy criterion was the presence or absence of T1 brain lesions at the final evaluation assessed by gadolinium-enhanced MRI; secondary efficacy parameters included annualized relapse rates, as well as changes from baseline to final evaluation in the EDSS and SNRS scores.

Participant flow, baseline data and protocol deviations
Of the 49 subjects enrolled in the study and randomized to receive treatment, 14 (29%) subjects were male, 35 (71%) subjects were female, and the median age was 41.0 years. Most subjects were white (94%).

Ninety-six percent of subjects in the cladribine 2.1 mg/kg treatment group completed the study while 70% of subjects in the placebo group completed the study. The reason for the difference in the withdrawal rates for the two treatment groups was due to the number of subjects who withdrew in the placebo group due to "other" reasons (worsening symptoms and moving out of state). None of the subjects in either group withdrew due to AEs.

The median duration of illness was 10 years with a median relapse rate of two per year. The median baseline EDSS score across all subjects was 3.5 and ranged from 1.0 to 6.5. Baseline EDSS scores ranged from 1.0 to 6.5 (median 3.5) for subjects randomized to receive placebo and from 2.0 to 6.5 (median 3.5) for subjects randomized to receive cladribine 2.1 mg/kg. The median baseline SNRS score across all subjects was 77 with a range of 43 to 98. The range of SNRS scores at baseline was similar for the placebo and cladribine 2.1 mg/kg treatment groups.

Outcomes and estimation
Cladribine 2.1 mg/kg treatment was superior to placebo treatment in subjects with RRMS with respect to the proportion of subjects having detectable MRI T1 enhanced lesions, the mean volume and number of T1 enhanced lesions, and median volume of T2 lesions at the Final evaluation of this study. Additionally, the treatment effect on annualized exacerbation rates was statistically significant. No statistically significant treatment effects were observed in the changes from baseline to endpoint for the EDSS score and the SNRS score.

2.4.8. Discussion on clinical efficacy

The efficacy of cladribine in RRMS has been evaluated in a single pivotal trial, a double-blind, placebo-controlled multi-centre phase III study (CLARITY); and in a supportive double-blind, placebo-controlled, single-centre phase II study (Scripps-C). The Scripps-C trial examined a total cumulative dose of 2.1 mg/kg as a parenteral formulation (applied subcutaneously), while the CLARITY trial used an oral formulation (tablets) in a cumulative dose of 3.5 mg/kg and 5.25 mg/kg. No dose-finding studies have been carried out in the population of the intended target indication and with the intended oral formulation.

The primary objective in the phase III study was to evaluate the qualifying relapse rate at 96 weeks for cladribine, administered at cumulative dosages of 3.5 mg/kg and 5.25 mg/kg, compared to placebo. Time to disability progression, a clinically highly relevant secondary endpoint in this study, was measured in terms of a 3-month sustained change in EDSS score. Regarding the primary analyses, statistically significant improvement was demonstrated for cladribine 3.5 mg/kg and 5.25 mg/kg in all endpoints. However, the smaller dose demonstrated a similar or even better clinically relevant effect for most of the parameters when compared to the higher dose. For this reason, the applicant agreed to withdrew the higher dose regimen.

The primary endpoint was the qualifying relapse rate at 96 weeks, which was reduced in a statistically significant difference for both active treatment groups ($p<0.001$) when compared to placebo. The annualized qualifying relapse rates were 0.15 for the cladribine 5.25 mg/kg treatment group, 0.14 for the cladribine 3.5 mg/kg treatment group, and 0.33 under placebo. Regarding time to disability progression, the analyses in the ITT population reached statistical significance over placebo. However, in the placebo group 82/437 patients had a sustained change in EDSS score compared to 62/456 patients in the 5.25 mg/kg group and 58/433 patients in the 3,5 mg/kg treatment group during a study period of 96 weeks. Thus, there is a difference compared to placebo of about 20 and 24 patients for a time period of 2 years, respectively. Considering the 10th percentile, time to disability progression was 13.6 month in the 5.25 mg/kg group, 16.4 month in the 3.5 mg/kg group and 10.8 month in the placebo group. The 25th percentile was not reached in any group. Therefore, a clinically relevant effect regarding disability progression has not been demonstrated, neither for the higher dose 5.25 mg/kg nor for the lower dose 3.5 mg/kg. According to the CHMP Guideline on the clinical investigation of medicinal products for the treatment of multiple sclerosis (CPMP/EWP/561/98 Rev. 1), the most relevant parameter for a disease-modifying drug (DMD) in MS is the accumulation of disability and relapse rate cannot be taken as a surrogate for disease progression.

Based on the baseline characteristics of the CLARITY trial, the included study population consisted of RRMS patients, rather mildly impaired with low disease activity. Efficacy results are considered to be modest in a low risk population. The applicant was requested by the CHMP to define a restricted target population with high disease activity in which the unfavourable safety profile could be considered more acceptable. Therefore the applicant applied for the following indication in a restricted target population:

MOVECTRO is indicated as disease-modifying therapy in relapsing-remitting multiple sclerosis for the following subjects:

- Patients with high disease activity and/or risk of disease progression defined as those with 2 or more relapses in the previous year and one or more T1 gadolinium-enhancing lesions.

Or

- Patients who are intolerant to beta-interferon or glatiramer acetate therapies.

Only 41 patients in the placebo group and 50 patients in the cladribine 3.5 mg/kg group meet the criteria for a high disease activity (HDA) patient group. In this small population, statistically significant and clinically relevant results could be demonstrated for the primary endpoint, annualized relapse rate: The annualized qualifying relapse rates were 0.22 for the cladribine 3.5 mg/kg treatment group, and 0.67 under placebo ($p<0.001$). Time to disability progression failed to demonstrate statistical significance. Time to disability progression was 13.5 months for the cladribine 3.5 mg/kg treatment group, and 5.4 months under placebo ($p=0.509$). Results should be carefully assessed with respect to the small number of patients in every treatment group. However, 78% of the patients had no 3-month sustained change under cladribine 3.5 mg/kg, but also 75.6 % had no 3-month sustained change under placebo. The clinical relevance of these results for the defined high disease activity group is therefore questionable. The CHMP also noted that there must have been in this HDA subgroup a relevant proportion of subjects DMD naive at baseline, for which a similar effect could have been reached with authorised DMDs.

Regarding patients who are intolerant to beta-interferon or glatiramer acetate therapies. only a small number of patients had taken any disease modifying drug pre-treatment, around 30% in each treatment group. Patients who had previously failed treatment with two or more DMDs on basis of efficacy had been excluded from the study. In the end, only 44 intolerants were included in

the placebo group, 45 intolerants in the 3.5mg/kg active treatment group, patients were pre-treated around 19 month. Importantly, patients that are intolerant to beta-interferons/glatiramer acetate may be mild RRMS / non-high active disease patients for which the risks of cladribine do not outweigh the benefits and not necessarily need to be treated with cladribine. In addition, the CHMP noted that information is lacking regarding how "intolerant" was defined (duration of prior treatment and proportion of patients intolerant to interferons and glatiramer acetate respectively). Time to disability progression failed to reach statistical significance when compared to placebo in this subgroup.

For reasons of safety, the Applicant proposed a more stringent treatment regimen whereby only patients with a normal lymphocyte count or no worse than a Grade 1 CTCAE lymphopenia would be eligible for re-treatment with cladribine. The subpopulation of the CLARITY study fulfilling these criteria consisted of 263 cladribine and 374 placebo treated patients, that means 61.2% of the "original low dose cladribine patients" and 86% of the "original low dose placebo patients" were included in this subpopulation. Efficacy results in this sub-population were comparable to those of the whole study population for all key clinical and MRI outcomes. In addition, efficacy results were generally consistent across HDA patients with and without revised re-treatment guidelines. However, these post-hoc analyses derived from a single pivotal trial involve small, not pre-defined sub-populations. It should also be considered that in the CLARITY trial re-treatment was initiated at a fixed pre-defined date and that the newly proposed flexible treatment regimen, where patients will start a new cycle of cladribine based on lymphocyte count, has not formally been evaluated.

2.4.9. Conclusions on the clinical efficacy

In conclusion, efficacy data for the subpopulations applied for were obtained from subgroup analyses and lack robustness. The optimal dose and the revised treatment regimen using the stricter re-treatment criteria have not been adequately investigated for the target population. Finally, the indication in patients who are intolerant to beta-interferon or glatiramer acetate is not acceptable as this population may include patients with mild to moderate disease activity.

2.4.10. Clinical safety

2.4.10.1. Patient exposure

Safety data from the CLARITY trial are the most informative as this is the only study in the indication and therapeutic regimen applied for. Patient exposure by cumulative dose in the CLARITY trial is summarised below.

CLARITY Study Randomized Treatment Group	**0 mg/kg (n=433) n (%)**	**Cladribine >0-1.75 mg/kg (n=20) n (%)**	**Cladribine >1.75-3.5 mg/kg (n=97) n (%)**	**Cladribine >3.5-5.25 mg/kg (n=458) n (%)**	**Cladribine >5.25-7.0 mg/kg (n=311) n (%)**	**All Subjects (n=1319) n (%)**
0 mg/kg	433 (100.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	435 (33.0)
Cladribine 3.5 mg/kg	0 (0.0)	8 (40.0)	81 (83.5)	341 (74.5)	0 (0.0)	430 (32.6)
Cladribine 5.25 mg/kg	0 (0.0)	10 (50.0)	16 (16.5)	117 (25.5)	311 (100.0)	454 (34.4)
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The integrated safety database comprises data from the CLARITY trial and from the following trials:

- Study 2-CdA-MS-SCRIPC, Cladribine treatment of relapsing-remitting multiple sclerosis ("Scripps-C"),
- Study 2-CdA-MS-SCRIPP, Cladribine clinical trial in the treatment of chronic progressive multiple sclerosis ("MS-Scripps"),
- Study 2-CdA-MS-001, Cladribine clinical trial in chronic non-remitting progressive multiple sclerosis ("MS-001"), and
- Study 2-CdA-MS-SCRIPB, Cladribine treatment of multiple sclerosis, a multicenter trial ("Scripps-B").

Patient exposure in the integrated safety database is summarised in the table below.

Table 3: Number and Percentage of Subjects by Study and Cladribine Tablets Equivalent Cumulative Dose Range - (Population: Subjects Receiving Study Drug at Any Time During the Studies)

Study	0 mg/kg (n=479)	Cladribine >0-1.75 mg/kg (n=33)	Cladribine >1.75-3.5 mg/kg (n=125)	Cladribine >3.5-5.25 mg/kg (n=548)	Cladribine >5.25-7.0 mg/kg (n=359)	Cladribine >7.0-8.75 mg/kg (n=19)	Cladribine >8.75 mg/kg (n=24)	All Cladribine Subjects (n=1108)	All Subjects (n=1587)
25643 (CLARITY)	433 (90.4)	20 (60.6)	97 (77.6)	458 (83.6)	311 (86.6)	0 (0.0)	0 (0.0)	886 (80.0)	1319 (83.1)
Scripps-B	0 (0.0)	1 (3.0)	0 (0.0)	6 (1.1)	3 (0.8)	1 (5.3)	0 (0.0)	11 (1.0)	11 (0.7)
Scripps-C	13 (2.7)	0 (0.0)	1 (0.8)	32 (5.8)	3 (0.8)	0 (0.0)	0 (0.0)	36 (3.2)	49 (3.1)
MS-Scripps	1 (0.2)	1 (3.0)	6 (4.8)	10 (1.8)	12 (3.3)	7 (36.8)	12 (50.0)	48 (4.3)	49 (3.1)
MS-001	32 (6.7)	11 (33.3)	21 (16.8)	42 (7.7)	30 (8.4)	11 (57.9)	12 (50.0)	127 (11.5)	159 (10.0)

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Note: Treatment groups refer to the cumulative dose over the entire study.

In addition to the integrated safety analysis, safety data are provided by 2 double-blind placebo-controlled studies (ONWARD and CLARITY extension studies), which are ongoing at the time of this submission. In January 19, 2009 (cut off date at time of evaluation), data were available for 525 subjects, 60 subjects enrolled in the ONWARD study and 465 subjects enrolled in the CLARITY Extension study. As these studies are blinded, exposure data are not currently available.

Among the 60 subjects enrolled in the ONWARD trial, the median age of enrolled subjects is 41.5 years (range: 21, 58). The majority of subjects are female (71.7%), and nearly all identified as 'White' (95.0%). The median body weight is 75.17 kg. All subjects enrolled have been diagnosed wit RRMS.

Among the 465 subjects enrolled in the CLARITY Extension trial at the time of this analysis, the median age of enrolled subjects is 41.0 years (range: 20, 67). The majority of subjects are female (65.2%), and nearly all identified as 'White' (97.0%). The median body weight is 68.00 kg.

2.4.10.2. Adverse events

Integrated safety database

Table 14: Common Treatment Emergent Adverse Events Occurring at Any Time During the Studies (At an Incidence Proportion >= 2.0% Higher Among All Cladribine Treated Subjects vs. Placebo (0 mg/kg))

(Population: Subjects Receiving Study Drug at Any Time During the Studies)

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

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CLARITY study

Of the 1319 subjects in the safety population of the CLARITY study, 1047 subjects (79.4%) reported a total of 7184 treatment emergent adverse events (TEAEs) in the three treatment groups. In the cladribine 5.25 mg/kg group, 381 of 454 subjects (83.9%) reported 2712 events. In the cladribine 3.5 mg/kg group, 347 of 430 subjects (80.7%) reported 2514 events, and in the placebo group 319 of 435 subjects (73.3%) reported 1958 events.

The most frequently reported TEAEs in the three trial groups were headache, nasopharyngitis, upper respiratory tract infection, nausea, and lymphopenia. Headache occurred slightly more frequently in the cladribine groups than in placebo (22.4% vs. 17.2%). The frequency of nasopharyngitis was comparable between cladribine and placebo-treated subjects (13.6 % for cladribine vs. 12.9% for placebo). The frequency of upper respiratory tract infections in the cladribine groups was greater than that observed in the placebo group (12.0% vs. 9.7%). Nausea was reported in 11% of the cladribine 5.25 mg/kg group and in 9.0% of placebo subjects. A dose-effect was seen, as a greater proportion of subjects treated with cladribine 5.25 mg/kg (31.5%) compared to cladribine 3.5 mg/kg (21.6%) experienced lymphopenia. Among the other system organ classes there were no notable differences between the cladribine and placebo groups in the nature or frequency of TEAEs reported during the trial.

The system organ class (SOC) with the greatest frequency of adverse events was the infection and infestations SOC. The incidence of infections and infestations was 48.9%, 47.7% and 42.5%, for the cladribine 5.25 mg/kg, cladribine 3.5 mg/kg, and placebo treatment groups, respectively. Most of these infections were viral in nature and involved the upper respiratory tract. Reports of herpes

infection were common in the cladribine-treated subjects. The incidence of herpes simplex (oral herpes, herpes simplex, genital herpes, and herpes virus infection) was greater in the cladribine 5.25 mg/kg group compared to the cladribine 3.5 mg/kg and placebo groups. Twenty subjects experienced herpes zoster, and were exclusively in the cladribine treatment groups. Twelve subjects were in the cladribine 5.25 mg/kg treatment group and 8 subjects were in the cladribine 3.5 mg/kg treatment group. The majority of these herpes zoster cases were assessed by the investigators as mild to moderate in severity. All cases resolved without sequela, except for the single case of herpes oticus (Ramsay-Hunt), which was associated with persistent, intermittent right-sided ear pain, but which was reported to have stabilized by the end of the trial. There were 3 cases of herpes varicella (one in each study arm). All cases of herpes varicella resolved without any complication.

Lymphopenia, an expected event based on the mechanism of action of cladribine, occurred more frequently in the cladribine treatment groups (26.7%) as compared to the placebo group (1.8%). A greater proportion of subjects treated with cladribine 5.25 mg/kg (31.5%) compared to cladribine 3.5 mg/kg (21.6%) experienced lymphopenia. A similar dose effect was also noted for neutrophils and leucopenia.

The cardiac safety of cladribine tablets was assessed in a sub-population of RRMS patients (N=135) from the pivotal Phase III CLARITY trial. This ECG sub-study in the target population of RRMS subjects was designed to evaluate potential acute and/or accumulative effects of cladribine on the ECG time-intervals and T-wave morphology, with a particular emphasis on the heart rate-corrected QT interval (QTcF primary; QTcB supportive). Moreover, subjects included in this sub-study underwent PK sampling in order to allow for concentration/QT analysis. The ECG evaluation did not indicate any effect of cladribine tablets on heart rate, AV conduction, or cardiac depolarization as measured by the PR and QRS interval durations. The morphological changes showed no clinically important signal of cladribine effect. In addition, the data showed no clear evidence of an acute cladribine concentration-dependent effect on cardiac repolarization.

2.4.10.3. Serious adverse event/deaths/other significant events

Deaths

In the CLARITY-study four deaths in the cladribine treatment groups (two in each treatment group) occurred during the controlled phase of the trial vs. two deaths in the placebo group. One death in the cladribine-treated subjects was in a 21-year old female due to exacerbation of latent tuberculosis. This subject received one treatment cycle of oral cladribine and developed pancytopenia. 6 months post-treatment she died due to severe exacerbation of latent tuberculosis. The Applicant stated that the immunosuppressant activity of cladribine therapy likely contributed to the tuberculosis reactivation. Death from another female, who received a total cladribine dose of 3.5 mg/kg and died from pancreatic carcinoma with liver infiltration 9 months after her last treatment, was assessed as unlikely related to cladribine. In the placebo group a completed suicide and a haemorrhagic stroke with fatal outcome occurred. No deaths had occurred in either of the ongoing studies, ONWARD or CLARITY Extension as of the data cut-off date of 10 August 2010.

Malignancies

In total, 22 cases of malignancies were reported with the use of cladribine at cut-off date 1st August 2010 in the whole clinical programme in multiple sclerosis. In addition, two cases were reported in placebo treated patients (one basal cell carcinoma and one ovarian cancer). In the controlled phase of completed studies, 5 malignancies in cladribine treated patients were reported vs. 1 in placebo patients.

Completed Controlled Studies (5)

Study	Event (PT)	Treatment group (mg/kg)	Cladribine dose received (mg/kg)	# of courses of cladribine received	Event latency (in years)
MS-001	Cervix carcinoma	5.25	5.25	N/A	< 1 (9 months)
CLARITY	Cervix carcinoma in situ	5.25	3.9	4	< 1 (10 months)
CLARITY	Ovarian cancer	3.5	1.8	2	1
CLARITY	Pancreatic carcinoma metastatic	3.5	3.8	4	1.5
CLARITY	Malignant melanoma	3.5	3.7	4	< 1

Completed Uncontrolled Studies (5)

Study	Event (PT)	Treatment group (mg/kg)	Cladribine dose received (mg/kg)	# of courses of cladribine received	Event latency (in years)
MS-SCRIPPS (Ext. Phase)	Basal cell carcinoma	7 / 2.5	9.5	N/A	4.5
MS-SCRIPPS (Ext. Phase)	Basal cell carcinoma	7 / 3.5	10.5	N/A	3.8
MS-SCRIPPS (Ext. Phase)	Bladder transitional cell carcinoma	3.5 / FU	3.5	N/A	2.2
MS-001 (Ext. Phase)	Colon cancer	1.75 / 5.25	7	N/A	3.5
MS-001 (Ext. Phase)	Basal cell carcinoma	1.75 / 1.75	3.5	N/A	3.5

Post studies (3)

Study	Event (PT)	Treatment group (mg/kg)	Cladribine dose received (mg/kg)	# of courses of cladribine received	Event latency (in years)
MS-SCRIPPS	Basal cell carcinoma	7	7	N/A	2.8
CLARITY	Choriocarcinoma	5.25	5.5	6	2.5
CLARITY	Bladder cancer	3.5	3.7	4	3

Ongoing studies (9)

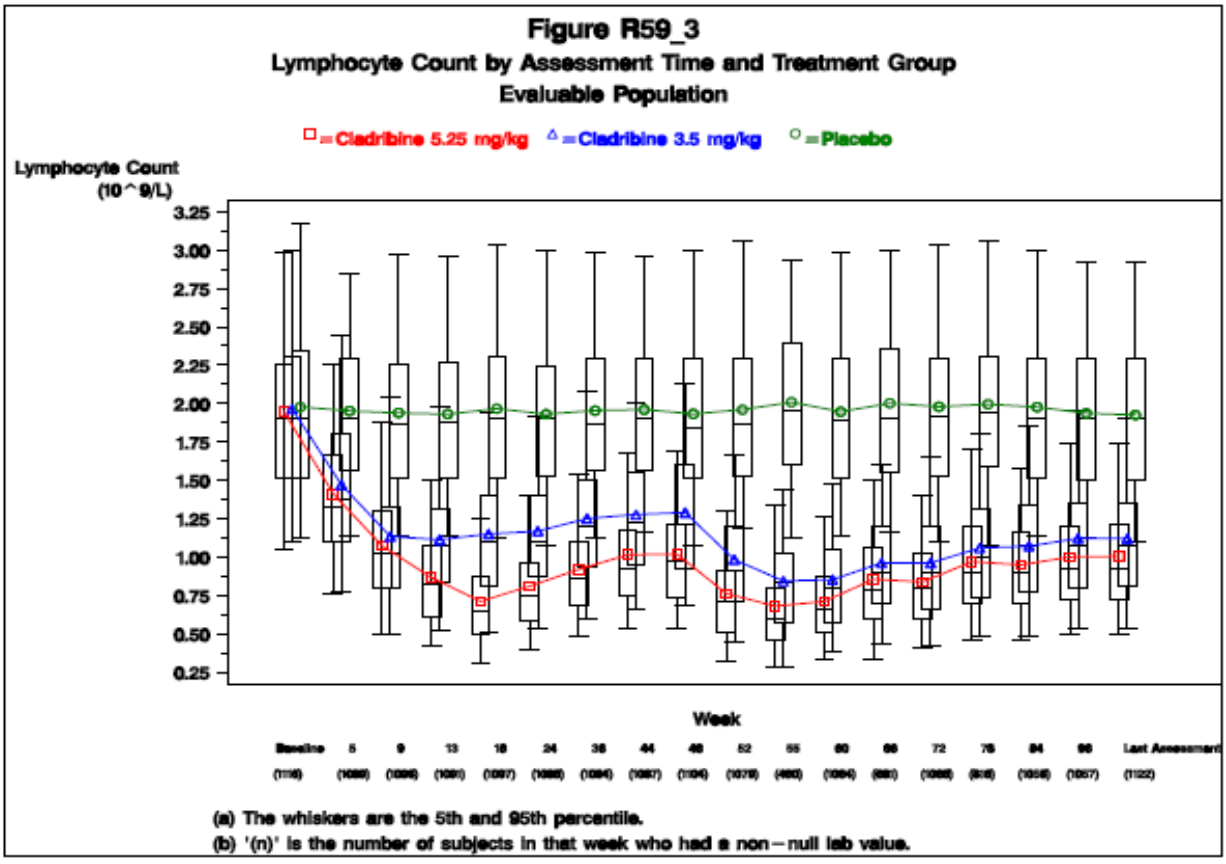
Study	Event (PT)	Treatment group (mg/kg)	Cladribine dose received (mg/kg)	# of courses of cladribine received	Event latency (in years)
CLARITY EXT	Ovarian cancer	3.5 / 3.5	5.3	6	3.7
CLARITY EXT	Malignant melanoma	3.5 / placebo	3.5	4	3.3
CLARITY EXT	Thyroid cancer	5.25 / placebo	5.24	6	3.3
CLARITY EXT	Rectosigmoid cancer	3.5 / 3.5	7.2	8	3.8
CLARITY EXT	Breast cancer	3.5 / 3.5	7.3	8	3.3
CLARITY EXT	Basal cell carcinoma of the scalp	3.5 / Rebif	3.76	4	3.2
CLARITY EXT	Malignant melanoma	5.25 /3.5	4.38	5	3.8
CLARITY EXT	Renal cell carcinoma	5.25 / 3.5	8.75	10	4
ONWARD	Squamous cell carcinoma	3.5	3.5	4	2.2

The RR based on patients in all studies (also including the malignancies perceived in the CLARITY-extension study, cut-off date 01 march 2010) indicated a 5-fold increase in the risk of cancer but with a broad CI (95% -CI 0.67- 38.43). At cut-off date 01 August 2010 for methodological reasons the Applicant presented a differing calculation of RR, which only includes malignancies in the controlled phase of completed studies (5 malignancies in cladribine treated patients vs. 1 in placebo-treated). According to the Applicant the most meaningful risk estimates in order to prevent confounding by time since randomization are those derived from data where the length of follow-up is similar in the two cohorts of patients treated with cladribine and placebo exposed patients. Therefore, the relative risk of malignancies was estimated based on the controlled-phases of the cladribine studies in patients with MS (CLARITY and the four double-blind controlled studies conducted with parenteral cladribine). The RR is 2.31 (95%CI 0.27 – 19.81), suggesting a two-fold increase in the risk of cancer among cladribine exposed patients, statistically not significant. It is agreed that RR calculation based on all studies might be biased. However, renunciation of further

observation time is a clearly anticonservative approach. 22 malignancies in cladribine treated patients in the overall clinical program vs. 2 in the placebo group is indicative of a malignancy risk increasing by exposure time

Lymphopenia and risk of infection

To characterize the time course and recovery of the lymphocytes following cladribine exposure, the best and largest data set comes from the oral experience in the CLARITY study. Lymphopenia occurred more frequently in the cladribine treatment groups (26.7%) as compared to the placebo group (1.8%). A dose-effect was seen, as a greater proportion of subjects treated with cladribine 5.25 mg/kg (31.5%) compared to cladribine 3.5 mg/kg (21.6%) experienced lymphopenia. Severe or life-threatening lymphopenia (CTCAE laboratory Grade 3 or 4 lymphopenia) occurred in 314 subjects (36%) in the cladribine groups. Among those, the absolute lymphocyte counts resolved to grade 0 or 1 in approximately only 50% of these subjects. The cladribine tablets 5.25 mg/kg treatment, compared to the 3.5 mg/kg treatment, contributed disproportionately to the frequency of the development of Grade 3 or 4 lymphopenia: In the CLARITY study, 45% of subjects developed a Grade 3 or 4 lymphopenia at any time over the 96 weeks in study, compared to 26% of subjects in the 3.5 mg/kg cladribine tablets treatment group. Only 3 subjects in the 3.5 mg/kg treatment group (0.7%) developed a Grade 4 lymphopenia. By contrast, 13 subjects in the 5.25 mg/kg treatment group (2.9%) developed a Grade 4 lymphopenia. Thirty five subjects were identified with persistent Grade 3 lymphopenia at final evaluation on study (none with persistent grade 4). Most of them (71%, n=25) with the high dose and 29% (n=10) of them with the low dose treatment regimen.



Treatment induces preferably lymphopenia, which is most pronounced and makes most of reduction of WBC. A rapid drop of all lymphocyte subsets (T-cells, B-cells, NK cells) was seen and the lymphopenic effect was especially pronounced for T cells. Cladribine induces a pronounced and longstanding suppression of CD4+ and in a comparatively lesser extent of CD8+ T-lymphocytes. CD4+ and CD8+ T-lymphocytes count did not recover at the end of the study (week 96). The importance of T helper cells is known from HIV as T helper cells are markedly decreased by infection with HI-virus. Clinical categories are used for indicating the severity of immunosuppression by absolute CD4+ count/µl: Category A (> 500/µl, Category B (500-200/µl) and category C (< 200/µl). The CD4+ count during the CLARITY-study in the high dose group the mean was between 200 and 300 /µl for several months, indicating a severe immunosuppression,

which did not recover at the end of the study. The nadir of memory and naïve T lymphocytes occurred at week 16. Also a pronounced suppression of B-Lymphocytes, with a nadir at week 16 and week 52 was observed, with partial recovery at the end of the trial. From the application of cladribine in hairy cell leukemia it is known that complete recovery of T-and B-lymphocytes can take up to two years. Long-term effects of this immunosuppression are unknown.

One or more serious infections occurred in 4.6% of cladribine-treated subjects and 1.9% of placebo subjects. Within the Infections and infestations SOC, SAEs reported by 2 or more cladribine treated subjects included pneumonia, urinary tract infection, herpes zoster, pyelonephritis, sepsis, upper respiratory tract infection, urosepsis, adnexitis, and cellulitis. The development of Grade 3 or Grade 4 lymphopenia is associated with an increased risk of adverse events, particularly the development of an infectious disease event. In their response to the CHMP concern over the risk of lymphopenia, the applicant provided a correlation analysis across the treatment groups in the CLARITY study for the maximum grade lymphopenia attained by subject and the development of any infectious adverse event in any subject during study. The correlation demonstrates a statistically significant correlation for the increased likelihood of developing an infectious adverse event in the cladribine tablets 5.25 mg/kg treatment group, but not for the 3.5 mg/kg treatment group. In particular, the relationship between severe lymphopenia and the risk of developing herpes zoster has been evaluated. Ten of the 20 subjects who developed herpes zoster experienced Grade 3 or 4 lymphopenia during the study, suggesting an association between severe lymphopenia and increased risk of herpes zoster.

Other SAEs
Hepatobiliary System Disorders: The overall frequency of SAEs in the SOC of "Hepatobiliary System Disorders" was similar between the cladribine and placebo-treated groups (0.8% for placebo and 1.1% for cladribine. Events of interest were one report of hepatitis, one of hepatitis acute, and one of hepatitis toxic in the cladribine group, and one report of hepatitis toxic in the placebo group. One case of "hepatitis acute" was judged by the investigator as probably related to cladribine.

Skin and subcutaneous tissue disorders: 4 cladribine-treated subjects (0.4%) experienced 5 SAEs (hidradenitis, lichen sclerosus, purpura, generalized rash, skin reaction) whereas no SAEs were experienced in the placebo group. In the cladribine >0-1.75 mg/kg group, one subject experienced purpura secondary to thrombocytopenia, and disseminated violaceous cutaneous plaques and a generalized rash in the setting of fulminant tuberculosis. One of these events may have been an allergic skin reaction to cladribine and is discussed below:

2.4.10.4. Laboratory findings

Laboratory parameters evaluated include routine hematology (hemoglobin, WBC, neutrophils, lymphocytes, eosinophils, and platelets), specialty hematology (CD4+ and CD8+ T-lymphocytes), and clinical chemistry (creatinine, creatine kinase, bilirubin, AST, ALT, and alkaline phosphatase). The reduction of neutrophils was dose-dependent but milder than that of lymphocytes, and in most subjects without clinical relevance. Monocytes were reduced in a similar percentage of subjects as those with reduced neutrophils. Moderate decreases of erythrocytes, haematocrit and haemoglobin were also observed in cladribine treated patients compared to placebo-treated patients. Median platelet counts decreased to a maximum of 10-15% from baseline by week 9 and 13 in the cladribine treatment groups and decreased to about 19% from baseline at week 52 after retreatment (cladribine 5.25 mg/kg). Slight decrease of calcium, increase of alkaline phosphatase and increase of creatine kinase were perceived in cladribine treated patients compared to placebo-treated patients.

2.4.10.5. Safety in special populations

<u>Elderly</u>
As the study population of CLARITY study was restricted to patients ≥18 years and ≤ 65 years, there are no safety data in elderly. There was a trend for more pronounced lymphopenia with age, but this refers to patients younger than 65 years of age.

<u>Renal impairment /liver impairment</u>
Patients were excluded from the CLARITY-study if they had the presence of systemic disease, that in the opinion of the investigator might interfere with the subjects safety, compliance or evaluation

of the condition under study (e.g. amongst others clinically significant hepatic or renal disease). An analysis was done for patients with impaired liver parameters at baseline. For patients with baseline impaired liver parameters there were signs for further impairment of hepatic function. For patients with renal impairment no sufficient data are available.

Pregnancies
Subjects who were pregnant or lactating were excluded from all studies and use of adequate contraception was required in study participants. Nonetheless, 17 pregnancies were reported among the cladribine-treated subjects and 6 pregnancies were reported among the placebo subjects. 10 of the 17 pregnancies in the cladribine group were terminated by voluntary or medical abortion and in 4 of the 17 pregnant subjects spontaneous abortion/ miscarriage occurred. One abortion was not specified. Two patients in the cladribine groups had delivery of a healthy infant. In the placebo group 2 pregnancies were terminated by voluntary abortion, 1 miscarriage occurred and 3 patients had delivery of a healthy infant. Nevertheless no data or follow-up data about clinical examination of the newborns, no information about reasons for medical abortion or results is available, and examinations of the abortus have not been done.

2.4.10.6. Safety related to drug-drug interactions and other interactions

Interferon-beta
The ongoing ONWARD study is assessing the effect of co-administration of cladribine with interferon-beta in MS patients. It is a Phase II, randomized, double-blind, placebo-controlled oral cladribine tablets (total cumulative dose 3.5 mg/kg) as an add-on therapy to injectable interferon-beta (IFN-beta) treatments (Rebif 44 micrograms; Avonex 30 mcg, or Betaferon 250 mcg), in MS subjects with active disease. In the original ONWARD protocol, subjects on stable regimens of IFN-beta were to be randomized 2:2:1 to receive add-on treatment with cladribine tablets at 3.5 mg/kg (2 courses), cladribine tablets at 5.25 mg/kg (4 courses), or placebo during the first 48 weeks of the trial, followed by re-treatment with 2 courses of cladribine or placebo during the second 48 weeks. However, evaluation of the first 38 randomized subjects revealed an increased frequency of grade 3 and 4 hematological toxicity compared to the previous dosing experience with cladribine monotherapy. No subject developed an SAE or medical complication because of the grade 3 or grade 4 hematological toxicity. Interferons are also associated with lymphopenia and neutropenia, and consequently the combination of the two therapies could lead to an additive or synergistic hematological toxicity. Following the review of these data and upon the recommendation of the Data Safety Monitoring Board, the protocol was amended and the cladribine 5.25 mg/kg treatment group was eliminated.

In the CLARITY study, IFN-beta (Rebif 44 mcg TIW) was a rescue option. Nine (of 456), 11 (of 433) and 27 (of 437) subjects received a rescue treatment with IFN-beta in the cladribine 5.25 mg/kg group 3.5 mg/kg group and placebo group, respectively. Among the 20 cladribine rescued subjects, 15 had a lymphopenia CTCAE toxicity up to grade 1 or higher (up to grade 3) at the time of rescue. Three subjects presented with an increase in the severity of the lymphopenia following the start of IFN-beta (1 subject increased from toxicity grade 1 to toxicity grade 2; 1 subject increased from toxicity grade 0 to toxicity grade 1; 1 subject increased from toxicity grade 1 to toxicity grade 3), 11 subjects presented with no changes in the lymphopenia severity, and 6 subjects presented an improvement in the lymphopenia severity. No other remarkable changes occurred in the blood cell formulas of these subjects after rescue. Of the 20 rescued subjects, 3 subjects experienced 6 adverse events within the Infections and infestations SOC, beginning 0.5 to 5 months after the start of IFN-beta treatment. These infections were of mild to moderate severity.

Glucocorticoids
A high percentage of patients in the CLARITY-study received concomitant systemic glucocorticoids (47% of the placebo and 28% of the cladribine treated subjects). Overall, the incidence of events in the "Infections and infestations" SOC was higher for both placebo and cladribine-treated subjects receiving corticosteroids, compared to the respective groups not receiving corticosteroids (placebo without corticosteroids 36,7%, cladribine without corticosteroids 47,9%). The incidence of Infections and infestations among placebo subjects treated concomitantly with corticosteroids (51.2%) was comparable to the incidence observed among cladribine subjects treated concomitantly with corticosteroids (52.3%).

2.4.10.7. Discontinuation due to adverse events

In the CLARITY trial, 4.3% of the patients withdrew from treatment due to adverse events. Disease progression was cited as a reason for treatment withdrawal in 2.6% of the patients. In the ongoing CLARITY Extension study, 4/465 subjects (0.9%) have withdrawn from treatment prematurely and no subjects have withdrawn due to either an adverse event or lack of efficacy. One subject was withdrawn due to loss to follow-up and 3 were classified as 'other' reasons.

2.4.10.8. Revised dosing recommendations and impact on the safety of cladribine tablets

The 5.25 mg/kg dose, compared to the 3.5 mg/kg one, contributed disproportionately to the frequency of the development of Grade 3 or 4 lymphopenia. Thus, withdrawal of the cladribine tablets 5.25 mg/kg dose is supported. In addition, the applicant proposed to limit re-treatment at the time of the second or subsequent courses with cladribine to subjects who have a normal Absolute Lymphocyte Count (ALC) or an ALC no worse than a Grade 1 lymphopenia to further reduce potential risk attendant with the use of cladribine tablets in RRMS. The overall short course dosing regimen to achieve a target dose of cladribine tablets 3.5 mg/kg is unchanged. Finally, the applicant suggested to restrict the treatment duration to 4 courses, in line with the safety experience gained from the clinical trials.

In the subpopulation presented by the Applicant with stricter treatment criteria only 9.5% of subjects on cladribine experienced Grade 3 or 4 lymphocyte toxicity, versus 0.3% of those on placebo at any time during week 0 to 96 of the CLARITY study. This is better compared to the low dose group in which 25.6% of subjects treated with cladribine 3.5 mg/kg had one or more Grade 3 or 4 lymphocyte toxicity episode, as compared to 0.5% of placebo subjects. Grade 4 lymphopenia occurred in 0.7% of the patients in the low-dose group, whereas no patient experienced grade 4 lymphopenia in the revised re-treatment subpopulation. Only one patient (0.4%) in the re-treatment subpopulation had persistent grade 3 lymphopenia at the time of last assessment (Week 96). Whereas 10 patients (2.3%) in the "original low-dose group" had persistent grade 3 lymphopenia at week 96. Persistent grade 4 lymphopenia did not occur at all at week 96 in both populations. No other grade 3 or 4 toxicities were observed at Week 96 for WBC count, platelet count, neutrophil count or haemoglobin concentration in the re-treatment subpopulation. The WBC, lymphocyte, neutrophil and platelet counts were measured and lymphocyte surface markers (CD3, CD4 [helper T cells], CD8 [suppressor/ cytotoxic T cells], CD4/CD8 ratio and CD19 [B-lymphocytes],) were assessed. Generally, although decreasing in a similar pattern, the nadirs of their median values at each treatment period and the median value at the last assessment visits were higher in the re-treatment subpopulation compared with those in the whole safety population of the CLARITY study.

The proportion of subjects who experienced any TEAE in the subpopulation with stricter re-treatment criteria was 77.6% and 73.5% for cladribine and placebo groups respectively. With respect to the CLARITY study, 80.7% of subjects in the cladribine 3.5 mg/kg group reported one or more TEAEs versus 73.3% of subjects who were on placebo. A total of 6.1% and 5.3% of cladribine tablets and placebo-treated subjects in the revised re-treatment population experienced one or more SAEs respectively. The main SAEs included infections with one or two events of pneumonia, pyelonephritis, influenza, herpes zoster, salpingo-orophoritis and one malignant melanoma. These results confirm those of the CLARITY study, in which 8.4% of subjects treated with cladribine 3.5 mg/kg experienced one or more SAEs versus 6.4% of those on placebo.

The rate of infections in this specific population was lower vs. placebo compared to the original low-dose group: 46.4% and 43.6%, respectively, compared to the "original low-dose group" in which 47.7% of subjects who received 3.5 mg/kg cladribine experienced events of infections versus 42.5% of those on placebo. The most common infections in the specific population included nasopharyngitis, upper respiratory tract infection, urinary tract infection, influenza and bronchitis.
Only one subject (0.4%) who received cladribine tablets in the revised re-treatment group discontinued treatment because of an AE (nausea). In the CLARITY study, 3.5% of subjects on cladribine 3.5 mg/kg versus 2.1% of those on placebo discontinued treatment due to AEs.

No death occurred in the revised re-treatment subpopulation. One case of malignancy was reported.

2.4.10.9. Long-term Safety

From the CLARITY study it is known that lymphopenia does not recover to baseline values at week 96. Thirty five subjects were identified with persistent Grade 3 lymphopenia at final evaluation on study (none with persistent grade 4). Most of them (71%, n=25) with the high dose and 29% (n=10) of them with the low dose treatment regimen. Only one patient (0.4%) in the re-treatment subpopulation (with stricter criteria for re-treatment) had persistent grade 3 lymphopenia at the time of last assessment, whereas 10 patients (2.3%) in the "original low-dose group" had persistent grade 3 lymphopenia at week 96. The duration of complete recovery of lymphopenia is unknown from the trial data.

In the 96 week ongoing ONWARD-study, evaluation of the first 38 randomized subjects revealed an increased frequency of grade 3 and 4 haematological toxicity compared to the previous dosing experience with cladribine monotherapy and the study protocol was amended (elimination of the cladribine high-dose group). In both CLARITY-extension and ONWARD studies, the information available about the reported cases of malignancies is indicative of a malignancy risk potentially increasing by exposure and time.

2.4.10.10. Post marketing experience

There is no post-marketing experience with cladribine in multiple sclerosis. Experience with the safety profile of cladribine has been acquired in hairy cell leukemia. In Europe, cladribine for intravenous infusion was first approved in Sweden in 1993 for the treatment of HCL and is approved widely in the Member States. Cladribine s.c. is also approved in the treatment of HCL. In some European Member States the approved therapeutic indication also includes certain other lymphoid malignancies. According to the SPC only one treatment cycle is recommended in hairy cell leukaemia whereas in MS a repetitive oral dose regimen with resulting higher cumulative doses is proposed. It is known from the HCL setting that complete recovery of T- and B-lymphocytes can take up to two years.

3.4.10.11 Treatment delay

From the PKPD-model Model Simulation of the effect of treatment delay caused by lymphocyte count and probability of developing a Grade 3 Lymphopenia there are signs that probability of Grade 3 lymphopenia increases by time of delay of treatment, that means that probability increases if grade 2 lymphopenia persists for a longer time. This is biologically plausible and a longer treatment delay/ longer recovery time of grade 2 lymphopenia should be considered as exclusion criterion for further treatment.

2.5. Discussion on clinical safety

The percentage of patients with severe and prolonged lymphopenia (grade 3 or 4 toxicity) was high, especially in the high-dose group. Among those who developed grade 3 or 4 lymphopenia, the absolute lymphocyte counts resolved to grade 0 or 1 in approximately only 50% of these subjects. The system organ class with the greatest frequency of adverse events was the infection and infestations SOC, and the development of Grade 3 or Grade 4 lymphopenia has been shown to be associated with an increased risk of development of an infectious disease complication.

The 5.25 mg/kg dose contributed disproportionately to the frequency of the development of Grade 3 or 4 lymphopenia. Thus, withdrawal of this dose is supported. Safety data for the subpopulation meeting the stricter criteria for re-treatment suggest a lower extent of immunosuppression. This subpopulation consisted of 263 cladribine and 374 placebo treated patients i.e. 61.2% of the "original low dose cladribine patients" and 86% of the "original low dose placebo patients". In this subpopulation only 9.5% of subjects on cladribine tablets experienced Grade 3 or 4 lymphocyte toxicity, versus 0.3% of those on placebo at any time during week 0 to 96 of the CLARITY study. This is indeed better compared to the low dose group in which 25.6% of subjects treated with cladribine 3.5 mg/kg had one or more Grade 3 or 4 lymphocyte toxicity episode, as compared to 0.5% of placebo subjects. Grade 4 lymphopenia occurred in 0.7% of the patients in the low-dose group. To have in mind in the high dose group 5.25 mg/kg 45% of the patients developed a Grade 3 or 4 toxicity. Only one patient (0.4%) in the subpopulation with stricter criteria for re-treatment

had persistent grade 3 lymphopenia at the time of last assessment, whereas 10 patients (2.3%) in the "original low-dose group" had persistent grade 3 lymphopenia at week 96.

Data on complete recovery of lymphopenia and neutropenia are not available from the present clinical development program in MS, and it is known from data for cladribine in hairy cell leukemia that complete recovery of T-and B-Lymphocytes can take up to 2 years. Safety data for the subpopulation meeting the stricter criteria for re-treatment, whereby only patients with a normal lymphocyte count or no worse than a Grade 1 CTCAE lymphopenia would be eligible for re-treatment with cladribine, suggest a lower extent of immunosuppression. However, safety of the changed treatment-regimen has not been sufficiently demonstrated in patients with high disease activity, which was only a small subpopulation of the CLARITY trial.

The disproportion of number of malignancies in the cladribine groups compared to placebo during the whole clinical trial program is another major concern. In the overall clinical trial program, 22 cases of malignancies were reported in cladribine arms versus two cases in the placebo arm. Four malignancies were seen in cladribine treated subjects versus none in the placebo group of the CLARITY-study. Additionally, two cases were reported in cladribine subjects following completion of the trial (bladder cancer and choriocarcinoma) versus one in the placebo group. The relative risk for malignancies indicates a 5-fold increase among those cladribine-exposed subjects in all studies, although with wide confidence interval (CI (95% -CI 0.67- 38.43)). . Non-clinical data suggest no carcinogenicity risk. However the genotoxicity data and the pharmacological properties (alkylation, impairment of immuno-surveillance) of cladribine call for extreme caution. Immunodeficiency can lead an increased risk for the development of malignancies, in particular for those tumours associated with viral antigens, e.g. cancers of the genitourinary tract (e.g. HPV), Kaposi Sarkoma, B-cell-Lymphoma (Human Herpes Virus 8, EBV). It should also be noted that secondary malignancies are a common AE under treatment of hairy cell leukemia with Litak (cladribine s.c.), but are also per se expected in patients with hairy cell leukemia. Due to the mechanism of action of cladribine, it is likely that malignancy risk increases with cumulative dose. The submitted data are in fact indicative of a malignancy risk potentially increasing with exposure and time.

As a dose-finding study has not been done there might be still a lower cumulative dose that is sufficiently efficacious in the high disease activity population but has a better safety profile.

2.6. Conclusions on the clinical safety

Serious safety concerns have been raised, in particular the increased number of malignancies observed in the clinical trials. Even higher malignancy risk may be expected with increasing exposure and time. With the stricter criteria for re-treatment, data suggest that extent of immunosuppression will be lower. However, safety of the changed treatment-regimen has not been sufficiently demonstrated in patients with high disease activity, which was only a small subpopulation of the CLARITY trial.

2.7. Pharmacovigilance

2.7.1. Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of the follow up measures should the application be granted a marketing authorisation.

2.7.2. Risk management plan

The applicant submitted a risk management plan, which included a risk minimisation plan. The CHMP, having considered the data submitted in the application is of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level.

2.7.3. 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.

2.7.4. Benefit-risk balance

2.7.4.1. Benefits

2.7.4.1.1. Beneficial effects

Currently, there is no oral disease modifying medication approved for the treatment of relapsing-remitting multiple sclerosis. An oral formulation would avoid the disadvantages associated with the use of parenteral disease-modifying therapies.

The efficacy of cladribine tablets in RRMS has been evaluated in one double-blind, placebo-controlled multi-centre phase III study (CLARITY), and one supportive double-blind, placebo-controlled, single-centre phase II study (Scripps-C). The primary objective in the phase III study was to evaluate the qualifying relapse rate at 96 weeks for cladribine, administered at cumulative dosages of 3.5 mg/kg and 5.25 mg/kg, compared to placebo. Time to disability progression, a secondary endpoint, was measured in terms of a 3-month sustained change in EDSS score.

The endpoints were chosen in accordance to the guideline according to the CHMP Guideline on the clinical investigation of medicinal products for the treatment of multiple sclerosis (CPMP/EWP/561/98 Rev. 1). It is noted that according to this guideline, the most relevant parameter for a disease modifying drug in MS is the accumulation of disability and relapse rate cannot be taken as a surrogate for disease progression.

Statistically significant improvement was demonstrated for cladribine 3.5 mg/kg and 5.25 mg/kg in all endpoints in the ITT population of the pivotal CLARITY study in the primary analyses. However, a clinical relevant effect regarding disability progression has not been demonstrated for any of the two doses.

Given the toxicity of cladribine, the applicant applied for a restricted indication targeting patients for which the unfavourable safety profile might be more acceptable:

- Patients with high disease activity and/or risk of disease progression defined as those with 2 or more relapses in the previous year and one or more T1 gadolinium-enhancing lesions,
or
- Patients intolerant to beta-interferon or glatiramer acetate.

In the subgroup meeting the high disease activity definition, statistically significant and clinically relevant results could be demonstrated for the primary endpoint, annualized relapse rate. However, time to disability progression failed to demonstrate statistical significance in this sub-population. Time to disability progression also failed to reach statistical significance in the subgroup intolerant to beta-interferon or glatiramer acetate.

For reasons of safety, the applicant proposed more stringent treatment regimen including only patients with a normal lymphocyte count or no worse than a Grade 1 CTCAE lymphopenia at re-treatment. Efficacy results in this sub-population were comparable to those of the ITT population.

2.7.4.1.2. Uncertainty in the knowledge about the beneficial effects.

Efficacy data in the target population lack robustness. They are derived from post-hoc analyses from a single pivotal trial and result in very small subgroup being analysed:
- 41 patients in the placebo group and 50 patients in the cladribine 3.5 mg/kg group in the high disease activity group.
- 44 patients in the placebo group and 45 in the Cladribine 3.5mg/kg group in the intolerant group.

The high disease activity subgroup might include a relevant proportion of subjects DMD naive at baseline, for which a similar effect could have been reached with authorised DMDs used in RRMS.

The subgroup intolerant to beta-interferon or glatiramer acetate can include patients with mild to moderate disease activity for which the risks of cladribine do not outweight the benefits.

The CLARITY trial re-treatment was initiated at a fixed pre-defined date. The newly proposed flexible treatment regimen, where patients will start a new cycle of cladribine based on lymphocyte count, has not formally been evaluated.

2.7.4.2. Risks

2.7.4.2.1. Unfavourable effects

Cladribine is a purine analogue. Serious safety concerns have been identified in the clinical programme for RRMS.

Severe lymphopenia occurred in 36% of subjects in the cladribine groups. Among those, the absolute lymphocyte counts resolved to grade 0 or 1 in approximately only 50% of these subjects. Infection and infestations related adverse events were reported with the greatest frequency. The development of Grade 3 or Grade 4 lymphopenia has been shown to be associated with an increased risk of development of an infectious disease complication. However, safety data for the subpopulation meeting the stricter criteria for re-treatment introduced by the applicant suggest a lower extent of immunosuppression.

The disproportion of number of malignancies in the cladribine groups compared to placebo during the whole clinical trial program is another major concern. In the overall clinical trial program, 22 cases of malignancies were reported in cladribine arms versus two cases in the placebo arm. Four malignancies were seen in cladribine treated subjects versus none in the placebo group of the CLARITY-study. The relative risk for malignancies indicates a 5-fold increase among those cladribine-exposed subjects in all studies, although with wide confidence interval The risk ratio estimated for only the controlled phases of the completed cladribine studies indicates a 2-fold increase in the risk of cancer among cladribine exposed patients. Immunodeficiency is associated with an increased risk for the development of malignancies, in particular for those tumours associated with viral antigens. Secondary malignancies are common under treatment of hairy cell leukemia, but are also per se expected in patients with hairy cell leukemia.

2.7.4.2.2. Uncertainty in the knowledge about the unfavourable effects

The dataset primarily consists of the single pivotal 96 weeks-CLARITY-study. Data from ongoing CLARITY-extension and ONWARD studies is limited, and so is the overall safety dataset.

Data on complete recovery of lymphopenia and neutropenia are not available from the present clinical development program in MS, and it is known from data for cladribine in hairy cell leukemia that complete recovery of T-and B-Lymphocytes can take up to 2 years. With the stricter criteria for re-treatment data suggest that extent of immunosuppression will be lower. However, safety of the changed treatment-regimen has not been sufficiently demonstrated in patients with high disease activity, which was only a small subpopulation of the CLARITY trial.

Serious safety concerns have been raised, in particular with regard to the increased number of malignancies observed in the clinical trials. Even higher malignancy risk may be expected with increasing exposure and time.

As a dose-finding study has not been done there might be still a lower cumulative dose that is efficacious in the high disease activity RRMS population with a better safety profile.

2.7.4.2.3. Importance of favourable and unfavourable effects

Serious safety concerns have been raised, in particular with regard to the increased number of malignancies observed in the clinical trials. Even higher malignancy risk may be expected with

increasing exposure and time. Efficacy data in the target population with high disease activity have been obtained from a small subpopulation of a single pivotal clinical trial and are not robust enough to outweigh the safety concerns. Therefore, risk-benefit balance is not considered to be favourable, as per Article 12 of Regulation (EC) No 726/2004.

2.7.4.2.4. Benefit-risk balance

The CHMP concluded that the risk-benefit balance is not considered to be favourable, as per Article 12 of Regulation (EC) No 726/2004.

2.7.4.3. Discussion on the benefit-risk balance

The applicant applied for a Conditional Marketing Authorisation during the evaluation procedure. Their justification is outlined below:

The applicant considers that relapsing remitting sclerosis is a seriously debilitating disease. In their view, there is a significant unmet medical need for medications with simplified dosage regimens, improved routes of administration and novel mechanism of action to improve efficacy and treatment adherence while maintaining an acceptable safety profile justifying the need for immediate availability of cladribine.

The applicant argues that data show statistical and clinically meaningful effect on all primary and secondary endpoints in the overall RRMS population in the Clarity study. Those findings remain clinically relevant when subgroups of patients with HDA are studied and are at least comparable to those documented for currently approved DMDs. Findings also show statistically significant and medically meaningful treatment effect on relapsed related outcomes and all key MRI outcomes for the subgroup of patients intolerant to prior treatment with beta-interferon or glatiramer acetate. With respect to safety, lymphopenia, infections and malignancies are considered as identified or potential risks. However, the applicant believe that with specific mitigation measures in place, the benefit of cladribine outweigh the risks.

Finally, the applicant states that there are currently very limited options available for RRMS patients with HDA, as well as for patients intolerant to current injectable therapies. The currently available treatment options, specifically for the HAD patients, have serious and potentially fatal adverse reactions, leaving HDA patients without treatment options. Thus it is deemed important to provide immediate access to Movectro to patients in need for alternative treatment.

The CHMP position is outlined below.

All four requirements in Article 4 of Commission Regulation (EC) 507/2006 need to be satisfied, i.e.:
1. It fulfils an unmet medical need,
2. It is likely that the applicant will be in a position to provide the comprehensive clinical data,
3. It has a positive Risk Benefit Analysis, and
4. The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

- Unmet medical need and benefit to public health of the immediate availability on the market:
Regulation 507/2006 on granting of conditional marketing authorization recognizes the public health benefits of making a product immediately available on the market to address an unmet medical need. According to this regulation 'unmet medical needs' is defined as a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected. The CHMP acknowledged that there is no widely authorised DMD for oral use in the populations applied for. However, authorised therapeutic alternatives do exist. It is arguable whether the oral route of administration of Movectro per se constitutes a major therapeutic advantage over authorised alternative therapies, and there is no comparative data between Movectro and other authorised DMD. Moreover, serious safety concerns

have been identified with Movectro and the optimal dose and the revised treatment regimen using the stricter re-treatment criteria have not been adequately investigated for the target population. Therefore, the CHMP does not consider that the potential benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

- Positive Risk Benefit Analysis and Additional comprehensive clinical data:
Regulation 507/2006 on granting of conditional marketing authorization states, that although the data upon which an opinion on a conditional marketing authorisation is based may be less complete, the risk-benefit balance, as defined in Article 1(28a) of Directive 2001/83/EC should be positive. The CHMP noted the ongoing clinical programme and the new study proposed by the applicant in case a conditional approval is granted. However, the CHMP concluded that the benefit-risk balance for Movectro in the indication applied for is not favourable at this time.

Overall, not all criteria needed for granting a Conditional Marketing Authorisation have been met.

Some members of CHMP did not agree with the CHMP's negative opinion recommending the refusal of the granting of the marketing authorisation of Movectro. They consider that the efficacy has been sufficiently demonstrated in the population applied for as the effect on all primary and secondary endpoints is consistent among the Clarity study overall population and the subgroups analysed. Although potential serious safety concerns have been shown, these can be mitigated with the stricter re-treatment guidelines proposed by the applicant, and an adequate risk management plan and risk minimisation measures.

2.7.4.4. Risk management plan

The CHMP, having considered the data submitted in the application is of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level.

2.7.5. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Movectro in the treatment of:

- relapsing-remitting multiple sclerosis patients with high disease activity and/or risk of disease progression defined as those with 2 or more relapses in the previous year and one or more T1 gadolinium-enhancing lesions.

or

- relapsing-remitting multiple sclerosis patients who are intolerant to beta-interferon or glatiramer acetate therapies.

was unfavourable and therefore did not recommend the granting of the conditional marketing authorisation.

The grounds for the decision are as follows:

- Serious safety concerns have been raised, in particular with regard to the increased number of malignancies observed in the clinical trials. Even higher malignancy risk may be expected with increasing exposure and time. Efficacy data in the target population with high disease activity have been obtained from a small subpopulation of the clinical trial and are not robust enough to outweigh the safety concerns. Therefore, risk-benefit balance is not considered to be favourable, as per Article 12 of Regulation (EC) No 726/2004.

- The optimal dose and the revised treatment regimen using the stricter re-treatment criteria have not been adequately investigated for the target population, which is of particular concern given the observed ceiling effect in the overall study population, the questionable dose-

dependent effect in the small patient population with high disease activity, and the dose-dependent safety profile.

- The indication in patients who are intolerant to beta-interferon or glatiramer acetate is also not considered acceptable as this population may include patients with mild to moderate disease activity and, due to the current safety concerns, cladribine should not be used in such patients.

- The following criteria needed for granting a Conditional Marketing Authorisation have not been met:
    - The Risk-Benefit balance is unfavourable
    - Fulfilment of unmet medical need has not been sufficiently demonstrated;
    - The benefit to public health of the immediate availability on the market of the medicinal product concerned does not outweigh the risks inherent in the fact that additional data are still required

2.8. Re-examination, overall conclusions and recommendation

Re-examination of the CHMP opinion of 23 September 2010

Following the CHMP conclusion that Movectro was not approvable for the following indication:

MOVECTRO is indicated as disease-modifying therapy in relapsing-remitting multiple sclerosis (MS) for the following subjects:

- Patients with high disease activity and/or risk of disease progression defined as those with 2 or more relapses in the previous year and one or more T1 gadolinium-enhancing lesions.

or

- Patients who are intolerant to beta-interferon or glatiramer acetate therapies,

the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented their detailed grounds for re-examination in writing and at an oral explanation to the CHMP. Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) Neurology with additional expertise in oncology, inviting the experts to provide their views on the CHMP questions in relation to the grounds for refusal, taking into account the applicant's response.

Ground 1: *Serious safety concerns have been raised, in particular with regard to the increased number of malignancies observed in the clinical trials. Even higher malignancy risk may be expected with increasing exposure and time. Efficacy data in the target population with high disease activity have been obtained from a small subpopulation of the clinical trial and are not robust enough to outweigh the safety concerns. Therefore, risk-benefit balance is not considered to be favourable, as per Article 12 of Regulation (EC) No 726/2004.*

Applicant's position:

The applicant undertook the following steps:

- Revision of the indication for MOVECTRO to optimise the benefit-risk balance in a restricted population with a high unmet medical need, notwithstanding a positive primary analysis result.

- Re-analysis of all available malignancy information for a comprehensive assessment of this potential risk

- Re-assessment of the impact of the re-treatment guidelines on the newly-proposed indication to ensure its effectiveness to minimise risk and maintain efficacy.

- Critical re-analysis of the benefit-risk balance for the intended patient population to support the newly proposed indication

- Revision of the indication for MOVECTRO to optimise the benefit-risk balance in a restricted population with a high unmet medical need, notwithstanding a positive primary analysis result

The proposed revised indication submitted with the grounds was:
MOVECTRO is indicated as a single disease modifying therapy in highly active relapsing-remitting multiple sclerosis (MS) for the following adult patient groups:

- Patients with high disease activity, defined by two or more relapses in the previous year, and one or more T1 gadolinium enhancing lesions or at least 9 T2 hyperintense lesions in cranial MRI.
or
- Patients who despite treatment with disease modifying drugs (DMDs) have persistent disease activity, defined by one or more relapses in the previous year, and one or more T1 gadolinium enhancing lesions or at least 9 T2 hyperintense lesions in cranial MRI.

The applicant considers that the three disease characteristics fundamental to the proposed indication, frequency of relapses, Gd enhancement on cranial MRI, and T2 lesion burden on cranial MRI, are indicative of a high level of disease activity and indicate a particular RRMS patient is at higher risk of subsequent disease progression. Efficacy of Movectro in the High Disease Activity component of the indication is summarised in the table below.

	Placebo (n= 122)	**Cladribine 3.5 mg/kg (n=112)**	**All Cladribine (3.5 ,g/kg and 5.25mg/kg) (n=232)**	
Annualised Relapse Rate	0.47	0.18	0.17	Both p<0.001*
Relative Reduction ARR (Cladribine vs PBO)[1]		61.7%	63.8%	
Proportion of Subjects Relapse-Free	54.1%	75.0%	75.9%	Both p<0.001**
Time to 3-month Sustained Disability Progression, months[2]	5.4	13.6	10.8	p = 0.002*** (Clad 3.5 mg/kg) p < 0.001*** (combined Clad)
Proportion of Subjects Sustained Disability-Free	75.4%	90.2%	90.1%	p = 0.004** (Clad 3.5 mg/kg) p<0.001** (combined Clad
T1-Gd+ Lesions[3]	1.28 (2.11)	0.12 (0.38)	0.08 (0.30)	Both p <0.001****
Active T2 Lesions[4]	1.85 (2.38)	0.40 (0.73)	0.34 (0.61)	Both p <0.001****
CU Lesions[5]	2.26 (2.88)	0.45 (0.80)	0.38 (0.67)	Both p <0.001****

The High Disease Activity subgroup is defined as having two or more relapses, and one or more T1 Gd+ lesions or > 9 T2-hypertintense lesions at baseline.
* 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, presence/absence of high disease activity population and their interaction and with log of time on study as an offset variable.
** p-value based on Wald Chi-square test from analysis of endpoint using a logistic regression model with fixed effects for treatment group, presence/absence of high disease activity and their interaction

***p-value based on a Cox proportional hazard model with fixed effects for treatment group, presence/absence of high disease activity and their interaction
**** p-value calculated based on parametric ANCOVA model on ranked data with fixed effects for treatment group, presence/absence of high disease activity, and their interaction and baseline number of T1 Gd+ lesions as a covariate.
[1]Calculated as the ratio of the difference in annualised relapse rate (placebo - cladribine) relative to the annualised relapse rate in the placebo group.
[2]The 5th percentile estimated from Kaplan-Meier survival curve.
[3] Mean (SD) number of T1 Gadolinium-enhancing lesions per patient per scan over 96 weeks
[4] Mean (SD) number of active T2 lesions per patient per scan over 96 weeks
[5] Mean (SD) number of CU lesions per subject per scan over 96 weeks

Efficacy of Movectro in the Previously Treated Patients Component of the indication is summarised in the table below.

	Placebo (n= 135)	**Cladribine 3.5 mg/kg (n=104)**	**All Cladribine (3.5 mg/kg + 5.25mg/kg) (n=241)**	
Annualised Relapse Rate	0.39	0.21	0.18	Both p<0.001*
Relative Reduction ARR (Cladribine vs PBO)[1]		46.2%	53.9%	
Proportion of Subjects Relapse-Free	57.0%	74.0%	76.3%	p=0.007** (Clad 3.5 mg/kg) p<0.001** (combined Clad)
Time to 3-month Sustained Disability Progression, months[2]	8.1	11.2	11.2	p = 0.285*** (Clad 3.5 mg/kg) p<0.208*** (combined Clad)
Proportion of Subjects Sustained Disability-Free	76.3%	83.7%	83.0%	p = 0.165** (Clad 3.5 mg/kg) P=0.117** (combined Clad)
T1-Gd+ Lesions[3]	1.06 (2.03)	0.10 (0.31)	0.10 (0.34)	Both p <0.001****
Active T2 Lesions[4]	1.54 (2.23)	0.40 (0.63)	0.34 (0.63)	Both p <0.001****
CU Lesions[5]	1.91 (2.77)	0.45 (0.70)	0.39 (0.69)	Both p <0.001****

The Persistent Disease Activity subgroup is defined as having one or more relapses, and one or more T1 Gd+ lesions or ≥ 9 T2 hyperintense lesions at baseline despite prior DMD treatment.
[1]Calculated as the ratio of the difference in annualised relapse rate (placebo - cladribine) relative to the annualised relapse rate in the placebo group.
[2]The 10th percentile estimated from Kaplan-Meier survival curve
[3] Mean (SD) number of T1 Gadolinium-enhancing lesions per patient per scan over 96 weeks
[4] Mean (SD) number of active T2 lesions per patient per scan over 96 weeks
[5] Mean (SD) number of CU lesions per subject per scan over 96 weeks

The applicant considered that analyses for the newly defined patient population demonstrated a meaningful clinical benefit and statistical significance of cladribine tablets vs. placebo for relapse and disability progression measures over 96 weeks. Data from the ongoing blinded CLARITY extension study will provide additional data regarding long term safety and efficacy. Although consisting of somewhat different relapsing MS populations and study designs, the ongoing ORACLE MS and ONWARD studies will further elucidate the efficacy and safety of cladribine tablets.

At the time of the oral explanation, the applicant further modified the proposed indication as follows (additions underlined) to address comments raised by the SAG neurology and the CHMP on the appropriateness of the indication:

MOVECTRO is indicated as a single disease modifying therapy in highly active relapsing-remitting multiple sclerosis (MS) for the following adult patient groups

- Patients with high disease activity, defined by two or more <u>disabling</u> relapses in the previous year, and one or more T1 gadolinium enhancing lesions or at least 9 T2 hyperintense lesions.
  or

- Patients who despite treatment with disease modifying drugs for at least one year have persistent disease activity, defined by one or more relapses in the previous year while on therapy, and one or more T1 gadolinium enhancing lesions or at least 9 T2 hyperintense lesions.

- Re-analysis of all available malignancy information for a comprehensive assessment of this potential risk

Pathogenesis of malignancies and the role of immunosuppression:

The available literature provides relevant insights on the impact of potent immunosuppression on increased risk of malignancies. Infection-related cancers (e.g., non-Hodgkin's lymphoma, squamous cell carcinoma Kaposi's sarcoma) are associated with immune deficiency. Their incidence is increased in renal transplantation patients treated with potent immunosuppressors, or in patients with HIV/AIDS. However, there is insufficient evidence linking commonly occurring epithelial cancers to infectious aetiology, and the role of immune surveillance in the aetiology of most cancers is unclear. Rates of most of the common epithelial cancers are not increased in immunosuppressed patients, suggesting that immunosurveillance plays a relatively smaller role, if any, in the pathogenesis of other cancers. Development of secondary malignancies in patients with Hairy Cell Leukaemia (HCL) is controversial. Several studies have reported that patients with HCL are at increased risk of developing secondary cancers. This increased risk has been considered to be due to several factors. The authors concluded that nucleoside analogues, such as cladribine, did not add to the increased risk of secondary malignancies, already associated with the diagnosis of CLL and HCL. Although encouraging, these data cannot be properly extrapolated to cladribine use in MS in view of the profound differences in background risk, patient population characteristics and treatment dosing regimens.

Reports of malignancies in clinical trials conducted with cladribine for the treatment of MS and onset latency:

In the grounds for this re-examination, the Applicant presented an updated comprehensive assessment of malignancies as a stand-alone safety review and included the evaluation of all data available as of 5 November 2010, regardless of source or type of study. The distribution of the events and onset latency are detailed in the table below.

Study	Subject Number	Event (PT)	Treatment group (mg/kg) (a)	Cladribine dose received (mg/kg) (b)	Latency (f)
Completed Controlled Studies ([6]5+1 placebo)					
MS-001	MS-1/207	Cervix carcinoma	5.25	5.25	< 1 (9 months)
CLARITY	CLARITY/071-0010	Cervix carcinoma in situ	5.25	3.9	< 1 (10 months)
CLARITY	CLARITY/129-0020	Ovarian cancer	3.5	1.8	1
CLARITY	CLARITY/101-0007	Pancreatic carcinoma metastatic	3.5	3.8	1.5
CLARITY	CLARITY/172-0013	Malignant melanoma	3.5	3.7	< 1
MS-SCRIPPS	MS-Scripps/12720	Basal cell carcinoma	Placebo	N/A	< 1 (9.5 months)
Extension Phase of Completed Controlled Studies (5)					
MS-SCRIPPS (Ext. Phase)	MS-Scripps/05071c	Basal cell carcinoma	7.0/2.75	9.54	4.6
MS-SCRIPPS (Ext. Phase)	MS-Scripps/54533	Basal cell carcinoma	7.0/3.5	10.5	3.8
MS-SCRIPPS (Ext. Phase)	MS-Scripps/12720	Bladder transitional cell carcinoma	3.5 / Fu[g]	3.5	2.2
MS-001	MS-001/110	Colon cancer	1.75 / 5.25	7	3.5

Study	Subject Number	Event (PT)	Treatment group (mg/kg) (a)	Cladribine dose received (mg/kg) (b)	Latency (f)
(Ext. Phase)					
MS-001 (Ext. Phase)	MS-001/210	Basal cell carcinoma	1.75 / 1.75	3.5	3.5
Completed Uncontrolled Studies (1)					
SCRIPPS-A	Scripps-A/50113	Skin cancer	9.13	4.58	0.7 - 1.4
Post-Study ([11] 10+ 1 placebo)					
MS-SCRIPPS	MS-Scripps/05071c	Basal cell carcinoma	7.0	7	2.8
MS-SCRIPPS	MS-Scripps/05071c	Skin Cancer	7.0/2.75	9.54	11.5
CLARITY	CLARITY/100-0001	Choriocarcinoma	5.25	5.5	2.5
CLARITY	CLARITY/147-0006	Bladder cancer	3.5	3.7	3
Scripps-C	430012M06 USA	Oesophageal carcinoma	5.25	5.25	8.6
Scripps-C	98549	Breast cancer	5.25	5.25	9
Scripps-C	98549	Skin Cancer	5.25	5.25	8
MS-SCRIPPS	94832	Breast cancer	3.5 / 3.5	6.8	8.4
MS-SCRIPPS	53073	Breast cancer	7	7	7
MS-SCRIPPS	51521	Squamous cell carcinoma	7.0 / 5.25	12.26	12.3
CLARITY	CLARITY/018-0022	Ovarian cancer	Placebo	N/A	At least 2
Ongoing Studies (12h)					
CLARITY EXT	CLARITY Extension/014-0005	Ovarian cancer	3.5 / 3.5	5.3	3.7
CLARITY EXT	CLARITY Extension/089-0004	Malignant melanoma	3.5 / placebo	3.5	3.3
CLARITY EXT	CLARITY Extension/093-0003	Thyroid cancer	5.25 / placebo	5.24	3.3
CLARITY EXT	CLARITY Extension/038-0001	Rectosigmoid cancer	3.5 / 3.5	7.2	3.8
CLARITY EXT	CLARITY Extension/014-0013	Breast cancer	3.5 / 3.5	7.3	3.3
CLARITY EXT	CLARITY Extension/143-0005	Basal cell carcinoma of the scalp	3.5 / Rebif[d]	3.76	3.2
CLARITY EXT	CLARITY Extension/089-0010	Malignant melanoma	5.25e /3.5	4.38	3.8
CLARITY EXT	CLARITY Extension/094-0002	Renal cell carcinoma	5.25 / 3.5	8.75	4
CLARITY EXT	CLARITY Extension/166-0008	Rectal Cancer h	3.5 / 3.5	5.25	4.5
CLARITY EXT	CLARITY Extension/078-0002	Squamous cell carcinoma h	3.5 / 3.5	5.25	3.7
CLARITY EXT	CLARITY Extension/035-0002 (actual 170-0006)	Basal cell carcinoma h	3.5/placebo	3.5	3.6

Study	Subject Number	Event (PT)	Treatment group (mg/kg) (a)	Cladribine dose received (mg/kg) (b)	Latency (f)
ONWARD	ONWARD/023-0001	Squamous cell carcinoma	3.5/not yet unblinded for extension period	3.5	2.2

a For parenteral studies, conversion to oral dose

b Cladribine dose received (or oral equivalent) at time of the event

c Subject 05071 experienced two BCC : one in the post-study period (i.e. after the placebo controlled phase, but before the extension uncontrolled phase) and one in the extension uncontrolled phase.

d Rebif as rescue medication

e Subject was randomised to high dose group in CLARITY but did not receive courses 5 & 6 because of lymphopenia

f Latency = time in years between the first dose of cladribine and the diagnosis of the event

g Follow-Up

h Three additional cases reported after data cut-off date of 21-Jun-2010

Source Safety issue review 12_11-2010

Overall, there is a numerical asymmetry in the number of malignancies in patients who received cladribine compared to the placebo groups. As of 5 November 2010 a total of 33 malignancy events have been reported from all clinical trials in patients treated with cladribine, 2 events have been reported in patients treated with placebo. However, a methodologically appropriate comparison can only be conducted on data from the placebo-controlled phase of three studies. Any comparative analysis after this phase must take into account differences in patient numbers, overall exposure and patient follow-up observation time.

Epidemiological analysis of malignancy events reported with the use of cladribine in MS patients:

The relative risk (RR) (incidence rate ratio) and risk difference (RD) were calculated for the 0-96 weeks of the placebo-controlled phases of completed studies. Although malignancy events were reported in the extension studies (completed and ongoing) where subjects have been followed for a longer time period, RR and RD could not be calculated for the total population exposed to cladribine because the exposure to placebo was much shorter. In randomised trials with open-label extension periods or randomised cross-over of some patients in the placebo group to subsequent active treatment, estimating relative risks can introduce a bias against the active treatment known as "confounding by time since randomisation".

Six malignancies (5 in the cladribine group and 1 in the placebo group) were included by the applicant in the analysis of cases that occurred during the 0-96 week placebo-controlled phase of the five completed placebo-controlled studies of cladribine in patients with MS (CLARITY and four studies with parenteral cladribine). The patient-years of exposure in these studies were 1,771.3 patient-years for cladribine and 819.7 patient-years for placebo, corresponding to an incidence rate of malignancies of 2.8 and 1.2 per 1,000 patient-years for cladribine and placebo-treated patients, respectively. The relative risk and risk difference for malignancies in patients treated with cladribine derived from the controlled phase in clinical trials for MS is shown below.

Study phase	Relative risk (95% CI)	Risk difference (95% CI)
Controlled phase of controlled studies	2.31 (0.27 – 19.81)	0.0016 (-0.0018 – 0.0050

In order to put in perspective the frequency of cancer cases that were reported in the overall clinical trial population exposed to cladribine with population-based cancer incidence data, standardised incidence ratios (SIR) and 95% confidence intervals were calculated. Standardisation was performed by age-group, gender, and country. Incidence rates for the general population were retrieved from the Cancer Incidence in Five Continents (CI5C) for the calculation of incidence rates. For the calculation of the SIR the following malignancy out of 33 cases were not included:

- Ten (10) cancers diagnosed after the end of the study period, as no valid denominator was available for this period.

- One cervix carcinoma in situ because cervical carcinoma in situ is not dealt with in the Incidence of Cancer in Five Continents, Vol IX.
- Six (6) non-melanoma cancers diagnosed during studies (1 skin cancer not otherwise specified, 4 BCC and 1 SCC), as NMSC is generally reported to cancer registries incompletely, if at all.
- Three (3) cases from the ongoing studies, reported after 21 June 2010, because the denominator (patient-years of exposure) has been estimated up to that date.

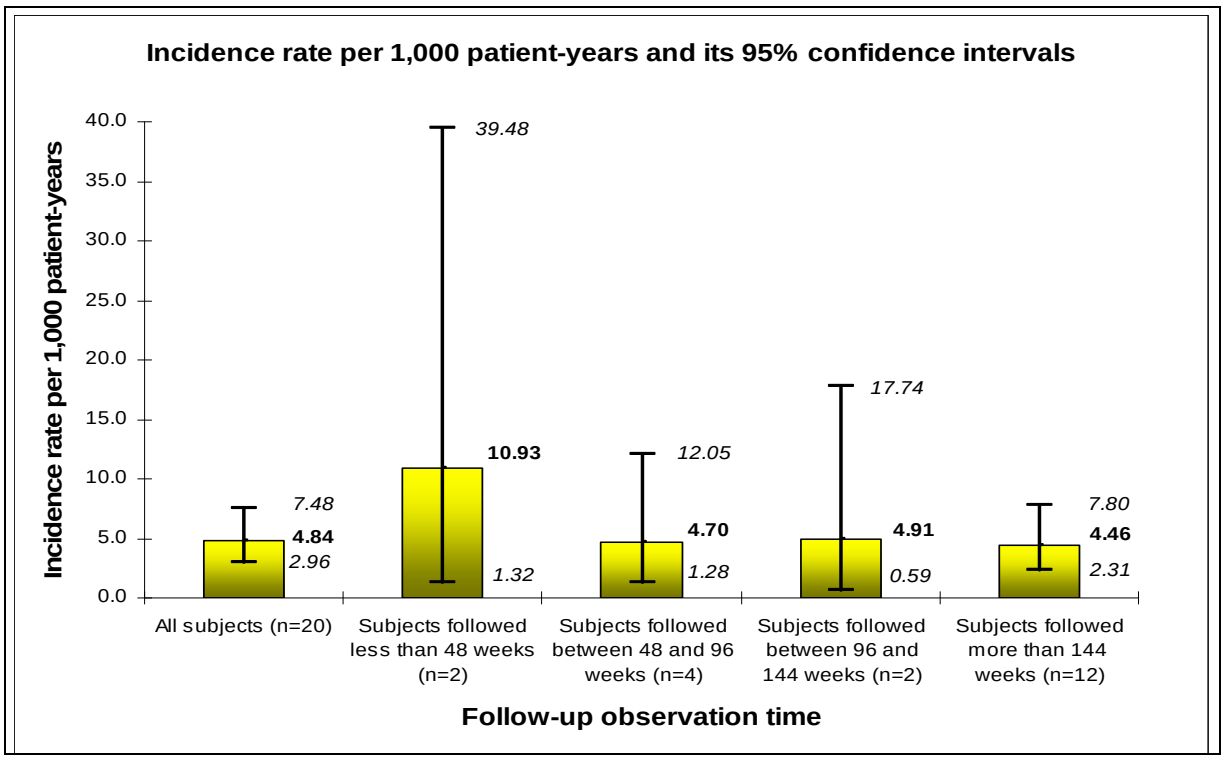
SIR estimations were performed on results derived from three different patient populations:
- CLARITY study
- All controlled and completed studies (controlled and uncontrolled phases).
- All clinical trials with cladribine in patients with MS.

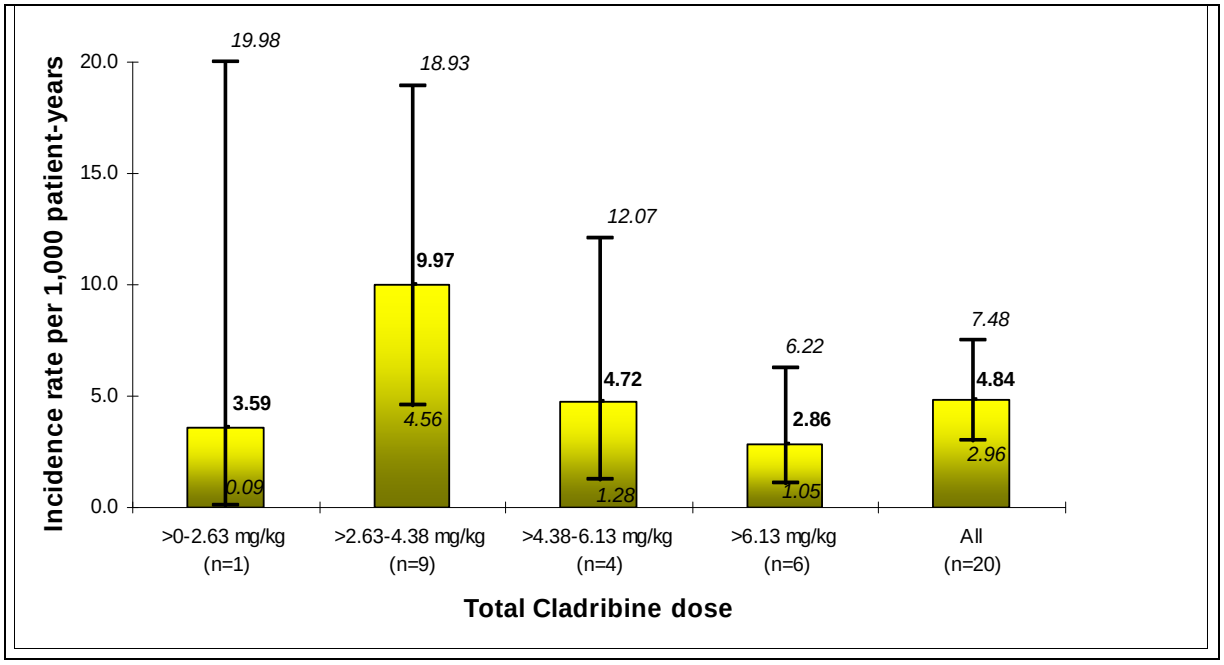
The following table provides the data and estimates of the SIRs and 95% confidence intervals for categories of studies

Studies	Exposure	Number of cancer events		Standardised Incidence Ratios	
		Observed	Expected	SIR	95% CI
CLARITY	cladribine	3	2.99	1.00	0.21 – 2.93
	placebo	0	1.44	0	0.00 – 2.57
Completed controlled studies (controlled and uncontrolled phases)	cladribine	6	5.30	1.13	0.42 – 2.47
	placebo	0	2.12	0	0.00 – 1.74
Completed controlled studies (controlled and uncontrolled phases) + 3 ongoing studies.(1)	cladribine	13	9.45	1.38	0.73 – 2.35
	placebo	0	2.77	0	0.00 – 1.33
(1)Includes time gap and Scripps-A					

Analysis of malignancy risk with maximal time of observation and with total cumulative dose:

The Incidence rate of malignancies by maximal time of observation and by total cumulative dose calculated by the applicant excluding the post study cases is illustrated in the figures below. In addition to the 20 events observed in cladribine-exposed patients during studies, 10 events were reported post-study and 3 in the ongoing studies after 21 June 2010, which have not been considered in the incidence rates calculations due to the lack of a proper denominator. For the same reason one placebo-exposed event reported post-study has also not been included in the incidence calculations.





The applicant considered that available data do not support a causal relationship for the risk of malignancy in MS patients treated with cladribine having regard to the following considerations. The Applicant concluded that assessment of available data regarding malignancy events is inconclusive and therefore does not allow the establishment of a causal relationship or quantification of risk in MS patients treated with cladribine at present. The number of reported cases is insufficient to accurately estimate the risk. The relative risk and standardised incidence ratio estimates are unstable and not statistically significant as indicated by the wide confidence intervals including unity. The range of events, the latencies and the presence of confounding factors and gender-related characteristics, indicate that these malignancies are likely to be background events in the patient population and are not related to a drug effect. The types of malignancies reported are not consistent with those commonly associated with immunosuppression. The applicant also proposed that long term safety of oral cladribine tablets will be monitored

through post-marketing surveillance as well as in two large follow-up safety studies. Additional risk minimisation activities, including a comprehensive educational programme for prescribers and patients, going beyond routine pharmacovigilance being applied to all marketed MS therapies, are proposed to ensure the safe and effective use of cladribine tablets in patients with RRMS.

- Re-assessment of the impact of the re-treatment guidelines on the newly-proposed indication to ensure its effectiveness to minimise risk and maintain efficacy

Lymphopenia is an adverse event directly related to the mode of action of cladribine. In the CLARITY-study higher frequency of lymphopenia was reported with the higher dose. The frequency of infectious adverse events and herpes virus infections increased with severity of lymphopenia. In order to minimise the development of high grade or persistent lymphopenia and its clinical manifestations, re-treatment will be limited, at the time of the second and subsequent courses with cladribine tablets, to patients who meet strict haematological criteria including a normal ALC (absolute lymphocyte count) or an ALC no worse than Grade 1. If necessary, the respective course can be delayed for up to 3 months to allow for haematological recovery.

The applicant assessed the impact of the re-treatment guideline as a risk-minimisation measure, and the impact on the efficacy (see tables below). They concluded that the re-treatment guidelines have a measurable effect on minimising patient risk of severe lymphopenia and its clinical manifestations while maintaining efficacy of cladribine tablets in the patient population following introduction of these treatment guidelines.

Lymphopenia, **ITT Population** **CLARITY study**	**Placebo Population** **N=435**	**Safety population** **3.5 & 5.25 mg/kg** **N=884**	**Safety population** **3.5 mg/kg only** **N=430**	**Re-treatment population** **N=263**
Patients with lymphopenia grade 3 or 4 at any time during study (%)	**0.5%**	**35.5%**	**25.6%**	**9.5%**
Patients with persistent lymphopenia grade 3 or 4 at last assessment (%)	**0%**	**3.6%**	**2.3%**	**0.4%**
Patients with any serious adverse event at any time during the study (%)	**6.4%**	**8.7%**	**8.4%**	**6.1%**
Patients with infections at any time during the study (%)	**42.5%**	**48.9%**	**47.7%**	**46.4%**
Patients with herpes zoster at any time during the study (%)	**0%**	**2.3%**	**1.9%**	**1.1%**

Key Efficacy Results	Proposed indication* N=182 (3.5 mg/kg)	Proposed indication plus re-treatment population** N=110 (3.5 mg/kg)
Relative reduction in relapse rate	56.1%	60.5%
Absolute increase in % of patients free of disability progression	10.9%	10.6%

* Proposed indication is Patients with ≥ 2 relapses and ≥ 1 T1 Gd+ lesion or ≥ 9 T2-hyperintense lesions Or Patients with Prior DMD therapies and ≥ 1 relapses and ≥ 1 T1 Gd+ lesion or ≥ 9 T2-hyperintense lesions.
** Re-treatment population consists only of patients with normal ALC or Grade 1 lymphopenia at re-treatment.

- Re-analysis of the benefit-risk balance for the intended patient population to support the newly proposed indication by the applicant

Analyses for the newly defined patient population demonstrated a meaningful clinical benefit and statistical significance of cladribine tablets vs. placebo for relapse and disability progression measures over 96 weeks.

The safety profile for cladribine is shaped by its underlying mechanism of action – a preferential and prolonged reduction in circulating levels of CD4+, CD8+ and CD19+ lymphocytes. These effects result in cladribine's beneficial effect on the CNS inflammatory process in MS, which may be associated with an increase in the risk of infections. In order to minimise the development of high grade or persistent lymphopenia and its clinical manifestations, re-treatment guidelines are proposed. A comprehensive assessment of available data regarding malignancy events is inconclusive and therefore does not allow the establishment of a causal relationship or quantification of risk in MS patients treated with cladribine at present. The number of reported cases is insufficient to accurately estimate the risk. The relative risk and standardised incidence ratio estimates are unstable and not statistically significant as indicated by the wide confidence intervals including unity. The range of events, the latencies and the presence of confounding factors and gender-related characteristics, indicate that these malignancies are likely to be background events in the patient population and are not related to a drug effect. The types of malignancies reported are not consistent with those commonly associated with immunosuppression. New analyses performed do not suggest an increase risk of malignancy with increasing dose or time of observation. The long term safety of oral cladribine tablets will be monitored through post-marketing surveillance as well as in two large follow-up safety studies and additional risk minimisation activities proposed to ensure the safe and effective use of cladribine tablets in patients with RRMS. The clinical development programme and RMP are coordinated so as to ensure timely data collection and proper updating on a regular basis to the Authorities.

Within the targeted patient population, orally-administered cladribine will likely improve patient compliance. The safety and tolerability profile of cladribine tablets does not include the toxicities and tolerability issues that commonly cause discontinuation of parenteral therapies, including flu-like symptoms, hepatotoxicity, and the occurrence of neutralising antibodies that may affect the efficacy of other DMDs.

According to the applicant, the clinical benefits of cladribine tablets outweigh the risks under the proposed conditions of use for the following reasons:

- the favourable effects are based on an assessment of tangible and clinically meaningful outcomes as defined by the number of patients who are free of relapses and disability progression
- the unfavourable effects observed in the ITT population are considered to be manageable by means of the proposed risk minimisation measures
- the uncertainty with respect to an unfavourable effect of malignancy:
    - Pharmaco-epidemiological assessment of the available data does not suggest an increased risk compared to the general population as reflected by the wide confidence intervals.
    - in addition no relationship between malignancies and cladribine's total cumulative dose or duration of exposure has been observed.

A comparison of the benefit-risk impact in the restricted population after implementation of the re-treatment criteria clearly demonstrates favourable benefit while minimising the risk. (See table 18)
The above tabulation summarising the new analysis supports the positive benefit impact of restricting the patient population and the positive risk minimisation impact of the re-treatment guidelines:

- The favourable effects as measured by the number of relapses avoided and the number of patients who are free of disability progression are improved when compared to the ITT population. This positive effect is maintained after incorporation of the re-treatment guidelines
- the unfavourable effects observed in the ITT population have substantially decreased in areas of specific concern, such as the number of patients with herpes zoster or persistent lymphopenia, through the implementation of the re-treatment guidelines
    - The re-treatment guidelines decrease the number of serious infections observed from 10 (of 430) to 7 (of 263) after the implementation of the re-treatment guidelines. The number of patients in the group also decreased following the introduction of the re-treatment guidelines which leads to a slight (and negligible) increase in the incidence rate (2.7% versus 2.3%).

The newly-proposed indication focuses on patients at high risk of recurrent relapses and disease progression and for RRMS patients with active disease who are not candidates for other therapies, e.g. due to suboptimal response with a prior DMD, and/or problematic adverse reactions. There is a need for treatment options for these patients. Cladribine tablets are an appropriate treatment option for these patients in terms of efficacy, safety/tolerability, and ease of therapeutic delivery.

CHMP position

The CHMP agreed that the efficacy of cladribine 3.5 mg/kg was statistically significantly superior to placebo with regard to annualised relapse rate and proportion of subjects relapse-free as well as a number of imaging parameters for both subpopulations. The differences are considered by the CHMP to be clinically meaningful although modest. Differences to placebo with regard to disability-related endpoints favoured cladribine, but achieved statistical significance only for the high disease activity subpopulation. The CHMP noted some limitations in the efficacy database affecting the interpretation of the efficacy results:
- Analyses of efficacy results in placebo-treated patients suggest that the population included in the study may be rather mildly affected and with a low disease progression rate considering that the population is claimed to be one with high disease (or persistent) disease activity.
- Most patients in the CLARITY study (about 70%) did not use prior disease modifying drugs (DMD) before randomisation. It remains unclear whether even for patients with high disease activity the same effect could not have been reached with first line DMDs, especially as no active comparator was included in the trials.

With respect to safety, the CHMP considered the conclusions of the applicant are premature. It is agreed with the applicant that extrapolation from and comparison with cancer populations with regard to cancer risk in MS patients should be interpreted with caution. However, a potential signal of increased cancer risk has emerged from the cladribine trials in MS because of a disproportionate number of malignancies among patients exposed to cladribine as compared to the number of cancers in unexposed patients.

It is noted that antimetabolites including cladribine are normally not considered carcinogenic, but their marked suppressive effects on CD4(+) T-lymphocytes may cause reactivation of dormant virus (Epstein-Barr, HPV etc.) and increase the risk of the typical cancers seen in organ transplanted patients or in HIV-infected patients (mainly B-cell malignant lymphoma, skin cancers (squamous cell carcinoma) and Kaposi's Sarcoma. The fact that there is no clear linkage between the development of secondary solid tumours of epithelial origin and cancer chemotherapy does not exclude an association. Most patients with cancer will die of their primary before a solid tumour with a long latency period (breast, colorectal, and lung cancer) can be clinically detectable.

Among a total of 33 malignancy events that have been reported from all clinical trials, the extension phases and post-follow-up period, conducted with cladribine oral or parenteral formulations none were classified as MDS/AML or B-cell lymphoma. About half of all events (15/33) were skin cancers. Twelve of the 15 skin cancers were non-melanoma cancers (6 BCC, 3 SCC, and 3 "skin cancers"). Non-melanoma skin cancers are very common in organ-transplanted patients. However, only the risk of SCC seems to be associated to the level of global immunosuppression. The three cases of malignant melanoma are difficult to interpret in the context of known carcinogenic effects of cytostatics or immune system suppression and more data are needed to confirm or refute. Concerning the remaining 18 cases of solid tumours, it is correct that for epithelial (solid) tumours the latency to develop them exceeds the duration of treatment time. Nevertheless that subclinical present malignancies become faster overt cannot be ignored. The fact that there is no clear linkage between the development of secondary solid tumours of epithelial origin and cancer chemotherapy as argued by the applicant does not exclude an association. Most patients with cancer will die of their primary before a solid tumour with a long latency period (breast, colorectal, and lung cancer) can be clinically detectable.

In conclusion, there is an increased number of malignancies observed among patients exposed to cladribine as compared to the number of cancers in unexposed patients without adequate explanation. Cladribine is a cytotoxic agent. The lymphopenia is the intended effect. Reduced immune-surveillance associated with profound and persistent lymphopenia poses a risk of opportunistic infections and malignancies. Considering the high number of events observed in a limited safety database from a controlled clinical setting and the mechanism of action of cladribine, a causal relationship is not unlikely. The exclusion of the high dose, in combination with the stricter

re-treatment guidelines are agreed to be limiting the risk of lymphopenia, but the potential risk for malignancies persists. Therefore serious concerns remain on the long term safety. Efficacy data in the restricted population with high disease activity or persistent disease activity despite treatment with DMD are not robust enough to outweigh the safety concerns.

A minority of CHMP members expressed a divergent position. They consider that the efficacy of Movectro is sufficiently documented and the proposed safety post-authorisation studies adequately address the safety concerns. The criteria for granting a Conditional Marketing Authorisation are considered to be fulfilled.

- ***Ground 2:*** *The optimal dose and the revised treatment regimen using the stricter re-treatment criteria have not been adequately investigated for the target population, which is of particular concern given the observed ceiling effect in the overall study population, the questionable dose-dependent effect in the small patient population with high disease activity, and the dose-dependent safety profile.*

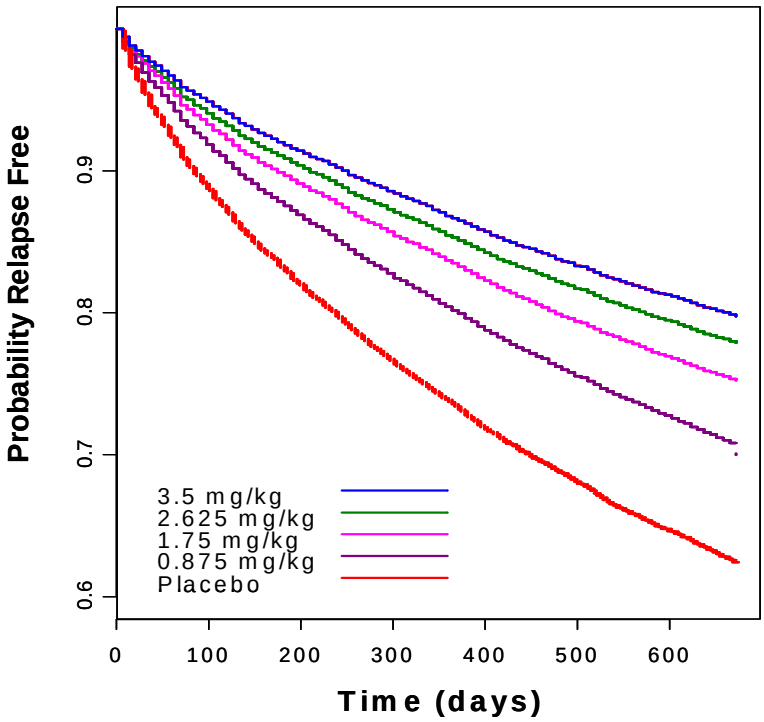
Applicant's position

No traditional multiple ascending dose study was performed in subjects with MS. However, the existing data from the Phase II and Phase III trials in MS with parenteral cladribine, have provided a proper basis to inform the development of an oral tablet formulation of cladribine for use in a short-course dosing regimen. The final tablet formulation was selected based on favourable physicochemical and stability parameters as well as comparative non-clinical and clinical evaluation. When cladribine was assessed as a potential treatment for MS, its dose ranges, toxicity, and PK in human subjects were known from studies in which it was tested in haematological malignancies.

From the parenteral cladribine studies, the dose range of 0.7 to 2.1 mg/kg/year was identified as providing acceptable efficacy, safety, and tolerability profiles for treatment of MS. Adverse events were dose related, and occurred with an increased frequency and level of severity at doses ≥2.8 mg/kg/year. The cladribine tablet 5.25 mg/kg treatment regimen was developed to provide the equivalent of the parenteral cladribine exposure of 2.1 mg/kg demonstrated to be effective in the Scripps-C trial while the cladribine tablet 3.5 mg/kg treatment regimen provided a lower dose for assessment of efficacy, safety, and tolerability at two-thirds of the total cladribine tablet 5.25 mg/kg exposure.

In the CLARITY trial, with regard to these pre-specified primary and secondary efficacy outcomes, subjects assigned to the cladribine tablets 3.5 mg/kg and 5.25 mg/kg arms derived similar efficacy. However, modelling and simulation analyses of cladribine exposure (predicted by the important variables of cladribine tablets dose administered and individual creatinine clearance) in individual subjects from CLARITY indicates a clinical dose response, such that subjects with the intended cladribine dosage (3.5 mg/kg) derived greater clinical benefit, and those subjects receiving less than the intended dosage were more likely to experience a relapse (see Figure below).

Figure - Probability of being relapse-free* over 96 weeks of Patients receiving the full Proposed dosage (3.5 mg/kg) versus those receiving less than the proposed dosage



*** percentage of patients not experiencing relapse**

According to the applicant, this figure demonstrates that doses below the proposed 3.5 mg/kg result in lower efficacy. Based on the safety profiles of the two treatment regimens evaluated, the Applicant has withdrawn the high dose (5.25 mg/kg) from the proposed indication. Comparing patients treated with the low dose (3.5 mg/kg) to those treated with the high dose, the low dose patients experienced considerably fewer adverse reactions, most importantly regarding the clinical manifestations of severe lymphopenia. Therefore, these findings support the selection of 3.5 mg/kg as the appropriate dose for treatment in the target patient population as it optimises the benefit-risk balance.

CHMP position

No adequate dose-finding studies in the intended target RRMS population, and with the intended oral formulation were performed. Simulation should be interpreted with caution and obviously does not carry the same strength of evidence as a proper clinical dose-finding study. The lower end of dose efficacy curve has not been sufficiently evaluated. In view of the serious safety concerns, whether a lower dose with a better benefit/risk ratio exists should have been established.

- ***Ground 3****: The indication in patients who are intolerant to beta-interferon or glatiramer acetate is also not considered acceptable as this population may include patients with mild to moderate disease activity and, due to the current safety concerns, cladribine should not be used in such patients.*

Applicant's position

The Applicant believes that this ground has been addressed by the inclusion of a disease activity/severity qualification in this component of the newly-proposed indication.

CHMP position

It is re-iterated that even for this subgroup under placebo relapse rate is small (0.39 under placebo vs. 0.21 under cladribine 3.5. mg/kg), percentage relapse free high (57% under placebo vs. 74% under cladribine 3.5 mg./kg). Percentage of subjects being disability free did not differ (76% vs. 84% respectively. Thus disease in this subgroup remains mild and the difference in effect does not outweigh the safety problems.

- ***Ground 4****: The following criteria needed for granting a Conditional Marketing Authorisation have not been met:*
    - *The Risk-Benefit balance is unfavourable*
    - *Fulfilment of unmet medical need has not been sufficiently demonstrated;*
    - *The benefit to public health of the immediate availability on the market of the medicinal product concerned does not outweigh the risks inherent in the fact that additional data are still required*

Applicant's position

Favourable Benefit-risk balance:

RRMS is a seriously debilitating disease affecting multiple functional systems (e.g. motor, sensory, visual and urinary) as well as potentially resulting in cognitive impairment. Symptoms can be present in isolation or can affect several systems simultaneously. As a consequence of accumulating physical and cognitive disability, the disease has a strong socioeconomic burden. The lifespan of MS patients is shortened by about 8-12 years as demonstrated in the Danish population. A more recent review concludes that life expectancy is reduced by 5-10 years. On top of a reduced life expectancy, multiple sclerosis has a significant impact on the quality of life of patients. Natural history studies indicate that it takes a median time of only 8 years to reach the irreversible disability level of EDSS 4 and 20 years to reach the level EDSS 6. It has also been demonstrated that quality of life (physical and mental components) worsened as EDSS scores deteriorated and that brain lesions and atrophy as seen by MRI were associated with a deteriorated sexual function and mental health. Studies have also observed a 75% increased annualised divorce rate. Thus not only is life expectancy reduced in MS patients, but their quality of life is profoundly impacted, such that patients may be willing to take significant, even potentially fatal risks associated with treatment.

The applicant's position on the benefit-risk balance in the proposed restricted indication is detailed under Ground 1.

Fulfilment of the unmet medical need:

The mainstay of MS therapy for at least 10 years has been the interferons and glatimer acetate. Even though these drugs have had a significant positive impact on the lives of MS patients, their usefulness is limited over time as illustrated by the high discontinuation rates: every third patient with MS stops disease-modifying treatments within 5 years.

For the patients who discontinue first line therapy because of high disease activity, the current standard of care is natalizumab, which is the only centrally approved therapy across the EU focusing on the needs of high disease activity patients. Natalizumab shows strong efficacy but has substantial safety risks (e.g. PML: the incidence of PML has been reported this week as 1.34/1000 patient years in Europe and increases over time). Of the estimated 400,000 patients with MS in the EU, only 16% of these patients are thought to have high disease activity. Currently in Europe, natalizumab is prescribed for 20,500 patients; this represents 5% of the total MS population or one-third of the patients with high disease activity. So, only a small number of patients within the MS population have high disease activity and not all of these patients are currently being treated with natalizumab. The other treatment options for high need patients are not universally available in the EU. Mitoxantrone (not available in all EU countries for MS) is limited to a narrow severe population due to its dose-related cardiotoxicity. Azathioprine is approved for MS in a limited number of EU countries. Therefore, for patients with high disease activity there are limited therapies available which do not meet the needs of all patients. Furthermore, these available therapies could also lead to serious and fatal adverse reactions.

As described above the size of effects attributable to cladribine tablets is clinically significant in respect to relapse activity and disability progression in the proposed patient population. The risk profile observed together with the substantial risk mitigation programme to support cladribine tablet's safe use contribute to the overall positive benefit-risk profile in the proposed patient population.

The benefit to public health of the immediate availability of MOVECTRO on the market:

Given what has been described in the previous section on the benefit-risk balance of cladribine tablets and the unmet medical need for the proposed patient population, it follows that the therapy should be introduced as a priority for patient care.

Information about the benefit of cladribine tablets in MS is available in the public domain and, using other pharmaceutical forms not authorised in this indication (Litak®, Leustatin®), can lead to uncontrolled use of cladribine in MS. The Applicant plans to implement a controlled distribution model. The short courses of cladribine tablets (5 days supply) will be held across the EU in specific limited numbers of "hubs". A pharmacist on receipt of a prescription will request drug be sent, dependent and tailored to the patients defined weight per the prescription. At this point of initiation of delivery, the company will "request" a confirmation that the risk minimisation activities have been followed. This will be in the format of a pre-defined checklist of actions related to the risk minimisation plan (e.g. TB screening, Pregnancy test and vaccine status). This completed form will trigger the shipment of the drug to the specific pharmacist within 24hrs or less across all EU countries. The Applicant's perspective is that the uncertainty of the risk of malignancy does not preclude immediate approval of cladribine tablets because the proposed comprehensive Risk Management Plan (RMP) will allow to monitor this potential risk in the post marketing setting in line with the recommendation of the EU MS guideline. This guideline states the following: "as a major category of products used or tested in MS are considered to act as immunomodulators, special attention should be paid to autoimmune disorders and the tumour facilitating/inducing potential of these products. Full assessment of this effect could be done post-marketing."

CHMP position

There is an unmet medical need in multiple sclerosis in patients with high disease activity or significant disease despite treatment with DMDs. Although treatment options are available, DMDs present different mechanism of action and different safety profiles. Therefore, new DMDs could potentially be a valuable addition to the existing DMDs in MS. It is also recognised that the oral route of administration is advantageous. Whether Movectro would fulfil such unmet medical need is not sufficiently demonstrated due to the limitations in the efficacy dataset and the serious concerns on the long term safety as underlined under ground 1. The CHMP considered that efficacy data in the restricted population with high disease activity or persistent disease activity despite treatment with DMD are not robust enough to outweigh the safety concerns. Therefore, the risk-benefit balance is not considered to be favourable and does not support a benefit to public health of the immediate availability of Movectro on the market. In conclusion, the CHMP confirms that the criteria needed for granting a Conditional Marketing Authorisation have not been met. A minority of CHMP members expressed a divergent view as they considered that those criteria have been met.

Scientific Advisory Group (SAG) Neurology

Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) Neurology with additional expertise in oncology, inviting the experts to provide their views on the CHMP questions in relation to the grounds for refusal, taking into account the applicant's response. The outcome of the SAG was as follows:

1. Efficacy in restricted subpopulations: What is the opinion of the SAG on the efficacy results in the two restricted multiple sclerosis populations as proposed by the Applicant (below)? Does the SAG consider these subpopulations meaningful, well-defined and easily distinguishable from other RRMS patients?

   Single disease modifying therapy in highly active relapsing-remitting multiple sclerosis (MS) for adult patients with two or more relapses in the previous year, and one or more T1 gadolinium enhancing lesions or at least 9 T2 hyperintense lesions in cranial MRI.

or

Single disease modifying therapy in highly active relapsing-remitting multiple sclerosis (MS) for adult patients who despite treatment with disease modifying drugs (DMDs) have persistent disease activity, defined by one or more relapses in the previous year, and one or more T1 gadolinium enhancing lesions or at least 9 T2 hyperintense lesions in cranial MRI.

The SAG agreed that the subgroup analysis performed by the applicant does point to a certain degree of efficacy of cladribine in these subgroups. However, the potential limitations in reliability of a post hoc subgroup analysis have to be considered. It should also be taken into account that there is only one pivotal trial. The group considered the effect modest in particular due to the overall low disease activity in the study population. For definite proof of efficacy, the SAG considered that a comparative study regarding both efficacy and safety, with a first line MS drug as comparator, would be necessary.

A priori there is no reason to apply different treatment criteria for drugs used as second line treatment in relapsing-remitting MS. Slight differences were noted when the applicant's proposed treatment criteria for cladribine were compared with those for an approved DMD. For the highly active MS group, the indication should specify "disabling" relapses, and with regard to T2 lesions, the indication should refer to T2 lesion increase.

2. Dose-response: Does the SAG consider the dose-response relationship with regard to efficacy and safety sufficiently established in patients with high disease activity? Could there be a dose with a more favourable benefit/risk profile, i.e. a dose that protects against MS exacerbations with less immunosuppression?

The SAG did not consider that the dose-response relationship for cladribine has been sufficiently established with regard to efficacy or safety. The lower end of the dose range after oral administration of cladribine has not been sufficiently explored. Additional dose-response studies are needed to define the efficacy and the efficacy/safety ratio for cladribine.

3. Lymphopenia and risk of infections: What is the opinion of the SAG about the risk associated with lymphopenia and potentially resulting infections in the perspective of the efficacy results in the two proposed sub-populations? In order to minimise the risks associated with lymphopenia, the Applicant has proposed treatment and re-treatment guidelines based on lymphocytes monitoring. Does the SAG consider these guidelines appropriate? How does the SAG view possible implications of the guidelines on efficacy?

The SAG considered that there is a risk of severe infections during treatment with cladribine which is related to the duration and grade of lymphopenia. The applicant recommends a complete blood count and differential before initiating cladribine therapy, and before each subsequent treatment course. The SAG considered that patients with severe lymphopenia at any time after the first two treatments should be re-analysed for their subsequent risk of infection or lymphopenia, including after the third and fourth course of treatment.

Laboratory tests for monitoring T lymphocytes should be developed. Antigenic- specific T cell responses should be monitored.

There is no major concern of any significant effect of the retreatment regimen on efficacy, although new data documenting both the efficacy of the proposed strategy, with preservation of the therapeutic effect would be desirable.

4. Risk of malignancies: What is the general view of the SAG on the potential risk of malignancies associated with cladribine? What is the SAG's opinion about the risk in the perspective of the efficacy results in the two proposed sub-populations?

The SAG considered that number of malignancies in the cladribine-treated group compared with the placebo group constitutes a serious concern. There was no clear explanation for these cases. Additional studies are needed to clarify the risk for malignancies.

Additional pharmacokinetic studies and preclinical studies should be considered by the applicant to further clarify the mechanism behind malignancies occurring during oral treatment with cladribine. Potentially toxic metabolites after oral administration of cladribine should be investigated.

Further analysis of the high age group in the cladribine MS studies should be performed in relation to the occurrence of malignancies.

Considering the above, the issue with malignancies occurring during oral treatment with cladribine cannot be solved post-marketing through a risk management plan.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant in writing and in an oral explanation and considered the views of the Scientific Advisory Group Neurology.

The latest restricted indication applied for by the applicant is as follows:

Movectro is indicated as a single disease modifying therapy in highly active relapsing-remitting multiple sclerosis (MS) for the following adult patient groups:

- Patients with high disease activity, defined by two or more disabling relapses in the previous year, and one or more T1 gadolinium enhancing lesions or at least 9 T2 hyperintense lesions.

or

- Patients who despite treatment with disease modifying drugs for at least one year have persistent disease activity, defined by one or more relapses in the previous year while on therapy, and one or more T1 gadolinium enhancing lesions or at least 9 T2 hyperintense lesions.

The CHMP agreed that the efficacy of cladribine 3.5 mg/kg was statistically significantly superior to placebo with regard to annualised relapse rate, proportion of subjects relapse-free as well as a number of MRI variables for both subpopulations. The differences are considered by the CHMP to be clinically meaningful although modest. Differences to placebo with regard to disability-related endpoints favoured cladribine, but achieved statistical significance only for the high disease activity subpopulation. The CHMP noted some limitations in the efficacy database affecting the interpretation of the efficacy results. Analyses of efficacy results in placebo-treated patients suggest that the population included in the study may be rather mildly affected and with a low disease progression rate considering that the population is claimed to be one with high disease (or persistent) disease activity. In addition, most patients in the CLARITY study (about 70%) did not use prior disease modifying drugs (DMD) before randomisation. It remains unclear whether even for patients with high disease activity the same effect could not have been reached with first line DMDs, especially as no active comparator was included in the trials.

In their grounds for the re-examination, the applicant presented an updated comprehensive assessment of malignancies as a stand-alone safety review and included the evaluation of all data available as of 5 November 2010, regardless of source or type of study. Overall, they recognise that there is a numerical difference in the number of malignancies in patients who received cladribine compared to the placebo groups. As of 5 November 2010 a total of 33 malignancy events have been reported from all clinical trials in patients treated with cladribine, 2 events have been reported in patients treated with placebo. They also argued that comparison is possible only if conducted on data from the placebo-controlled phase of all completed controlled studies. Any comparative analysis after this phase must take into account differences in patient numbers, overall exposure and patient follow-up observation time. The applicant considered that available data do not support a causal relationship for the risk of malignancy in MS patients treated with cladribine. They concluded that assessment of available data regarding malignancy events is inconclusive, and that the number of reported cases is insufficient to accurately estimate the risk.

The applicant also proposed that long term safety of oral cladribine tablets will be monitored through post-marketing surveillance as well as in two follow-up safety studies.

The applicant recognised that profound and persistent lymphopenia is an adverse event directly related to the mode of action of cladribine. In the CLARITY-study higher frequency of lymphopenia was reported with the higher dose. The frequency of infectious adverse events and herpes virus infections increased with severity of lymphopenia. In order to minimise the development of high grade or persistent lymphopenia and its clinical manifestations the applicant proposed re-treatment guidelines. The applicant assessed the impact of the re-treatment guideline as a risk-minimisation measure, and the impact on the efficacy. They concluded that the re-treatment guidelines have a measurable effect on minimising patient risk of severe lymphopenia and its clinical manifestations while maintaining efficacy of cladribine tablets in the patient population following introduction of these treatment guidelines.

The CHMP considered the conclusions of the applicant with regard to malignancies premature. It is agreed with the applicant that extrapolation from and comparison with cancer populations with regard to cancer risk in MS patients should be interpreted with caution. However, a potential signal of increased cancer risk has emerged from the cladribine trials in MS because of a disproportionate number of malignancies among patients exposed to cladribine as compared to the number of cancers in unexposed patients without adequate explanation. Cladribine is a cytotoxic agent interfering with DNA synthesis/repair. The lymphopenia is the intended effect. Reduced immune-surveillance associated with profound and persistent lymphopenia poses a risk of opportunistic infections and malignancies. Considering the high number of events observed in a limited safety database from a controlled clinical setting and the mechanism of action of cladribine, a causal relationship is not unlikely. The exclusion of the high dose, in combination with the stricter re-treatment guidelines are agreed to be limiting the risk of lymphopenia, but the potential risk for malignancies persists. Therefore serious concerns remain on the long term safety.

No further satisfactory data were provided with regard to the choice of the dose. No adequate dose-finding studies in the intended target RRMS population, and with the intended oral formulation were performed. Simulations should be interpreted with caution and obviously do not carry the same strength of evidence as a proper clinical dose-finding study. The lower end of dose efficacy curve has not been sufficiently evaluated. In view of the serious safety concerns, whether a lower dose with a better benefit/risk ratio exists should have been established.

Finally with the re-examination, the CHMP considered whether the application for Movectro met the requirements for a conditional marketing authorisation. Whether Movectro would fulfil such unmet medical need is not sufficiently demonstrated due to the limitations in the efficacy dataset and the serious concerns on the long term safety as underlined under ground 1. The CHMP considered that efficacy data in the restricted population with high disease activity or persistent disease activity despite treatment with DMD are not robust enough to outweigh the safety concerns. Therefore, the risk-benefit balance is not considered to be favourable and does not support a benefit to public health of the immediate availability of Movectro on the market and their proposal at this stage, to collect data on long term safety of oral cladribine tablets through post-marketing surveillance and via two follow-up safety studies.
In conclusion, the CHMP confirmed that the criteria needed for granting a Conditional Marketing Authorisation have not been met.

Recommendation following re-examination

Based on the CHMP review of data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the risk-benefit balance of Movectro in the treatment of highly active relapsing-remitting multiple sclerosis for the following adult patient groups:

- Patients with high disease activity, defined by two or more disabling relapses in the previous year, and one or more T1 gadolinium enhancing lesions or at least 9 T2 hyperintense lesions.

or

- Patients who despite treatment with disease modifying drugs for at least one year have persistent disease activity, defined by one or more relapses in the previous year while on therapy, and one or more T1 gadolinium enhancing lesions or at least 9 T2 hyperintense lesions.

was unfavourable and that the application did not satisfy the criteria for authorisation and recommended the refusal of the granting of the conditional marketing authorisation.

The grounds for the decision are as follows:

– Serious safety concerns remain, in particular with regard to the higher number of malignancies observed in clinical trials. Therefore serious concerns remain on the long term safety. Efficacy data in the restricted population with high disease activity or persistent disease activity despite treatment with disease modifying drugs are not robust enough to outweigh the safety concerns. Therefore the Risk-Benefit balance is not considered to be favourable.

– The lower end of dose efficacy curve has not been sufficiently evaluated. In view of the serious safety concerns, whether a lower dose with a better Risk-Benefit balance exists should have been established.

– The following criteria needed for granting a conditional marketing authorisation have not been met:

- The Risk-Benefit balance of the product is positive;
- Fulfilment of unmet medical need has not been sufficiently demonstrated;
- Consequently, the benefit to public health of the immediate availability on the market of the medicinal product concerned does not outweigh the risks inherent in the fact that additional data are still required.