MSJ Experimental Translational Clinical

Original Research Paper

Early MRI outcomes in participants with a first clinical demyelinating event at risk of multiple sclerosis in the ORACLE-MS study

Multiple Sclerosis Journal—Experimental, Translational and Clinical

January–March 2021, 1–11

DOI: 10.1177/2055217321990852

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Abstract

Background: In the Phase 3, 96-week ORACLE-MS study, cladribine tablets 10 mg (3.5 or 5.25 mg/kg cumulative dosage over two years) significantly reduced lesions associated with multiple sclerosis versus placebo in participants following a first clinical demyelinating event (FCDE).

Objective: To determine the timing of effects of cladribine tablets on lesion activity assessed by magnetic resonance imaging (MRI).

Methods: This *post hoc* analysis assessed the effect of cladribine tablets versus placebo in ORACLE-MS on secondary MRI endpoints including T1 gadolinium-enhancing (Gd+), new or enlarging T2 lesions, and combined unique active lesions assessed on MRI scans performed at screening and every 3 months thereafter.

Results: Compared to placebo, cladribine tablets 3.5 mg/kg treatment appeared to lead to a trend of reductions in the mean number of T1 Gd+ lesions by Week 13 (first post-baseline scan: 0.37 vs. 1.00), new or enlarging T2 (0.20 vs. 1.01) and combined unique active (0.29 vs. 1.91) lesions by Week 24. Low lesion counts were maintained with cladribine tablets throughout 96 weeks. Similar results were observed with the 5.25 mg/kg dosage.

Conclusion: In participants with an FCDE, cladribine tablets appeared to reduce lesion numbers within 13 weeks (time of first evaluation).

Keywords: First clinical demyelinating event, multiple sclerosis, magnetic resonance imaging, cladribine tablets, ORACLE-MS, lesions

Date received: 28 September 2020; accepted: 9 January 2021

Introduction

Effective treatment early in the disease course of multiple sclerosis (MS) has been shown to improve patient outcomes.[1,2] This is supported by data from several studies which suggest improvements in clinical and magnetic resonance imaging (MRI) measures are associated with initiating disease-modifying therapy (DMT) as early as the first clinical demyelinating event (FCDE) marking a patient at high risk for MS.[3–8]

Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are approved for the treatment of relapsing or active forms of MS. In the pivotal 96-week, Phase 3 CLARITY study treatment with cladribine tablets (3.5 or 5.25 mg/kg dose) significantly reduced the annualized relapse rate (ARR) in participants with relapsing-remitting MS (RRMS) versus placebo: 0.14 and 0.15 vs. 0.33 (both $P < 0.001$), respectively.[9] The effect of cladribine tablets was also investigated in participants with an FCDE in the Phase 3, 96-week, ORACLE-MS trial.[7] In the primary analysis of data from the double-blind initial treatment period (ITP), cladribine tablets (3.5 mg/kg or 5.25 mg/kg) significantly

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reduced the risk of conversion to clinically definitive MS (CDMS) per the Poser criteria (primary endpoint; 67% and 62% risk reduction, respectively) and MS per the 2005 McDonald criteria (secondary endpoint; 50% and 57% reduction, respectively) versus placebo (all $P < 0.0001$).[7]

In CLARITY, MRI benefits were observed at the first post-baseline MRI assessment (Week 24).[10] Clinical benefits, including reduction in number of relapses and higher proportion of participants with no relapse, were apparent by Week 12 after cladribine tablets treatment.[9,10] Early and more frequent MRI assessments would allow exploration of correlation between lesion activity and early clinical effects.[10,11] In ORACLE-MS, MRI scans were performed earlier, at ~3 months after commencement and every ~3 months thereafter. ORACLE-MS therefore provided an opportunity to evaluate temporal changes in MRI activity and onset of treatment effects on brain lesions. In the primary analysis of the ORACLE-MS MRI data during the ITP, treatment with cladribine tablets 3.5 mg/kg versus placebo reduced the median cumulative lesion count by 89.3% for T1 gadolinium-enhancing (Gd+) lesions, 78.8% for new/enlarging T2 lesions, and 84.3% for combined unique active (CUA) lesions (all $P < 0.0001$).[7] Similar results were found with cladribine tablets 5.25 mg/kg. Here we report an analysis of temporal changes in the number and volume of MRI lesions during the ORACLE-MS study and the timing of the effect of cladribine tablets on lesion activity in participants following an FCDE.

Methods

ORACLE-MS study design details have previously been published.[7] Participants with an FCDE were randomized 1:1:1 to cladribine tablets 3.5 or 5.25 mg/kg, or placebo (Figure 1, includes dosing strategy). The double-blind ITP was ≤96 weeks, with a planned follow-up of an additional 96 weeks (open-label maintenance period (OLMP)). The primary and key secondary efficacy endpoints of ORACLE-MS were time to conversion to CDMS per the Poser criteria and MS per the 2005 McDonald criteria.[7] Participants who converted to CDMS transitioned to OLMP and were treated with interferon beta-1a (IFN β-1a). MRI scans were performed at screening, Week 13 (first post-baseline scan), followed by Week 24 and every 12 weeks thereafter during the double-blind ITP, until CDMS conversion. An independent ethics committee approved ORACLE-MS and all participants provided written informed consent.

MRI endpoints and analysis

Key secondary MRI endpoints included cumulative numbers of T1 Gd+, new/enlarging T2, and CUA lesions over the ITP (up to the last available scan). Cumulative CUA was defined as the sum of the new T1 Gd+ lesions and the new/enlarging T2 lesions (without double-counting). Additional secondary MRI endpoints included change from baseline in volume of T1 Gd+ and T2 lesions over time.

MRI analyses were performed using data collected until the final database lock (June 8, 2012). The primary analysis presented in the original ORACLE-MS publication used an earlier cut-off date (Figure 1) and as such, some of the results presented in this re-analysis of the intent-to-treat (ITT) population data may differ from those previously presented.[7]

MRI-based endpoints were analyzed using analysis of covariance (ANCOVA) and negative binomial models, and adjusted for geographic region and baseline lesion number or volume. Cumulative lesion numbers for each participant were analyzed through negative binomial models using number of MRI scans as an offset variable (to adjust for variation in the numbers of MRI scans participants underwent). Mean numbers of lesions (per participant per scan) were analyzed through ANCOVA models on the rank-transformed data. For temporal analyses, the number and volume of T1 Gd+ and new/enlarging T2 lesions were evaluated based on descriptive statistics for each MRI assessment time point in participants remaining in the ITP. Formal statistical testing to compare the treated and placebo arms at each time point was not considered appropriate, since without adjusting for multiplicity the numerous tests can give rise to spurious results, and with multiplicity adjustment the tests may lack the power to detect true differences. Imaging data from participants who switched to IFN β-1a in the OLMP after CDMS conversion were excluded from subsequent analysis time points. Due to the administration schedule in the study (split across two 48-week periods), MRI results for time points in Year 1 (baseline; Weeks 13, 24, 36, and 48) reflect the effect of two treatment weeks of cladribine tablets totaling 1.75 mg/kg for participants randomized to the 3.5 mg/kg dosage, and four treatment weeks of 3.5 mg/kg cumulative for participants randomized to the 5.25 mg/kg dosage. Imaging in Year 2 was obtained after completion of treatment periods at the beginning of Years 1 and 2 in both dosage groups (Figure 1). Changes in lesion volume from

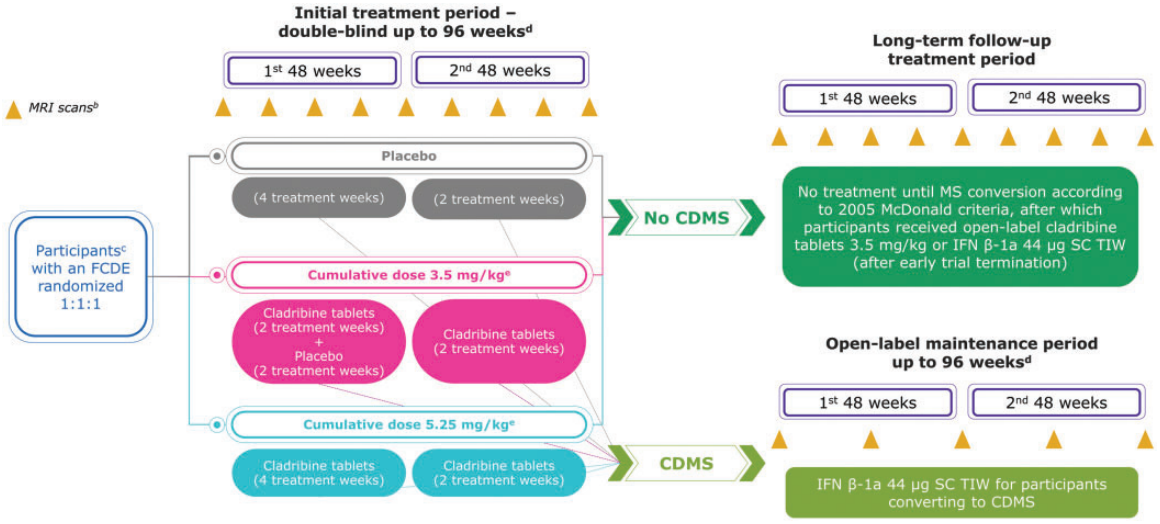

Figure 1. ORACLE-MS study design.[a]
[a]The primary analysis was initially planned for when ≥120 CDMS conversion events were reached; however, this was later amended to a specified cut-off date in August 2011 due to a suspension of the development of cladribine tablets following a negative opinion from regulatory authorities. However, since all participant information and 122 conversion events had been documented by the cut-off date, trial termination did not affect the primary analysis. In October 2011, the sponsor issued an early termination notice of ORACLE-MS.
[b]MRI scans were assessed at screening, Week 13 (first post-baseline scan), Week 24, and every 12 weeks thereafter during the initial treatment period and long-term follow-up period. Scans were performed every 24 weeks during the open-label maintenance period.
[c]Participants aged 18–55 years with EDSS score ≤5.0, ≥2 clinically silent lesions measuring ≥3 mm on T2-weighted scan, and a FCDE ≤75 days before screening.
[d]Time in the initial treatment and open-label maintenance periods was variable and depends on the time to CDMS conversion for each participant.
[e]Cladribine tablets were administered orally in 4 or 6 treatment weeks, adjusted for participants' weight to 0.875 mg/kg per week, and a total cumulative doses of 3.5 or 5.25 mg/kg over two years. The 3.5 mg/kg dosage was administered for 4–5 consecutive days in Weeks 1 and 5 during Year 1, followed by Weeks 48 and 52 (two treatment weeks in Year 2). The 5.25 mg/kg dosage was administered similarly, with an additional two weeks in Year 1 Weeks 9 and 13. To maintain blinding, placebo treatment was applied to the 3.5 mg/kg treated group during Weeks 9 and 13 of Year 1.
CDMS: clinically definite MS based on a second clinical events or EDSS progression; EDSS: Expanded Disability Status Score; FCDE: first clinical demyelinating event; IFN: interferon; MRI: magnetic resonance imaging; MS: multiple sclerosis; SC: subcutaneous; TIW: three times a week.

baseline to Week 96 were analyzed through ANCOVA models on the rank-transformed data in which the treatment effects of cladribine tablets 3.5 and 5.25 mg/kg were tested against placebo.

As these re-analyses used a later data cut-off than the primary analyses, *P*-values below 0.05 are considered nominally significant.

Results

Participants

Participant demographics, and disease and MRI characteristics at baseline, were well balanced across treatment groups (Table 1). Mean duration of follow-up in the double-blind ITP (final database lock) was 78.8, 75.4, and 66.1 weeks in the cladribine tablets 3.5 mg/kg, 5.25 mg/kg, and placebo groups, respectively. Results discussed here focus on the approved 3.5 mg/kg dose.

Mean cumulative number of MRI lesions

Compared with placebo, cladribine tablets 3.5 mg/kg treatment reduced the mean cumulative number of T1 Gd+ lesions (1.35 vs. 4.41, $P < 0.0001$; Figure 2(a)) and new/enlarging T2 lesions (2.19 vs. 5.08, $P < 0.0001$; Figure 2(b)) during the ITP, representing an 85.3% and 78.4% relative reduction, respectively. The mean cumulative number of CUA lesions was reduced by cladribine tablets 3.5 mg/kg versus placebo (3.31 vs. 9.34, $P < 0.0001$; Supplementary Figure S1), representing an 82.2% relative reduction. Similar outcomes were observed with

Table 1. Baseline demographics, and clinical and MRI characteristics in the ORACLE-MS study population.

	Placebo ($N = 206$)	Cladribine tablets 3.5 mg/kg ($N = 206$)	Cladribine tablets 5.25 mg/kg ($N = 204$)
Age in years, mean (SD)	32.2 (8.2)	31.7 (9.2)	31.9 (8.8)
Female, *n* (%)	138 (67)	130 (63)	132 (65)
Time from FCDE to randomization, days, mean (SD)	79.4 (17.9)	78.7 (16.0)	79.4 (17.6)
Classification[a] of FCDE, *n* (%)			
Monofocal	104 (50)	105 (51)	103 (50)
Multifocal	102 (50)	101 (49)	101 (50)
EDSS score, median (IQR[b])	1.5 (1–2)	1.5 (1–2)	1.5 (1–2)
Presence of T1 Gd+ lesions, *n* (%)			
Yes	73 (35)	74 (36)	90 (44)
No	133 (65)	132 (64)	114 (56)
Number of T1 Gd+ lesions, median (IQR)	0.00 (0–1.00)	0.00 (0–1.00)	0.00 (0–1.50)
Volume of T1 Gd+ lesions, mm^3, median (IQR)	0.0 (0.0–68.7)	0.0 (0.0–62.9)	0.0 (0.0–104.5)
Number of T2 lesions, *n* (%)			
<9	50 (24)	56 (27)	46 (23)
≥ 9	156 (76)	150 (73)	158 (77)
Volume of T2 lesions, mm^3, median (IQR)	1793.9 (721.0 –3790.8)	1692.4 (855.5 –4028.3)	1820.5 (819.7 –4772.7)

[a]Classified by investigator.
[b]IQR is a statistical dispersion between 75th and 25th percentiles or upper and lower quartiles (Q3, Q1).
FCDE: first clinical demyelinating event; EDSS: Expanded Disability Status Scale; Gd+: gadolinium-enhancing; MRI: magnetic resonance imaging; IQR: interquartile range; SD: standard deviation.

cladribine tablets 5.25 mg/kg (Figure 2 and Supplementary Figure S1).

Mean number of MRI lesions over time

Compared with placebo, treatment with cladribine tablets 3.5 mg/kg appeared to reduce the mean number of T1 Gd+ lesions (95% Confidence interval (CI)) by the earliest MRI assessment time point at Week 13 in the ITP (0.37 (0.15–0.59) vs. 1.00 (0.72–1.28)). Further reduction in T1 Gd+ lesions was observed at Week 24 (0.13 (0.06–0.20) vs. 0.92 (0.66–1.18)) which was maintained up to Week 48 in Year 1 (0.27 (0.13–0.41) vs. 0.87 (0.57–1.17); Figure 3(a)). At Week 60, the first MRI assessment time point after the second year treatment period, the mean number of T1 Gd+ lesions (95% CI) was 0.22 (0.07–0.37) with cladribine tablets 3.5 mg/kg versus 0.74 (0.46–1.02) with placebo; this trend was maintained throughout the second 48-week period. The decline in mean number of new/enlarging T2 lesions (95% CI) was seen from Week 13 to 24 following the first year treatment; new/enlarging T2 lesions decreased from 1.25 (0.77–1.73) to 0.20 (0.10–0.30) in the cladribine tablets 3.5 mg/kg group versus a change from 1.43 (1.07–1.79) to 1.01 (0.75–1.27) in the placebo group. Lesion numbers remained stable up to Week 48 (0.32 (–0.06 to 0.70) vs. 1.04 (0.79–1.29)) prior to the second year treatment of cladribine tablets (Figure 3(b)). After completing treatment at the beginning of Year 2, the mean number of new/enlarging T2 lesions (95% CI) at Week 60 remained lower in the cladribine tablets 3.5 mg/kg cohort versus placebo (0.25 (0.07–0.43) vs. 0.71 (0.44–0.98)). This effect was maintained for the duration of the study. Over the 96-week study, there was a gradual decline in the number of new/enlarging T2 lesions in the placebo group; but lesion burden remained higher than that observed in the cladribine tablets-treated cohort for each assessment. Similar trends were observed for the mean (95% CI) number of CUA lesions, with the initial decline occurring at Week 13, followed by further reduction by Week 24 in the cladribine tablets 3.5 mg/kg group (1.56 (0.98–2.14) to 0.29 (0.16–0.42)) versus placebo (2.41 (1.86–2.96) to 1.91 (1.46–2.36); Supplementary Figure S2).

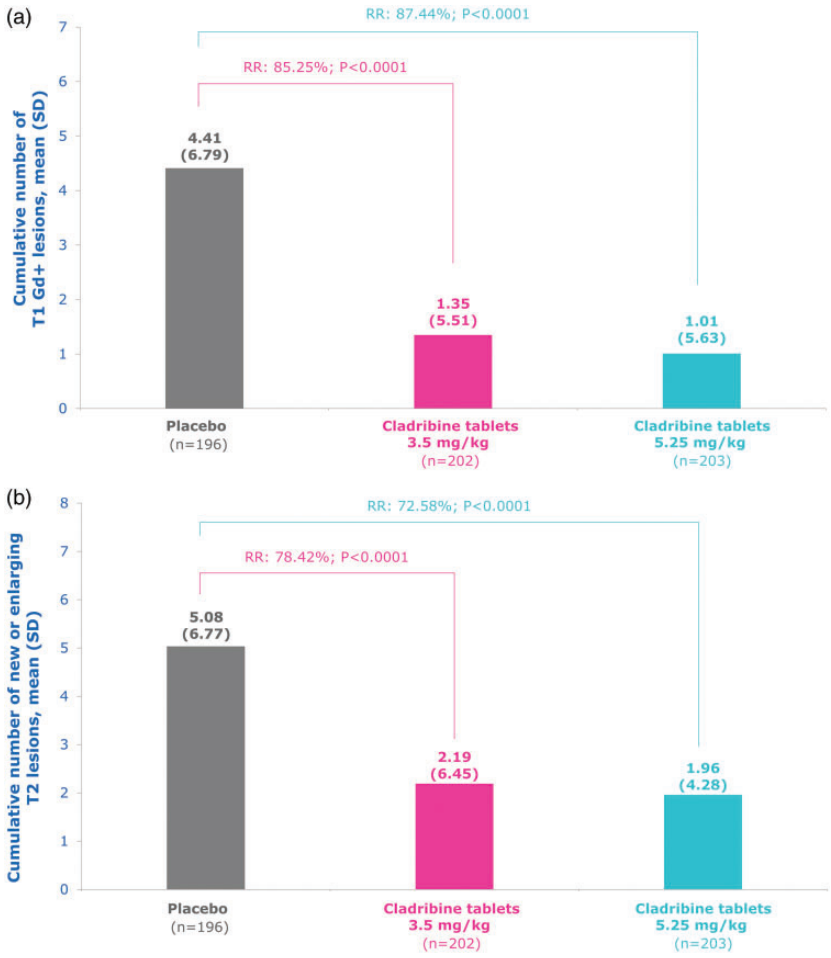

Figure 2. Mean cumulative number of MRI lesions over 96 weeks in the ITT population with cladribine tablets 3.5 mg/kg and 5.25 mg/kg compared with placebo: (a) T1 Gd+ lesions; (b) new or enlarging T2 lesions.
RR: Cumulative reduction on the number of lesions relative to placebo: (1 – ratio) × 100.
Gd+: gadolinium-enhancing; ITT: intent to treat; MRI: magnetic resonance imaging; RR: relative reduction; SD: standard deviation.

Cladribine tablets 5.25 mg/kg appeared to confer similar effects to the 3.5 mg/kg dosage. Mean lesion numbers shown at each time point in Figures 3 and Supplementary Figure S2 are for participants who had not converted to CDMS (Poser criteria) at that time point,[12] and remained in the ITP of the trial. Mean lesion numbers prior to treatment with IFN β-1a for participants who converted to CDMS and moved into the OLMP are shown in Supplementary Table S1.

Change in MRI lesion volume over time

Compared with placebo, cladribine tablets 3.5 mg/kg treatment appeared to result in a decrease from baseline in mean T1 Gd+ lesion volume (95% CI) at Week 13 (earliest MRI assessment in Year 1; –152.37 (–238.59 to –66.15) vs. 32.26 (–51.42 to 115.94) mm^3) and lasted up to Week 48 (end of Year 1; –143.71 (–239.25 to –48.17) vs. –5.89 (–60.90 to 49.12) mm^3). After completing treatment in the second year (cladribine tablets 3.5 mg/kg vs. placebo), the reduction in lesion volume continued from Week 60 (earliest MRI assessment in Year 2; –178.01 (–288.40 to –67.62) vs. –19.87 (–78.57 to 38.83) mm^3) to Week 96 (end of ITP; –126.64 (–215.52 to –37.76) vs. 48.63 (–18.60 to 115.86) mm^3; Figure 4). Similar reductions in the volume of T2 lesions at Week 48 and 96 were seen for cladribine tablets 3.5 mg/kg group versus placebo (Figure 5).

Discussion

Rapid disease control is crucial in early stages of MS, as inflammation-driven disease pathology develops more rapidly during this period.[13,14]

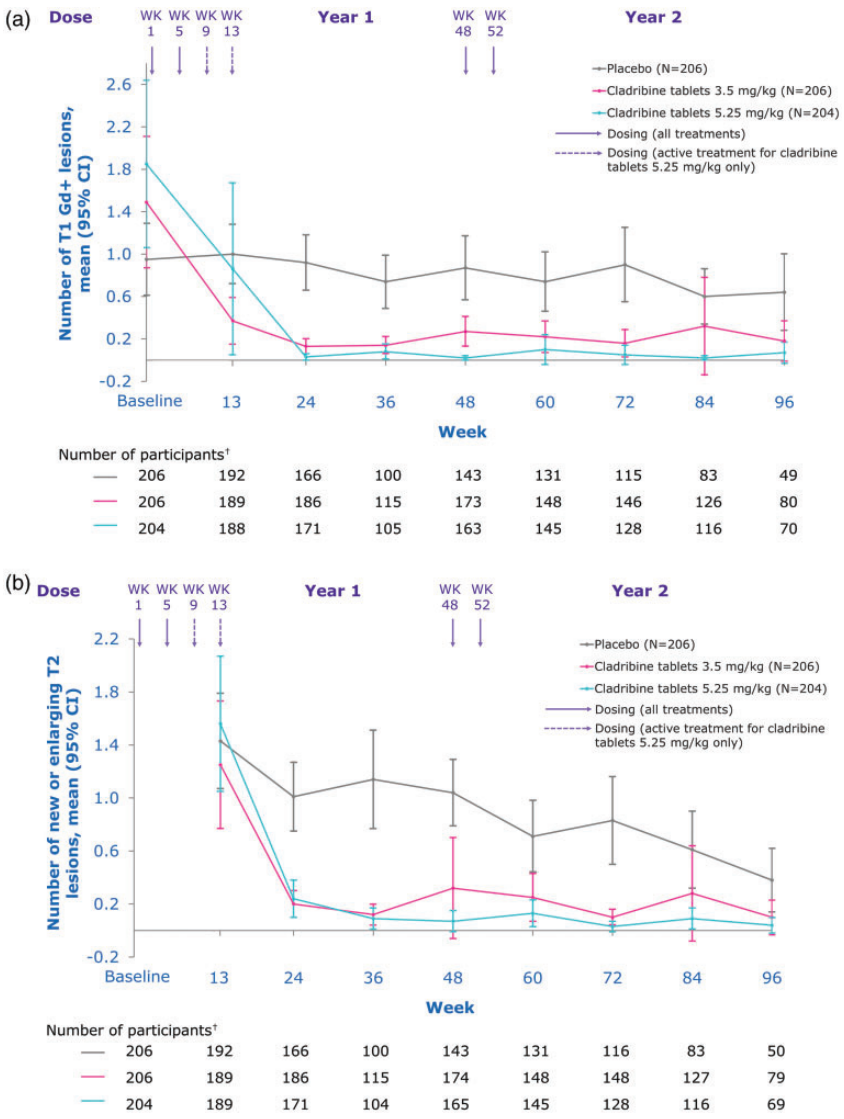

Figure 3. Mean number of lesions over 96 weeks with cladribine tablets 3.5 mg/kg and 5.25 mg/kg compared with placebo in the ITT population: (a) T1 Gd+ lesions; (b) new or enlarging T2 lesions*.
*New or enlarging T2 lesions were measured relative to T2 lesions present on the baseline scan, after treatment at the second MRI scan (Week 13).
†Participants continuing double-blind treatment; excludes participants who converted to CDMS and switched to open-label maintenance treatment.
Note: Solid and dotted purple arrows represent treatment week.
CDMS: clinically definite multiple sclerosis; CI: confidence interval; Gd+: gadolinium-enhancing; ITT: intent to treat; WK: week.

The number and size of early MRI lesions have been associated with worsening of MS.[6,15–18] The combination of improved accuracy in MS diagnosis with MRI and benefits associated with early disease control have provided rationale for early DMT treatment of MS, an approach that has been linked with improved clinical outcomes.[2–6,15,19] The current analysis of MRI outcomes from the ORACLE-MS study of participants with an FCDE who did not convert to CDMS (MRI data after CDMS conversion were excluded from this analysis) confirmed that treatment with cladribine tablets (3.5 and 5.25 mg/kg) reduced the cumulative number of MRI lesions and decreased the volume of T1 Gd+ and T2 lesions over 96 weeks versus placebo. Importantly, these improvements in lesion number and volume appeared to have occurred early (by Week 13 for T1 Gd+ lesions and Week 24 for new/enlarging

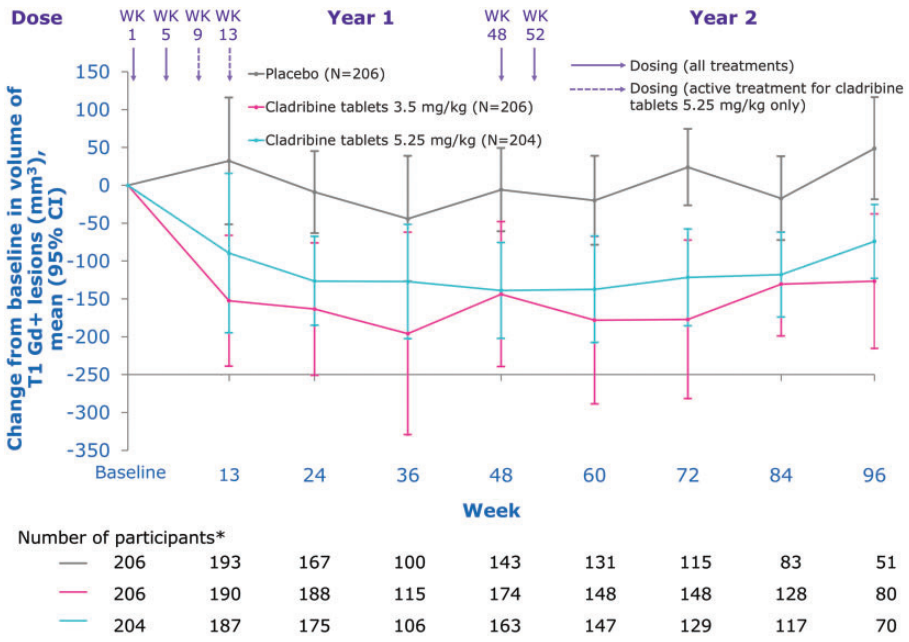

Figure 4. Mean change from baseline volume of T1 Gd+ lesions by visit over 96 weeks of treatment with cladribine tablets 3.5 mg/kg, 5.25 mg/kg, and placebo in the ITT population.
Baseline volume, mean (SD): 103.87 (295.12) mm^3 (placebo group); 167.45 (591.24) mm^3 (cladribine tablets 3.5 mg/kg group); 170.67 (559.96) mm^3 (cladribine tablets 5.25 mg/kg group).
*Participants continuing double-blind treatment; excludes patients who converted to CDMS and switched to open-label maintenance treatment.
Note: Solid and dotted purple arrows represent treatment weeks.
CDMS: clinically definite multiple sclerosis; CI: confidence interval; Gd+: gadolinium-enhancing; ITT: intent to treat; SD: standard deviation; WK: week.

T2 lesions) and persisted throughout the study period. There was no evidence of increasing MRI lesion numbers during the treatment-free period between dosage periods in Years 1 and 2, nor following redosing in Year 2 (at Weeks 48 and 52). Early MRI lesion effects have been seen before in studies of other DMTs in FCDE where the first post-baseline MRI scan occurred at Month 3 with subsequent scans collected every 3 months thereafter, similar to the ORACLE-MS study.[8,20] These studies showed noticeable reduction in CUA lesion number following IFN β-1a treatment and reduction in the risk of occurrence of new T1 Gd+ or T2 lesions following teriflunomide treatment at the three-month post-baseline MRI scan. These reductions were maintained for the duration of the studies. Results obtained in different studies should be compared cautiously because of the differences in MRI protocols and analysis and differences in the underlying populations.

The observed trends for declining lesions over time in the placebo group, particularly in the number and volume of new/enlarging T2 lesions and number of CUA lesions, likely reflect an enrichment of participants with lower disease activity. This enrichment occurred because participants who had converted to CDMS and thus transitioned to OLMP were excluded from the temporal analysis of MRI outcomes. A separate analysis of ORACLE-MS found that the highest rates of CDMS conversion in the placebo group occurred in participants with greater MRI activity;[21] mean lesion numbers were therefore impacted by exclusion of these participants. Exclusion of participants who converted to CDMS had less impact on mean lesion numbers in the active treatment groups, as fewer participants receiving cladribine tablets (either dosage) converted to CDMS (Supplementary Table S1); therefore, relative treatment effect at later time points (and overall) may be underestimated.

MRI findings in ORACLE-MS participants with an FCDE were consistent with those for CLARITY participants with RRMS treated with cladribine tablets, in which MRI-measured disease activity was significantly reduced with both doses of cladribine tablets versus placebo. Lesion reductions were evident at

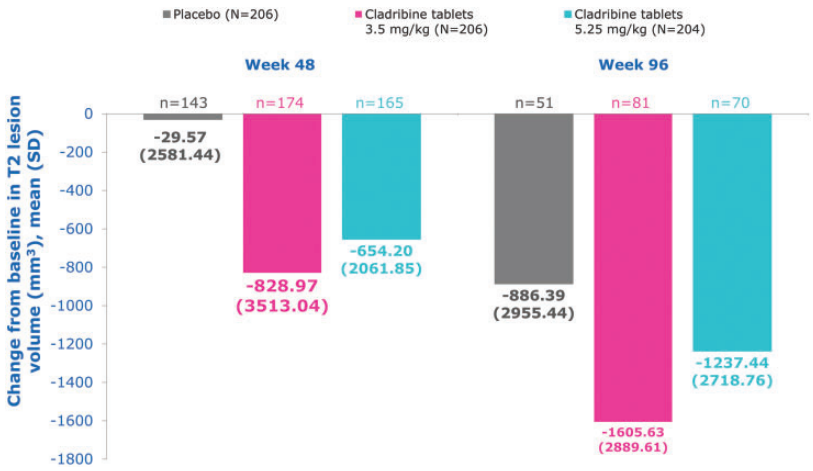

Figure 5. Mean change from baseline volume of T2 lesions at Weeks 48 and 96 during the initial treatment period with cladribine tablets 3.5 mg/kg, 5.25 mg/kg, and placebo.
Baseline volume, mean (SD): 3436.69 (4613.43) mm^3 (placebo group); 3435.22 (5184.12) mm^3 (cladribine tablets 3.5 mg/kg group); 3825.73 (5093.52) mm^3 (cladribine tablets 5.25 mg/kg group).
Note: '*n*' is the number of participants at each visit, excluding participants who converted to CDMS and switched to open-label maintenance treatment.
CDMS: clinically definite multiple sclerosis; SD: standard deviation.

the earliest MRI assessment (Week 24) during CLARITY following exposure when patients had at that time only received half the recommended cladribine tablets cumulative dose (1.75 of the 3.5 mg/kg dose or 2.625 of the 5.25 mg/kg dose).[10] This may explain the apparent clinical benefits (i.e., relapse measures) observed prior to Week 24.[9] ARR was already noticeably reduced 4 weeks after cladribine tablets (either dose) treatment versus placebo (0.23–0.27 vs. 0.42),[10] which implies that effects on MRI parameters occur earlier than Week 24. In ORACLE-MS, reduced MRI activity appeared to go hand-in-hand with reduced incidence of early CDMS conversion in both cladribine tablets groups versus placebo.[7] At the first post-baseline MRI assessment (Week 13), reductions in the mean number and volume of T1 Gd+ lesions were observed in participants treated with cladribine tablets versus placebo; differences in the probability of CDMS conversion began to emerge between treatment groups at approximately the same time.[7] By Week 24, the reductions of all MRI measures (T1 Gd+, new/enlarging T2, and CUA lesions) were more apparent in participants treated with cladribine tablets versus placebo. During this period, there was widening separation between treatment groups in the probability of CDMS conversion (<10% for both doses of cladribine tablets vs. ~15% for placebo).[7] The rate of MS conversion per 2005 McDonald criteria was ~40% for both doses of cladribine tablets versus ~65% for placebo by Week 24.[7] Confirmation of 2005 McDonald MS was based on the occurrence of clinical events or new MRI findings.[22] Therefore, it is to be expected that significant treatment effects on MRI activity were associated with reduced rates of conversion to 2005 McDonald MS. Consistent with other trials, similar correlative trends between reductions in MRI lesions and CDMS conversion were observed in studies of teriflunomide and IFN β-1a in participants with an FCDE.[4,8,20]

Differences in the onset of an effect on T1 Gd+ lesions and new/enlarging T2 lesions were perhaps to be expected and the overall timing of effect might be related to the mode of action of cladribine. T1 Gd+ lesions represent new lesions on MRI, reflecting breakdown of the blood–brain barrier and active inflammation.[23] T1 Gd+ lesions are short-lived (4–6 weeks), whereas T2 lesions may persist and provide a record of lesions occurring over time. The most plausible explanation for the mode of action of cladribine in MS is the preferential reduction of lymphocyte counts following administration.[24] However, no direct link has been made between the reduction of lymphocyte counts and cladribine clinical or MRI efficacy. In ORACLE-MS, total lymphocyte counts were reduced by Week 2 with a nadir at Weeks 9–12.[25] There has been considerable interest in the role of B cells in MS. In ORACLE-MS, B cell counts were reduced by 70% at Week 5

after treatment initiation.[25] Given these rapid changes in relevant lymphocyte populations, it would be of interest to determine the effect of cladribine tablets on MRI outcomes before Week 13. Obtaining this information is the objective of an ongoing Phase 4 study (MAGNIFY-MS; NCT03364036).[26]

The findings from ORACLE-MS generally provide support for the benefits of treatment intervention during early MS disease, as cladribine tablets treatment delayed or prevented MS according to the Poser criteria and 2005 McDonald criteria.[7] Further study would be needed to evaluate an additional benefit of institution of therapy at presentation with an FCDE meeting current MS diagnostic criteria, as there was a delay between an FCDE presentation and the start of the treatment period. The set interval between an FCDE and screening was within 75 days and the mean interval between FCDE and randomization was 79 days,[7] longer than in other studies. For comparison, the CHAMPS study of IFN β-1a enrolled participants within 27 days of an FCDE.[4] The relative delay of the treatment onset may have had a negative impact on the efficacy because of the accumulating evidence that the treatment power decreases with the increase of disease duration. Therefore, future controlled studies would be needed to establish the optimal timing for treatment initiation in FCDE. While ORACLE-MS results may support cladribine tablets' use early in the course of MS, the early clinical and MRI effects might be relevant when considering cladribine tablets following cessation of a previous DMT, including those associated with rebound disease.[10,27] These are the subject of ongoing Phase 4 clinical trials (CLADRINA: NCT04178005; CLICK-MS: NCT03933215; MASTER-2: NCT03933202).

Conclusion

Analysis of the MRI data from ORACLE-MS study in participants with an FCDE at risk of converting to CDMS showed that cladribine tablets appeared to reduce active lesion number and volume as early as 13 weeks (the time of first MRI evaluation). The reduction of active lesions is consistent with the observed reduction in incidence of CDMS conversion.

Conflict of Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: **MSF** has received honoraria or consultation fees from Actelion (Janssen/J&J), Alexion, Biogen Idec, Celgene (BMS), EMD Inc., Canada, an affiliate of Merck KGaA, Darmstadt, Germany, EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany, Sanofi-Genzyme, Hoffman La-Roche, Merck KGaA, Darmstadt, Germany, Novartis, Teva Canada Innovation; has received research support unrelated to this study from Sanofi-Genzyme Canada, Hoffman-La Roche, EMD Inc., Canada, an affiliate of Merck KGaA, Darmstadt, Germany; was a member of a company advisory board, board of directors, or other similar group for Actelion (Janssen/J&J), Alexion, Atara Biotherapeutics, Bayer Healthcare, Biogen Idec, Celgene (BMS), Clene Nanomedicine, GRI Bio, Hoffman La-Roche, Magenta Therapeutics, Merck KGaA, Darmstadt, Germany, MedDay, Novartis, Sanofi-Genzyme, Teva Canada Innovation; and has been a participant in a company sponsored speaker's bureau for Sanofi-Genzyme and EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany.

PKC declares being an advisor or consultant for Accordant, Biogen, Bristol Myers Squibb, Genentech/Roche, Genzyme/Sanofi, Janssen, Novartis, and Viela Bio, and receiving grants for clinical research from Actelion, Alkermes, Corrona LLD, Genentech/Roche, MedDay, NINDS, and Novartis.

GC has received, in the past 24 months, consulting and speaking fees from Novartis, Teva Pharmaceutical Industries Ltd., Teva Italia Srl, Sanofi Genzyme, Genzyme Corporation, Genzyme Europe, Merck KGaA, Darmstadt, Germany, Merck Serono S.p.A., Italy, an affiliate of Merck KGaA, Darmstadt, Germany, Celgene Group, Biogen Idec, Biogen Italia Srl, F. Hoffman-La Roche, Roche SpA, Almirall SpA, Forward Pharma, Medday, Excemed.

SS has received research study support from Biogen, Teva, Mallinckrodt, Sanofi Genzyme, and EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany, and served as a speaker/consultant for Sanofi Genzyme, EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany, and Genentech.

DD and **FD** are employees of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany.

YH and **DJ** are employees of Merck KGaA, Darmstadt, Germany.

AG is an employee of Ares Trading SA, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

LAL is an employee of EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany.

TPL has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany, Novartis, ONO, Pfizer, Teva Neuroscience.

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., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany, who reviewed and provided feedback on the manuscript. Writing and editorial support was provided by Ying Jean, PhD and Nick White of Ashfield (New York, NY, USA); funding was provided by the study sponsor. The authors had full control of the manuscript, and provided their final approval of all content.
The ORACLE-MS study: NCT00725985

Supplemental material

Supplemental material for this article is available online.

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