UCSF
UC San Francisco Previously Published Works

Title

The efficacy of cladribine tablets in CIS patients retrospectively assigned the diagnosis of MS using modern criteria: Results from the ORACLE-MS study

Permalink

https://escholarship.org/uc/item/9s1070q9

Journal

Multiple Sclerosis Journal - Experimental Translational and Clinical, 3(4)

ISSN

2055-2173

Authors

Freedman, Mark S
Leist, Thomas P
Comi, Giancarlo
et al.

Publication Date

2017-12-01

DOI

10.1177/2055217317732802

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

MSJ Experimental Translational Clinical

Original Research Paper

The efficacy of cladribine tablets in CIS patients retrospectively assigned the diagnosis of MS using modern criteria: Results from the ORACLE-MS study

Multiple Sclerosis Journal – Experimental, Translational and Clinical

October-December 2017: 1–14

DOI: 10.1177/2055217317732802

© The Author(s), 2017.
Reprints and permissions:
http://www.sagepub.co.uk/journalsPermissions.nav

Mark S Freedman, Thomas P Leist, Giancarlo Comi, Bruce AC Cree, Patricia K Coyle, Hans-Peter Hartung, Patrick Vermersch, Doris Damian and Fernando Dangond

Abstract

Background: Multiple sclerosis (MS) diagnostic criteria have changed since the ORACLE-MS study was conducted; 223 of 616 patients (36.2%) would have met the diagnosis of MS vs clinically isolated syndrome (CIS) using the newer criteria.

Objective: The objective of this paper is to assess the effect of cladribine tablets in patients with a first clinical demyelinating attack fulfilling newer criteria (McDonald 2010) for MS vs CIS.

Methods: A post hoc analysis for subgroups of patients retrospectively classified as fulfilling or not fulfilling newer criteria at the first clinical demyelinating attack was conducted.

Results: Cladribine tablets 3.5 mg/kg ($n = 68$) reduced the risk of next attack or three-month confirmed Expanded Disability Status Scale (EDSS) worsening by 74% vs placebo ($n = 72$); $p = 0.0009$ in patients meeting newer criteria for MS at baseline. Cladribine tablets 5.25 mg/kg ($n = 83$) reduced the risk of next attack or three-month confirmed EDSS worsening by 37%, but nominal significance was not reached ($p = 0.14$). In patients who were still CIS after applying newer criteria, cladribine tablets 3.5 mg/kg ($n = 138$) reduced the risk of conversion to clinically definite multiple sclerosis (CDMS) by 63% vs placebo ($n = 134$); $p = 0.0003$. Cladribine tablets 5.25 mg/kg ($n = 121$) reduced the risk of conversion by 75% vs placebo ($n = 134$); $p < 0.0001$.

Conclusions: Regardless of the criteria used to define CIS or MS, 3.5 mg/kg cladribine tablets are effective in patients with a first clinical demyelinating attack.

ClinicalTrials.gov registration: The ORACLE-MS study (NCT00725985).

***Keywords*:** Cladribine tablets, clinically isolated syndrome, conversion to clinically definite multiple sclerosis, early multiple sclerosis, efficacy, McDonald 2010 criteria

Date received: 27 April 2017; accepted: 7 August 2017

Introduction

Cladribine is a deoxyadenosine analogue prodrug which depletes lymphocytes through a preferential effect based on their kinase-to-phosphatase enzyme profile, producing discontinuous reductions in T and B cells with relatively minor and transient effects on innate immune cell types.[1,2] In June 2017 the European Medicines Agency's Committee for Medicinal Products for Human Use recommended granting marketing approval of cladribine tablets for relapsing forms of multiple sclerosis (MS). The oral cladribine for early multiple sclerosis (ORACLE-MS) clinical trial evaluated the efficacy of cladribine tablets in patients with clinically isolated syndrome (CIS) who were at high risk of conversion to clinically definite multiple sclerosis (CDMS) based on the Poser diagnostic criteria, i.e. experiencing a second clinical attack.[3–5] Treatment with cladribine tablets 3.5 and 5.25 mg/kg significantly delayed conversion to CDMS (defined by

Correspondence to:
Mark S Freedman
Department of Medicine, University of Ottawa and the Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, Ontario, K1H 8L6, Canada.
mfreedman@toh.ca

Mark S Freedman,
Department of Medicine (Neurology), University of Ottawa and the Ottawa Hospital Research Institute, Canada

Creative Commons CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Thomas P Leist,
Division of Clinical Neuroimmunology, Thomas Jefferson University, USA

Giancarlo Comi,
Department of Neurology and Institute of Experimental Neurology, Università Vita-Salute San Raffaele, Ospedale San Raffaele, Italy

Bruce AC Cree,
University of California San Francisco, USA

Patricia K Coyle,
Stony Brook University, Department of Neurology, USA

Hans-Peter Hartung,
Department of Neurology, Heinrich Heine University, Medical Faculty, Germany

Patrick Vermersch,
University of Lille, CHU Lille, LIRIC-INSERM U995, FHU Imminent, France

Doris Damian,
EMD Serono Inc, Billerica, USA

Fernando Dangond,
EMD Serono Inc, Billerica, USA

either a second attack or an increase in Expanded Disability Status Scale (EDSS) score confirmed over at least three months) with lower proportions converting compared to placebo (13% (27/206) for cladribine tablets 3.5 mg/kg, 15% (30/204) for cladribine tablets 5.25 mg/kg, and 34% (71/206) for placebo).[3] Treatment with cladribine tablets 3.5 mg/kg was associated with a 67% reduction in risk of conversion to CDMS vs placebo (hazard ratio (HR) 0.33, 95% confidence interval (CI) 0.21–0.51; $p < 0.0001$), and treatment with cladribine tablets 5.25 mg/kg was associated with a 62% reduction in risk of conversion to CDMS vs placebo; (HR 0.38, 95% CI 0.25–0.58; $p < 0.0001$). Cladribine tablets 3.5 mg/kg and 5.25 mg/kg also significantly delayed conversion to MS (according to the McDonald 2005 diagnostic criteria) relative to placebo (the main secondary endpoint of the ORACLE-MS study, post-amendment).[3,6]

The decision to start treatment for MS after a first attack is related to evidence of spatial and temporal dissemination of lesions, and in clinical practice, early optimisation of therapy for patients with MS may be important to improve long-term disease control.[7,8] Revisions were made to the MS diagnostic criteria in 2010 to improve accurate, early diagnosis in a significant number of patients presenting with a single event, by allowing magnetic resonance imaging (MRI) evidence to fulfil criteria for dissemination in time (DIT) and space (DIS).[9] More than one-third of the study population in ORACLE-MS met revised MS diagnostic criteria at enrolment (McDonald 2010 criteria).[3] Thus, this post hoc analysis of the ORACLE-MS study, based on the revised diagnostic criteria, was undertaken to assess the treatment effect of cladribine tablets on reduction of the risk of a second attack or confirmed EDSS worsening in a population of patients who fulfilled the more modern diagnostic criteria for MS or who remained CIS even by the newer definition.

Methods

The ORACLE-MS study was previously described in detail.[3] For every patient, eligibility for study enrolment and entry into each of the study periods, and diagnosis of conversion to either CDMS or MS (according to the McDonald 2005 criteria) was confirmed and approved by a sponsor-appointed study Adjudication Committee. Patients were aged 18–55 years with a first clinical demyelinating attack within 75 days before screening, at least two clinically silent lesions of at least 3 mm on a T2-weighted brain MRI scan, and an EDSS score of ≤5.0. Patients were randomised (1:1:1) to placebo, a cumulative dose of cladribine tablets 3.5 mg/kg or cladribine tablets 5.25 mg/kg bodyweight over a maximum of two years, the double-blind period of the study.

Patient subgroups

For this exploratory analysis, the McDonald 2010 criteria were used to identify patients with a first clinical demyelinating attack who met the definition of MS based on DIT and DIS by MRI.[9] Baseline MRI scans of study participants were retrospectively reviewed. Those fulfilling the following were classified as having MS according to the McDonald 2010 criteria: presence of T1 gadolinium-enhancing (Gd+) lesions at baseline with a T2 lesion count greater than the T1 Gd+ lesion count (DIT) AND at least one T2 lesion in at least two of the following MS-typical regions of the central nervous system: periventricular, juxtacortical and infratentorial (the spinal cord was not imaged in ORACLE-MS; only juxtacortical, periventricular and infratentorial regions were analysed) (DIS) or: presence of T1 Gd+ lesions at baseline with a T2 lesion count greater than the T1 Gd+ lesion count (DIT) AND multifocal (clinical) presentation using the classification according to the Adjudication Committee (DIS).

Subgroup efficacy analyses

The original ORACLE-MS study used time to conversion to CDMS (Poser criteria, time to next attack or three-month confirmed EDSS worsening) as a primary endpoint and time to conversion to MS according to the older diagnostic criteria (McDonald 2005) as a secondary endpoint.[3,4,6] In this post hoc analysis of the original study primary and secondary endpoints, data are presented for the subgroup of patients who were retrospectively found at baseline to fulfil the newer diagnostic criteria for MS (McDonald 2010) as well as the subgroup who, according to these criteria, would still be considered CIS.

The outcomes analysed for the two subgroups of patients were: time to next attack or three-month confirmed EDSS worsening (defined as an increase in the EDSS score of ≥1 point if baseline was ≥1 and ≤4.5, or of ≥1.5 points if baseline EDSS was 0, or of ≥0.5 point if baseline EDSS was ≥5, confirmed over ≥3 months); time to next evidence of disease activity (i.e. attack or any EDSS worsening or MRI event (defined as a new T1 Gd+ or new or enlarging T2 lesions on MRI)). MRI assessments of disease activity (number of new or persisting T1 Gd+ lesions, new or enlarging T2 lesions or combined unique active (CUA) lesions) were also analysed for the two subgroups.

Statistical methods

This was a post hoc analysis of the primary efficacy endpoint, main secondary endpoint and selected secondary efficacy endpoints (number of T1 Gd+ lesions, new or enlarging T2 lesions and CUA lesions) that had been analysed in the entire study population in the initial efficacy analysis of the ORACLE-MS study.[3] For the post hoc analysis of the primary and main secondary endpoint, the HRs (with 95% CIs) of cladribine tablets 3.5 mg/kg and cladribine tablets 5.25 mg/kg vs placebo were determined for each of the newly defined subgroups using the same statistical approach and methods used for the primary analysis of the primary efficacy endpoint as previously reported.[3] For each treatment in the newer subgroups, the cumulative probability of an event was estimated using the nonparametric Kaplan-Meier (KM) method. Because these reanalyses were post hoc and not pre-specified, no multiplicity adjustments were made to the resulting p values. Any difference observed between the groups where the p value was less than 0.05 by statistical testing should be regarded as nominally significant.

Results

Patient population

As previously described, baseline characteristics were well balanced across treatment groups in the ORACLE-MS study. In the ORACLE-MS population, 36.2% (223/616) of the presenting patients would have met the criteria for a diagnosis of MS at baseline using the newer criteria (McDonald 2010), while 63.8% (393/616) were still classified as CIS. The baseline demographics and disease characteristics for the groups of patients who did and did not meet MS diagnosis according to the newer criteria and their treatment assignments are shown in Tables 1(a) and 1(b).

Age, gender, race, EDSS, MRI and first clinical demyelinating attack characteristics were balanced across study treatments in both subgroups. Overall, higher MRI activity and T2 lesion load were observed in the group that met newer MS diagnostic criteria with a mean (±SD) number of T1 Gd+ lesions 3.86 (±6.76) compared with 0.05 (±0.26) in the group that did not. The mean number of T2 lesions was 41.88 (±36.48) for those meeting the newer criteria and 19.53 (±18.19) for those who did not (Table 1(b)).

The majority of second clinical events were relapses rather than confirmed EDSS worsening, as would be expected in a cohort of patients with early clinically manifest disease. There were 128 conversions to CDMS in the entire intent-to-treat (ITT) ORACLE-MS cohort ($n = 616$). Of these 128, 123 (96%) were attributed to a second relapse and five (4%) were due to three-month confirmed EDSS worsening. There were 52 conversions to CDMS in the subgroup of patients meeting newer criteria at baseline ($n = 223$). Of these, 51 (98%) were due to a second relapse and only one (2%) was due to three-month confirmed EDSS worsening.

Efficacy outcomes and endpoints

Efficacy in patients with early MS according to the newer criteria

In the subset of patients with MS at baseline, according to the newer criteria, cladribine tablets 3.5 mg/kg ($n = 68$) significantly reduced the risk of next attack or three-month confirmed EDSS worsening by 74% vs placebo ($n = 72$) (HR (95% CI) 0.26 (0.12–0.58); $p = 0.0009$; Figure 1). Cladribine tablets 5.25 mg/kg ($n = 83$) also reduced the risk of next attack or three-month confirmed EDSS worsening; the HR (95% CI) of 0.63 (0.34–1.16) was favourable but significance was not reached ($p = 0.14$). Baseline demographics and disease characteristics of the cladribine tablets 3.5 mg/kg and 5.25 mg/kg groups in the newer criteria-defined MS population showed no differences that would suggest a potential reason for this observation.

At the end of the double-blind period, KM estimates (95% CI) of the cumulative probability of experiencing another attack or three-month confirmed EDSS worsening in the subset of patients with MS at baseline according to newer criteria were 13.6% (4.3–23.0) for cladribine tablets 3.5 mg/kg and 23.0% (13.5–32.5) for cladribine tablets 5.25 mg/kg, compared with 37.4% (25.9–48.8) for the placebo group.

Efficacy in patients not meeting the newer MS criteria (i.e. patients who remained CIS)

In the subset of ITT patients retrospectively classified as not meeting newer criteria for MS at baseline (i.e. CIS), treatment with cladribine tablets 3.5 mg/kg ($n = 138$) significantly reduced, vs placebo ($n = 134$), the risk of next attack or three-month confirmed EDSS worsening by 63% (HR (95% CI) 0.37, (0.22–0.63); $p = 0.0003$) (Figure 2). Cladribine tablets 5.25 mg/kg ($n = 121$) also significantly reduced the risk of next attack or three-month confirmed EDSS worsening by 75% vs placebo (HR (95% CI) 0.25 (0.13–0.48); $p < 0.0001$).

Table 1. (a) Demographic characteristics and baseline disease activity (by newer diagnostic criteria subgroups).

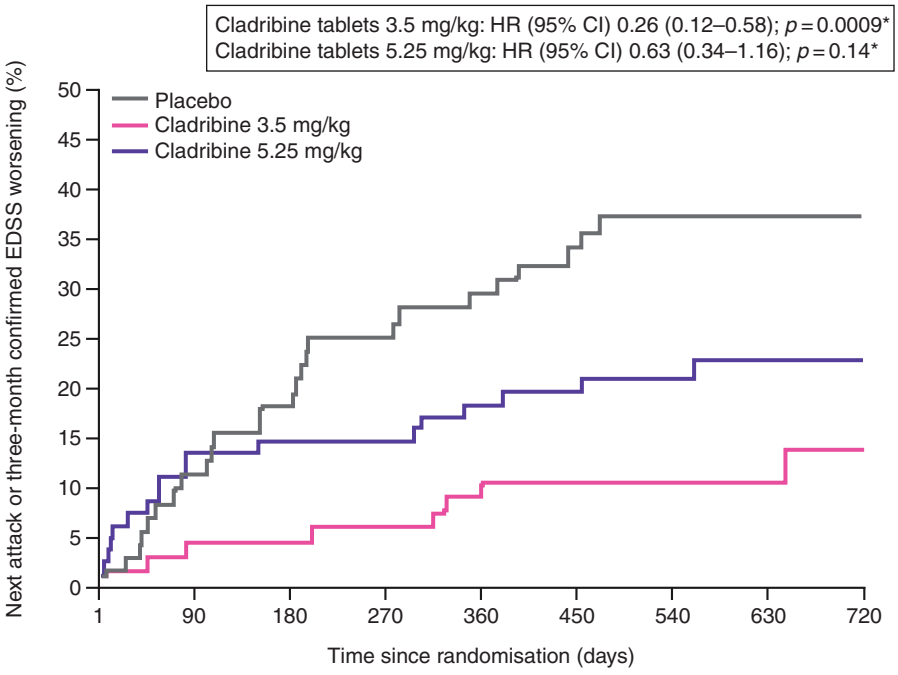
Characteristic	Value	Placebo ($N=206$)		Cladribine tablets 3.5 mg/kg ($N=206$)		Cladribine tablets 5.25 mg/kg ($N=204$)		All participants ($N=616$)	
		Satisfied newer MS criteria (yes)	Satisfied newer MS criteria (no)	Satisfied newer MS criteria (yes)	Satisfied newer MS criteria (no)	Satisfied newer MS criteria (yes)	Satisfied newer MS criteria (no)	Satisfied newer MS criteria (yes)	Satisfied newer MS criteria (no)
	n (%)	72 (35.0)	134 (65.0)	68 (33.0)	138 (67.0)	83 (40.7)	121 (59.3)	223 (36.2)	393 (63.8)
Age, years	Mean ± SD	31.83 ± 8.25	32.32 ± 8.18	29.12 ± 7.49	32.98 ± 9.63	29.75 ± 8.86	33.32 ± 8.52	30.23 ± 8.31	32.86 ± 8.80
Sex, *n* (%)	Female	46 (63.9)	92 (68.7)	42 (61.8)	88 (63.8)	56 (67.5)	76 (62.8)	144 (64.6)	256 (65.1)
Race, *n* (%)	White	70 (97.2)	124 (92.5)	66 (97.1)	131 (94.9)	76 (91.6)	115 (95.0)	212 (95.1)	370 (94.1)
	Black	1 (1.4)	0	0	0	2 (2.4)	2 (1.7)	3 (1.3)	2 (0.5)
	Asian	1 (1.4)	10 (7.5)	2 (2.9)	7 (5.1)	4 (4.8)	4 (3.3)	7 (3.1)	21 (5.3)
	Other	0	0	0	0	1 (1.2)	0	1 (0.4)	0
Time from FCDE to randomisation (days)	Mean ± SD	77.79 ± 18.14	80.27 ± 17.84	78.97 ± 13.80	78.51 ± 16.98	78.90 ± 17.77	79.66 ± 17.57	78.57 ± 16.72	79.47 ± 17.43
	Median	74.50	80.00	79.00	80.00	83.00	82.00	79.00	80.00
Monofocal[a]/multifocal[b] classification (by investigator), *n* (%)	Multifocal	38 (52.8)	64 (47.8)	45 (66.2)	56 (40.6)	48 (57.8)	53 (43.8)	131 (58.7)	173 (44.0)
Monofocal[a]/multifocal[b] classification (by adjudication committee), *n* (%)	Multifocal	44 (61.1)	61 (45.5)	41 (60.3)	53 (38.4)	43 (51.8)	53 (43.8)	128 (57.4)	167 (42.5)
Use of steroid treatment, *n* (%)	Yes	43 (59.7)	97 (72.4)	45 (66.2)	86 (62.3)	50 (60.2)	83 (68.6)	138 (61.9)	266 (67.7)
EDSS score	Mean ± SD	1.69 ± 0.86	1.63 ± 0.86	1.68 ± 0.83	1.58 ± 0.96	1.69 ± 0.83	1.51 ± 1.00	1.69 ± 0.84	1.57 ± 0.94

EDSS: Expanded Disability Status Scale; FCDE: first clinical demyelinating event; MS: multiple sclerosis; SD: standard deviation.
[a]Neurological signs and symptoms can be explained by only one single location. [b]Neurological signs and symptoms cannot be explained by only one single location.

Table 1. (b) Baseline MRI activity (by newer diagnostic criteria subgroups).

Characteristic	Value	Placebo ($N=206$)		Cladribine tablets 3.5 mg/kg ($N=206$)		Cladribine tablets 5.25 mg/kg ($N=204$)		All participants ($N=616$)	
		Satisfied newer MS criteria (yes)	Satisfied newer MS criteria (no)	Satisfied newer MS criteria (yes)	Satisfied newer MS criteria (no)	Satisfied newer MS criteria (yes)	Satisfied newer MS criteria (no)	Satisfied newer MS criteria (yes)	Satisfied newer MS criteria (no)
	n (%)	72 (35.0)	134 (65.0)	68 (33.0)	138 (67.0)	83 (40.7)	121 (59.3)	223 (36.2)	393 (63.8)
Number of T1 Gd+ lesions	Mean ± SD	2.69 ± 3.62	0.01 ± 0.09	4.41 ± 7.00	0.05 ± 0.25	4.42 ± 8.39	0.08 ± 0.38	3.86 ± 6.76	0.05 ± 0.26
T1 Gd+ lesion volume (mm^3)	Mean ± SD	296.93 ± 439.72	0.13 ± 1.49	489.79 ± 951.20	8.62 ± 60.09	404.82 ± 821.54	10.05 ± 72.80	395.89 ± 768.18	6.16 ± 53.89
Number of T1 hypointense lesions	Mean ± SD	9.19 ± 10.92	5.75 ± 6.73	10.84 ± 18.42	5.59 ± 6.97	10.77 ± 14.96	6.11 ± 8.31	10.28 ± 14.96	5.80 ± 7.32
Number of T2 lesions	Mean ± SD	38.18 ± 36.56	19.99 ± 18.02	42.37 ± 37.03	19.15 ± 18.62	44.70 ± 36.13	19.45 ± 18.04	41.88 ± 36.48	19.53 ± 18.19
Number of T2 lesions category, *n* (%)	<9 lesions	8 (11.1)	42 (31.3)	7 (10.3)	49 (35.5)	6 (7.2)	40 (33.1)	21 (9.4)	131 (33.3)
	≥9 lesions	64 (88.9)	92 (68.7)	61 (89.7)	89 (64.5)	77 (92.8)	81 (66.9)	202 (90.6)	262 (66.7)
T2 lesion volume (mm^3)	Mean ± SD	5368.39 ± 5956.94	2398.77 ± 3279.82	5904.40 ± 7811.16	2218.53 ± 2420.37	6192.59 ± 6601.45	2202.18 ± 2752.59	5838.60 ± 6780.84	2274.95 ± 2832.76

Gd+: gadolinium enhancing; MRI: magnetic resonance imaging; MS: multiple sclerosis; SD: Standard Deviation.



Number of participants at risk (Conversions):									
Placebo	72 (0)	63 (8)	58 (13)	53 (18)	48 (21)	40 (24)	31 (26)	15 (26)	1 (26)
Cladribine 3.5 mg/kg	68 (0)	65 (3)	65 (3)	63 (4)	59 (6)	55 (7)	48 (7)	33 (7)	6 (8)
Cladribine 5.25 mg/kg	83 (0)	70 (11)	68 (12)	68 (12)	62 (15)	59 (16)	51 (17)	28 (18)	3 (18)

Figure 1. Kaplan-Meier cumulative incidence curve. Time to next attack or three-month confirmed EDSS worsening in patients retrospectively classified as meeting newer diagnostic criteria for MS at baseline.
*Hazard ratio from Cox proportional hazards model with effects for treatment adjusted for the stratification factor (region); *p* values from two-sided Wald test.
CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; MS: multiple sclerosis.

At the end of the double-blind period, KM estimates (95% CI) of the cumulative probability of experiencing another attack or three-month confirmed EDSS worsening in patients not meeting newer criteria for MS at baseline were 14.2% (8.2–20.1) for cladribine tablets 3.5 mg/kg and 11.0% (5.0–16.9) for cladribine tablets 5.25 mg/kg, compared with 37.6% (28.5–46.7) for the placebo group.

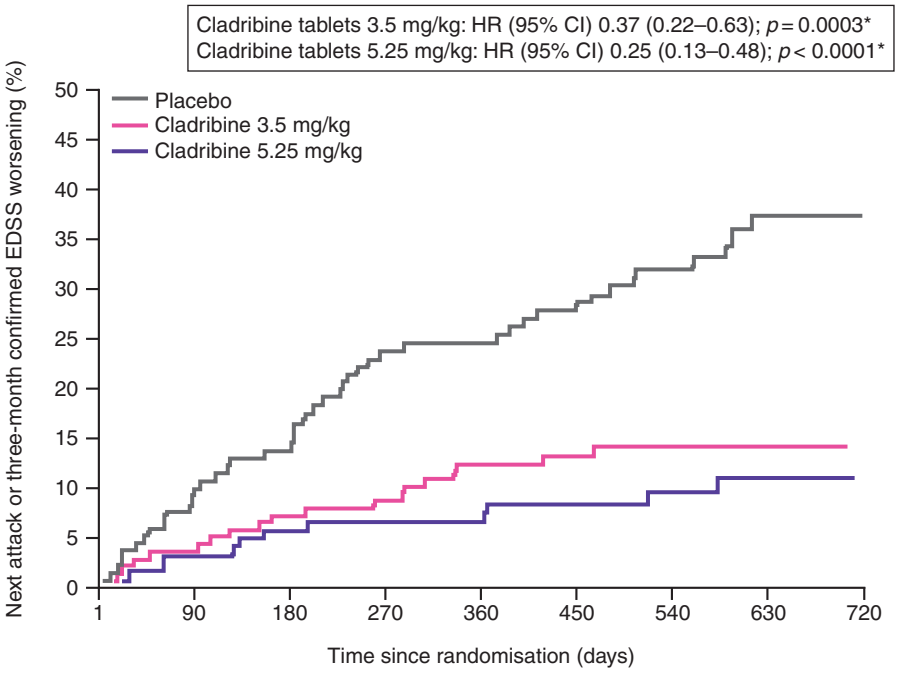
Time to next evidence of disease activity by newer subgroup definition

Time to next evidence of disease activity (i.e. attack or any EDSS worsening or MRI event (defined as a new T1 Gd+ or new or enlarging T2 lesions on MRI)) is shown in Figures 3 and 4. Patients meeting the newer criteria for MS at baseline had a higher risk of next evidence of disease activity compared to patients who did not. Compared with placebo, cladribine tablets significantly reduced the risk of next evidence of disease activity both in patients fulfilling newer MS diagnostic criteria and in those who did not meet them.

At the end of the double-blind period, KM estimates (95% CI) of the cumulative probability of experiencing disease activity in the subset of patients with MS at baseline according to newer criteria was 76.3% (66.1–86.5) for patients receiving cladribine tablets 3.5 mg/kg, 67.1% (56.9–77.3) for patients receiving cladribine tablets 5.25 mg/kg and 95.3% (90.1–100.4) for patients receiving placebo. In the subset of patients retrospectively classified as CIS according to the newer criteria, the KM estimates (95% CI) of the probability of experiencing disease activity were 45.9% (37.0–54.8) for cladribine tablets 3.5 mg/kg, 38.2% (28.9–47.6) for cladribine tablets 5.25 mg/kg and 82.8% (75.3–90.2) for the placebo group.

MRI outcomes by newer diagnostic criteria subgroups at baseline

Both doses of cladribine tablets, compared with placebo, were associated with significantly lower cumulative numbers of new or persisting T1 Gd+ lesions, new or enlarging T2 lesions and CUA lesions in



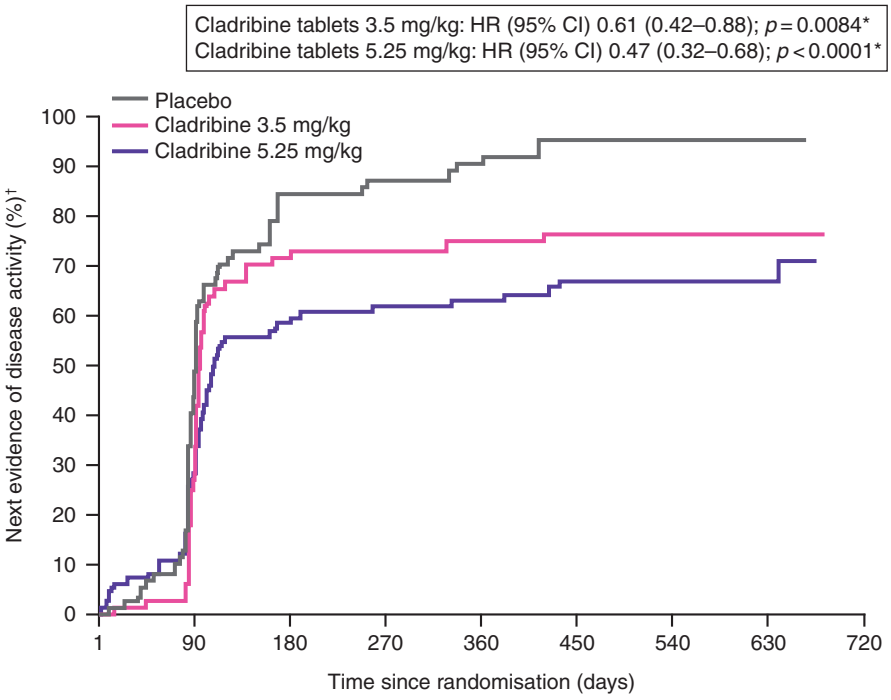
Number of participants at risk (Conversions):									
Placebo	134 (0)	116 (13)	110 (18)	97 (31)	94 (32)	87 (37)	64 (41)	37 (45)	5 (45)
Cladribine 3.5 mg/kg	138 (0)	132 (5)	126 (10)	124 (12)	114 (17)	102 (18)	88 (19)	55 (19)	3 (19)
Cladribine 5.25 mg/kg	121 (0)	117 (4)	112 (7)	109 (8)	106 (8)	93 (10)	78 (11)	52 (12)	3 (12)

Figure 2. Kaplan-Meier cumulative incidence curve. Time to next attack or three-month confirmed EDSS worsening in patients retrospectively classified as not meeting newer diagnostic criteria for MS at baseline (i.e. newer CIS definition).
*Hazard ratio from Cox proportional hazards model with effects for treatment adjusted for the stratification factor (region); *p* values from two-sided Wald test.
CI: confidence interval; CIS: clinically isolated syndrome; EDSS: Expanded Disability Status Scale; HR: hazard ratio; MS: multiple sclerosis.

patients meeting the newer MS diagnostic criteria and those who did not (Table 2). The design of the ORACLE-MS study involved analysis of the primary endpoint after the expected number of events had been reached, but before all patients completed the 96-week double-blind period. It should be noted that only 25% of the placebo patients in the ORACLE-MS study completed the 96-week double-blind treatment period, compared to 41% of the group treated with cladribine tablets 3.5 mg/kg and 36% of the group treated with cladribine tablets 5.25 mg/kg, a difference influenced by the differential incidence of conversion to CDMS. For each participant, the number of lesions analysed for the double-blind period was taken from the available MRI scans (no imputation was performed). Assuming that the patients who did not complete the double-blind period were those with more lesions on MRI scans, it is possible that the cladribine tablets treatment effects in the MRI data are underestimated.

Discussion

There are limited data on the efficacy of disease-modifying drugs in CIS or early MS patients and so the ORACLE-MS study provides an important source of evidence for the benefits of treating this patient population.[3] The study showed that annual treatment courses with cladribine tablets significantly delayed conversion to CDMS and also significantly reduced MRI lesion counts compared with patients receiving placebo following a first attack.[3] MS diagnostic criteria evolved and patients in ORACLE-MS were originally described as having a first clinical demyelinating attack, termed clinically isolated syndrome or CIS,[5] and did not meet the then current 2005 McDonald criteria for a diagnosis of MS. Since then, both the definition of MS and CIS have been updated with the 2010 McDonald criteria, effectively recognising that some patients fulfil DIT and DIS at the time of the first attack and reducing the number of people termed CIS. This allows for

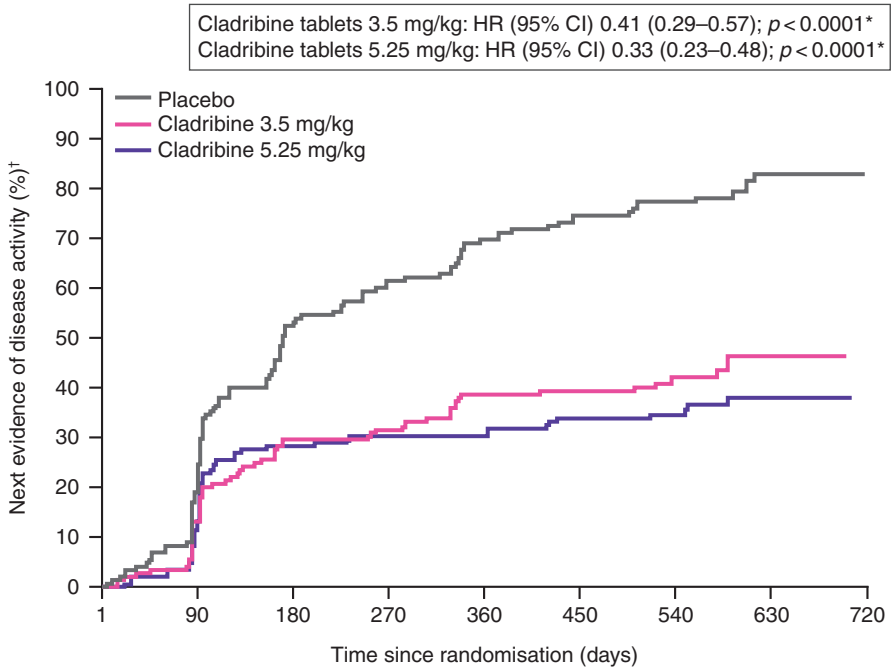


Number of participants at risk (Conversions):									
Placebo	71 (0)	40 (31)	11 (60)	9 (62)	6 (64)	2 (67)	2 (67)	2 (67)	0 (67)
Cladribine 3.5 mg/kg	67 (0)	49 (18)	19 (48)	17 (49)	16 (50)	13 (51)	11 (51)	6 (51)	1 (51)
Cladribine 5.25 mg/kg	82 (0)	59 (23)	34 (48)	31 (51)	30 (52)	26 (55)	22 (55)	9 (55)	0 (56)

Figure 3. Kaplan-Meier cumulative incidence curve. Time to next evidence of disease activity in patients retrospectively classified as meeting newer diagnostic criteria for MS at baseline.
†Next evidence of disease activity based on McDonald 2005 criteria (i.e. attack or any EDSS worsening or MRI event (defined as a new T1 Gd+ or new or enlarging T2 lesions on MRI)).
*Hazard ratio from Cox proportional hazards model with effects for treatment adjusted for the stratification factor (region); *p* values from two-sided Wald test.
CI: confidence interval; EDSS: Expanded Disability Status Scale; Gd+: gadolinium enhancing; HR: hazard ratio; MS: multiple sclerosis; MRI: magnetic resonance imaging.

earlier recognition of MS and potential therapeutic intervention.[9–11] Because treatment of patients at the CIS stage is still somewhat controversial, it was important to ascertain whether the efficacy of cladribine tablets established in the ORACLE-MS study was applicable to patients regardless of the criteria used to diagnose MS and CIS. After application of the newer MS diagnostic criteria (McDonald 2010), over one-third of the patients in ORACLE-MS would have been considered to have early MS vs CIS at baseline. It should be noted that there is a slight discrepancy in the numbers meeting these criteria at baseline (36.2%) compared with the original publication of the ORACLE-MS data (37%) due to five patients being categorised differently after re-examination of the clinical data.

The results of the current analysis are consistent with those for the original ITT population. In patients who did not meet McDonald 2010 criteria at baseline (i.e. patients presenting as CIS), treatment with cladribine tablets, compared with placebo, delayed conversion to CDMS. Treatment with cladribine tablets also reduced the risk of the next evidence of disease activity (i.e. loss of clinical activity free and/or MRI event-free status) in patients with early relapsing MS according to the newer diagnostic criteria. Including MRI measures for next evidence of disease activity leads to higher numbers of patients showing evidence than relying on clinical evidence only. This is a common feature of such analyses, and for the original ORACLE-MS study population (among patients whose lesion status was known), 57.1% for the cladribine tablets 3.5 mg/kg group and 67.0% for the 5.25 mg/kg group were T1-Gd+ lesion free during the double-blind period compared to only 21.6% in the placebo group. The proportion of patients with no new or enlarging T2 lesions was



Number of participants at risk (Conversions):

Placebo	130 (0)	103 (27)	60 (68)	40 (79)	37 (90)	30 (95)	21 (98)	11 (102)	1 (102)
Cladribine 3.5 mg/kg	137 (0)	118 (18)	95 (40)	91 (43)	76 (52)	70 (53)	61 (56)	33 (59)	1 (59)
Cladribine 5.25 mg/kg	121 (0)	106 (14)	85 (34)	82 (36)	78 (36)	61 (40)	49 (41)	30 (43)	1 (43)

Figure 4. Kaplan-Meier cumulative incidence curve. Time to next evidence of disease activity in patients retrospectively classified as not meeting newer diagnostic criteria for MS at baseline (i.e. newer CIS definition).
†Next evidence of disease activity based on McDonald 2005 criteria (i.e. attack or any EDSS worsening or MRI event (defined as a new T1 Gd+ or new or enlarging T2 lesions on MRI)).
*Hazard ratio from Cox proportional hazards model with effects for treatment adjusted for the stratification factor (region); *p* values from two-sided Wald test.
CI: confidence interval; EDSS: Expanded Disability Status Scale; Gd+: gadolinium enhancing; HR: hazard ratio; MS: multiple sclerosis; MRI: magnetic resonance imaging.

even lower (35.1% for the cladribine tablets 3.5 mg/kg group, 32.9% for the 5.25 mg/kg and 19.0% for the placebo group). Hence, MRI activity drives a lot of the next evidence of disease activity, even if restricted to MS-typical lesions only. However, the current analysis demonstrates strong evidence of the efficacy of cladribine tablets and supports the importance of treatment of patients with early MS. Clinical studies with cladribine tablets show that efficacy is consistent across patient subgroups with a spectrum of MS disease characteristics.[12–15]

The estimated treatment effects were favourable for both the cladribine tablets 3.5 mg/kg and 5.25 mg/kg groups. The KM cumulative incidence curve for time to next attack or three-month confirmed EDSS worsening for the 5.25 mg/kg cladribine tablets dose overlies the curve for placebo patients until 90 days; the trajectories beyond this time seem to stabilise, suggesting a similar efficacy for the two cladribine doses against placebo. Demographic data, MRI disease activity, characteristics of the first clinical demyelinating attack and EDSS at baseline did not show imbalances between the groups treated with cladribine tablets. Previous clinical studies with cladribine tablets have not shown dose dependency for clinical endpoints.[12–15] It is therefore surprising that, in this post hoc analysis, the group of patients receiving cladribine tablets 5.25 mg/kg appears to have a higher risk of next attack or three-month confirmed EDSS worsening than those treated with 3.5 mg/kg. However, an analysis of the effect of the two cladribine doses on lymphocyte subsets showed that while there is no dose effect on B lymphocytes, there is a greater effect on T lymphocytes seen with the 5.25 mg/kg

Table 2. Key MRI endpoints (by newer criteria subgroups).

Characteristic	Statistic	Placebo ($N=206$)	Cladribine tablets 3.5 mg/kg ($N=206$)	Cladribine tablets 5.25 mg/kg ($N=204$)
Satisfied newer MS criteria (yes)				
Mean number of new or persisting T1 Gd+ lesions per patient per scan	Mean ± SD	1.77 ± 2.19	0.71 ± 1.55	1.45 ± 8.34
Cumulative number of new or persisting T1 Gd+ lesions	Mean ± SD	8.13 ± 8.60	3.45 ± 9.19	2.11 ± 8.49
	Treatment group comparison[a], cladribine/placebo Ratio (SE)		0.21 (0.07)	0.20 (0.07)
	Lesion reduction relative to placebo (%)[d]		79.35 ($p < 0.0001$)	80.05 ($p < 0.0001$)
Satisfied newer MS criteria (no)				
Mean number of new or persisting T1 Gd+ lesions per patient per scan	Mean ± SD	0.56 ± 1.00	0.08 ± 0.30	0.04 ± 0.24
Cumulative number of new or persisting T1 Gd+ lesions	Mean ± SD	2.48 ± 4.59	0.31 ± 0.83	0.26 ± 1.83
	Treatment group comparison[a], cladribine/placebo Ratio (SE)		0.10 (0.03)	0.07 (0.02)
	Lesion reduction relative to placebo (%)[d]		89.99 ($p < 0.0001$)	92.63 ($p < 0.0001$)
Satisfied newer MS criteria (yes)				
Mean number of new or enlarging T2 lesions per patient per scan	Mean ± SD	1.77 ± 2.57	0.88 ± 1.79	1.24 ± 2.82
Cumulative number of new or enlarging T2 lesions	Mean ± SD	7.25 ± 7.94	5.03 ± 10.51	3.46 ± 5.48
	Treatment group comparison[b], cladribine/placebo Ratio (SE)		0.30 (0.08)	0.45 (0.11)
	Lesion reduction relative to placebo (%)[d]		69.90 ($p < 0.0001$)	55.22 ($p = 0.0015$)
Satisfied newer MS criteria (no)				
Mean number of new or enlarging T2 lesions per patient per scan	Mean ± SD	0.87 ± 1.29	0.16 ± 0.37	0.20 ± 0.50
Cumulative number of new or enlarging T2 lesions	Mean ± SD	3.95 ± 5.80	0.79 ± 1.40	0.93 ± 2.82

(continued)

Table 2. Continued

Characteristic	Statistic	Placebo ($N = 206$)	Cladribine tablets 3.5 mg/kg ($N = 206$)	Cladribine tablets 5.25 mg/kg ($N = 204$)
	Treatment group comparison[b], cladribine/placebo Ratio (SE)		0.19 (0.04)	0.21 (0.05)
	Lesion reduction relative to placebo (%)[d]		80.94 ($p < 0.0001$)	78.98 ($p = 0.0001$)
Satisfied newer MS criteria (yes)				
Mean number of combined unique active lesions per patient per scan	Mean ± SD	3.46 ± 3.68	1.47 ± 2.86	2.60 ± 8.91
Cumulative number of com bined unique active lesions	Mean ± SD	15.00 ± 14.96	7.79 ± 18.25	5.44 ± 10.49
	Treatment group comparison[c], cladribine/placebo Ratio (SE)		0.24 (0.06)	0.33 (0.08)
	Lesion reduction relative to placebo (%)[d]		76.37 ($p < 0.0001$)	67.42 ($p < 0.0001$)
Satisfied newer MS criteria (no)				
Mean number of combined unique active lesions per patient per scan	Mean ± SD	1.42 ± 2.02	0.24 ± 0.58	0.25 ± 0.71
Cumulative number of com bined unique active lesions	Mean ± SD	6.40 ± 9.31	1.09 ± 1.90	1.20 ± 4.35
	Treatment group comparison[c], cladribine/placebo Ratio (SE)		0.16 (0.03)	0.17 (0.04)
	Lesion reduction relative to placebo (%)[d]		84.41 ($p < 0.0001$)	83.54 ($p < 0.0001$)

CUA: combined unique active; Gd+: gadolinium enhancing; MRI: magnetic resonance imaging; MS: multiple sclerosis; SD: standard deviation; SE: standard error.
[a]From the analysis of the cumulative number of new or persisting T1 Gd+ lesions using a negative binomial model with treatment, region and baseline T1 Gd+ lesion count as covariates and the log of the number of scans as an offset variable.
[b]From the analysis of the cumulative number of new or enlarging T2 lesions using a negative binomial model with treatment, region and baseline T2 lesion count as covariates and the log of the number of scans as an offset variable.
[c]From the analysis of the cumulative number of CUA lesions using a negative binomial model with treatment, region and baseline T1 Gd+ lesion count as covariates and the log of the number of scans as an offset variable.
[d]Cumulative reduction on the number of lesions relative to placebo: (1 − ratio) × 100.

than with the 3.5 mg/kg dose.[16] Potentially, alterations of the relative B to T cell counts, or the proportions of lymphocyte subsets, may be important for dose-related effects, but this hypothesis requires further study. Nevertheless, based on the benefit:risk ratio seen with the lower dose, on 23 June 2017, the European Medicines Agency's Committee for Medicinal Products for Human Use recommended granting marketing approval for the use of cladribine tablets at the dose of 3.5 mg/kg as a treatment for relapsing forms of MS with approval granted by the European Commission on 25 August 2017.[17]

Treatment for MS can employ different strategies to optimise therapy. One involves initiating treatment with better-tolerated drugs which would be expected to be moderately effective in controlling the disease, and reserving more potent drugs with more complex safety profiles for use in case of on-going disease activity. The alternative strategy involves treatment with the most potent drugs early in the disease course with the aim of controlling disease activity, despite a potentially higher risk of side effects.[18] There has been a reluctance to use highly efficacious disease-modifying drugs in patients with early MS due to the perception of a sub-optimal risk-benefit ratio with currently available agents.[18] Moreover, there are few data to indicate that using highly efficacious therapies early in the MS disease course yields superior outcomes with an acceptable adverse event profile compared to the conservative tiered therapeutic escalation approach.

As shown in this study, patients with a first clinical demyelinating attack who satisfy the newer MS diagnostic criteria have a very high risk of earlier clinical or MRI disease activity. In this population the cladribine tablets 3.5mg/kg dose is very effective, reducing the risk of next attack or three-month confirmed EDSS worsening by 74%. There is also an increasing amount of evidence in favour of early treatment of patients with a first clinical demyelinating attack or early MS, with the goal of reducing the level of relapse activity.[7,18,19] A meta-analysis of 19 published randomised controlled clinical trials in relapsing–remitting MS (RRMS) reported a correlation between the effects of treatment on relapses and the effect of treatment on EDSS worsening.[20] Clinical and MRI parameters have been used in scoring systems to predict response to some treatments and help guide management decisions, and recently on-going MRI disease activity in combination with relapses during the first year of treatment was associated with significant short-term risk of treatment failure and EDSS worsening.[21,22]

Conclusions

Compared with placebo, cladribine tablets 3.5 mg/kg significantly reduced the risk of next attack or three-month confirmed EDSS worsening in patients with early relapsing MS according to newer MS diagnostic criteria. Moreover, this exploratory analysis shows that treatment with two short courses of cladribine tablets 3.5 mg/kg significantly delayed conversion to CDMS in patients not meeting newer MS diagnostic criteria (i.e. those still classified as CIS).

Acknowledgements

The authors would like to thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centres and at Merck KGaA, Darmstadt, Germany. Medical writing assistance was provided by Jackie Campbell of inScience Communications, Springer Healthcare, Chester, UK, and was funded by Merck KGaA, Darmstadt, Germany.

Conflicts of interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Mark S. Freedman has received honoraria or consultation fees from Actelion, Bayer HealthCare, Biogen Idec, Chugai, EMD Canada, Genzyme, Hoffman La Roche, Novartis, Sanofi, and Teva.

Thomas Leist has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Novartis, ONO, Pfizer, and Teva Neuroscience.

Giancarlo Comi has received consulting fees from Novartis, Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck, Receptors, Biogen Idec, Genentech-Roche, and Bayer Schering; lecture fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck, Biogen Dompè, Bayer Schering, and Serono Symposia International Foundation; and trial grant support from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Receptors, Biogen Idec, Genentech-Roche, Merck, Biogen Dompè, and Bayer Schering.

Bruce A. C. Cree has served as an advisor or consultant for: AbbVie Inc, Biogen, EMD Serono Inc, Genzyme Corporation, MedImmune, Novartis Pharmaceuticals Corporation, Shire, and Teva Neuroscience Inc.

Patricia K. Coyle is advisor or consultant for Accordant, Acorda Therapeutics, Bayer HealthCare,

Biogen, Celgene, EMD Serono, Genentech/Roche, Genzyme/Sanofi, Novartis, and Teva Pharmaceuticals USA. She has received grants for clinical research from Actelion, Alkermes, Genentech/Roche, MedDay, the National Institute of Neurological Disorders and Stroke (NINDS), and Novartis.

Hans-Peter Hartung has received honoraria for consulting, membership of steering committees and advisory boards, and speaking at symposia – with approval of the Rector of Heinrich-Heine-University – from Bayer Healthcare, Biogen Idec, Genzyme, MedImmune, Merck, Novartis Pharma AG, Teva, Sanofi-Aventis, Receptos, and Roche.

Patrick Vermersch has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Bayer, Novartis, Merck, GSK, Roche, and Almirall; and research support from Biogen, Sanofi-Genzyme, Bayer, and Merck.

Doris Damian and Fernando Dangond are employees of EMD Serono Inc, Billerica, MA, USA, a business of Merck KGaA, Darmstadt, Germany.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA – Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW).

References

1. Comi G, Hartung HP, Kurukulasuriya NC, et al. Cladribine tablets for the treatment of relapsing–remitting multiple sclerosis. *Expert Opin Pharmacother* 2013; 14: 123–136.
2. Hartung HP, Aktas O, Kieseier B, et al. Development of oral cladribine for the treatment of multiple sclerosis. *J Neurol* 2010; 257: 163–170.
3. Leist TP, Comi G, Cree BA, et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): A phase 3 randomised trial. *Lancet Neurol* 2014; 13: 257–267.
4. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. *Ann Neurol* 1983; 13: 227–231.
5. Morrissey SP, Miller DH, Kendall BE, et al. The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis. A 5-year follow-up study. *Brain* 1993; 116(Pt 1): 135–146.
6. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the ''McDonald Criteria''. *Ann Neurol* 2005; 58: 840–846.
7. Freedman MS, Selchen D, Arnold DL, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. *Can J Neurol Sci* 2013; 40: 307–323.
8. Ziemssen T, De Stefano N, Pia Sormani M, et al. Optimizing therapy early in multiple sclerosis: An evidence-based view. *Mult Scler Relat Disord* 2015; 4: 460–469.
9. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292–302.
10. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol* 2016; 15: 292–303.
11. Rovira À, Wattjes MP, Tintoré M, et al. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis – clinical implementation in the diagnostic process. *Nat Rev Neurol* 2015; 11: 471–482.
12. Comi G, Cook SD, Giovannoni G, et al. MRI outcomes with cladribine tablets for multiple sclerosis in the CLARITY study. *J Neurol* 2013; 260: 1136–1146.
13. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *New Engl J Med* 2010; 362: 416–426.
14. Giovannoni G, Cook S, Rammohan K, et al. Sustained disease-activity-free status in patients with relapsing–remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: A post-hoc and subgroup analysis. *Lancet Neurol* 2011; 10: 329–337.
15. Rammohan K, Giovannoni G, Comi G, et al. Cladribine tablets for relapsing–remitting multiple sclerosis: Efficacy across patient subgroups from the phase III CLARITY study. *Mult Scler Relat Disords* 2012; 1: 49–54.
16. Baker D, Herrod SS, Alvarez-Gonzalez C, et al.et al. Both cladribine and alemtuzumab may effect MS via B-cell depletion. *Neurol Neuroimmunol Neuroinflamm* 2017; 4: e360.
17. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) opinion summary, 23 June 2017, http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004230/WC500229786.pdf (accessed 23 June 2017).
18. Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: Revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol* 2015; 15: 273–279.

19. Freedman MS. Efficacy and safety of subcutaneous interferon-beta-1a in patients with a first demyelinating event and early multiple sclerosis. *Expert Opin Biol Ther* 2014; 14: 1207–1214.
20. Sormani MP, Bonzano L, Roccatagliata L, et al. Surrogate endpoints for EDSS worsening in multiple sclerosis. A meta-analytic approach. *Neurology* 2010; 75: 302–309.
21. Sormani MP, Rio J, Tintoré M, et al. Scoring treatment response in patients with relapsing multiple sclerosis. *Mult Scler* 2013; 19: 605–612.
22. Sormani MP, Gasperini C, Romeo M, et al. Assessing response to interferon-beta in a multicenter dataset of patients with MS. *Neurology* 2016; 87: 134–140.