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ORIGINAL RESEARCH

# Stability in Cognition and Employment in People with Relapsing Multiple Sclerosis Treated with Cladribine Tablets: Two-year Phase IV CLARIFY-MS Study

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## ABSTRACT

***Introduction***: Cognitive impairment can affect people with multiple sclerosis (MS) at all stages, negatively impacting their work performance and quality of life. This study aimed to report the cognitive function and employment status data for participants with highly active relapsing MS (RMS) treated with cladribine tablets (CladT) during the 2-year, prospective, open-label, exploratory, single-arm, multicentre, phase IV CLARIFY-MS study.

***Methods***: In this post hoc analysis, changes in cognitive function at month (M)12 and M24 (vs baseline) were measured using the Brief International Cognitive Assessment for MS (BICAMS) battery. Additional analyses were conducted to assess clinically meaningful 4- and 8-point changes in Symbol Digit Modalities Test (SDMT) scores. The employment status of

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participants was determined through a survey at baseline and M24.
***Results***: BICAMS parameter scores remained stable over 2 years in CladT-treated participants. As determined by a 4- and 8-point change, a high proportion of participants had increased or stable SDMT scores at M24 versus baseline. The mean annualised percentage brain volume change (PBVC) in participants was low. No correlation was found between changes in BICAMS parameter scores and annualised PBVC. Furthermore, no major differences in the employment status of participants were observed over 2 years, with > 40% of participants being in full-time employment during the study.
***Conclusions***: Most CLARIFY-MS participants had increased or stable information processing speed at M24 (vs baseline), as determined using clinically meaningful 4- and 8-point changes in SDMT scores. Overall, the cognitive function and employment status of CladT-treated participants with highly active RMS remained stable over 2 years.
***Trial Registry Details***: URL: https://clinicaltrials.gov/ct2/show/NCT03369665; ClinicalTrials.gov Identifier: NCT03369665.

## PLAIN LANGUAGE SUMMARY

Multiple sclerosis (MS) is an autoimmune condition where the immune system (the body's natural defence system) mistakenly attacks myelin, a protective layer found around the nerve cells in the brain and spinal cord. These attacks may contribute to cognitive decline, which impacts the ability of people with MS to think, learn, and remember, causing problems in daily life and work. Cognitive decline often appears as slower information processing speed and difficulties with memory and verbal fluency. Cladribine tablets are an oral medication for treating relapsing forms of MS, taken in two short courses over two consecutive years. Each treatment course consists of two treatment weeks, one at the beginning of the first month and one at the beginning of the second month. Relapses are periods where new MS symptoms appear or existing symptoms worsen over 24 h or longer. In the CLARIFY-MS study, researchers studied the changes in cognitive function and employment status over 2 years in people with highly active relapsing MS treated with cladribine tablets. The majority of participants in CLARIFY-MS showed increased or stable information processing speed at 24 months compared to the start of the study. Overall, cognitive function, including verbal learning and visual memory, remained stable over 2 years. Most participants who were employed full-time at the start of the study retained their employment status even after 2 years. The stability in cognitive function and employment status observed during CLARIFY-MS supports previously reported positive quality-of-life findings in people with highly active relapsing MS treated with cladribine tablets.

**Keywords:** BICAMS; Cladribine tablets; CLARIFY-MS; Cognition; Employment; Multiple Sclerosis; MS; Relapsing MS; SDMT; Work

**Key Summary Points**

**Why carry out this study?**

Cognitive impairment can affect people with multiple sclerosis (MS) at all stages, negatively impacting their work performance and overall quality of life.

Cladribine tablets (CladT; 3.5 mg/kg cumulative dose over 2 years) are a high-efficacy therapy indicated for the treatment of relapsing MS (RMS).

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This study aimed to report cognitive function and employment data from people with highly active RMS treated with CladT during the 2-year phase IV CLARIFY-MS study.

**What was learned from the study?**

Most CLARIFY-MS participants had increased or stable information processing speed at 24 months (vs baseline), as determined using clinically meaningful 4- and 8-point changes in Symbol Digit Modalities Test (SDMT) scores.

Overall cognitive function, including verbal learning and visuospatial memory, remained stable over 2 years (vs baseline).

Most CladT-treated participants who were employed full-time at baseline retained their employment status after 2 years in the study.

## INTRODUCTION

Cognitive impairment can affect people with multiple sclerosis (PwMS) at all stages; however, assessing its clinical effects is challenging [1]. These effects include loss of memory function, reduced information processing speed (IPS), and changes in executive function, which make activities of daily life difficult [2]. Furthermore, it has detrimental effects on the health-related quality of life (HRQoL) of PwMS, including reduced social activity, increased physical dependence, poor disease management, and fewer benefits from rehabilitation, thereby affecting activities of daily living [3]. As PwMS experience the negative effects of cognitive impairment daily, effective recognition and care are important. Earlier research has demonstrated that a slower IPS in PwMS is a predictor of unemployment and reduced working hours [4]. For PwMS, the ability to work may be compromised, resulting in various work-related challenges such as absenteeism, low productivity, job changes, reduced working hours, and unemployment. Consequently, this imposes a significant economic burden on both PwMS and their caregivers [5, 6]. In addition to socioeconomic costs, the inability to work may substantially affect the HRQoL and psychological well-being of PwMS [6, 7].

In PwMS, brain atrophy begins early in the disease course and is a strong indicator of future physical and cognitive dysfunction [8]. Several disease-modifying therapies (DMTs) are available for treating MS; however, studies demonstrating their effects on different aspects of cognition are limited. Studies assessing the effects of DMTs on cognition in PwMS have mostly focused on evaluating IPS using the Symbol Digit Modalities Test (SDMT) [9]. Although a decline in IPS is the most prevalent cognitive impairment in PwMS, a significant subset of individuals experience specific memory difficulties without marked IPS decline. [10]. As impairments in cognitive domains have been previously linked to the employment status of PwMS [11, 12], an investigation capturing a broader cognitive profile is warranted.

DMTs may facilitate small to moderate improvements in cognitive function [9] and enhance overall work productivity in PwMS [13]. Randomised controlled trials have reported several clinical and safety outcomes of cladribine tablets (CladT) but have not fully evaluated their effects on cognitive function and the employment status of people with highly active relapsing MS (RMS) [14, 15]. The CLARIFY-MS study (NCT03369665) evaluated the HRQoL of CladT-treated people with highly active RMS. The 2-year final analysis of CLARIFY-MS data showed that CladT treatment significantly improved participants' physical and mental health composite scores (PHCS and MHCS) on the Multiple Sclerosis Quality of Life-54 (MSQoL-54) instrument, with a substantial proportion of the participants achieving clinically relevant improvements in HRQoL [16]. Herein, we report data on cognitive function and employment status in participants with highly active RMS treated with CladT during the 2-year CLARIFY-MS study.

## METHODS

### Study Design

The CLARIFY-MS study was a 2-year, prospective, open-label, exploratory, single-arm, multicentre,

phase IV study designed to assess the effects of CladT on HRQoL, along with other efficacy and safety outcomes, in people with highly active RMS (Figure S1). The primary endpoints were changes in the MSQoL-54 PHCS and MHCS at month (M)24 versus baseline. The results of the 2-year final analysis have been reported previously [16].

Adults with highly active RMS (aged ≥ 18 years) and an Expanded Disability Status Scale score of ≤ 5.0 were eligible for this study. Highly active RMS was defined as ≥ 1 relapse in the previous year and ≥ 1 T1 gadolinium-enhancing lesion or ≥ 9 T2 lesions while receiving treatment with other DMTs or ≥ 2 relapses in the previous year regardless of the DMT received. Detailed inclusion and exclusion criteria have been reported previously [16, 17]. The CLARIFY-MS study was conducted in accordance with the principles outlined in the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice. Participants were required to provide written informed consent prior to the initiation of any study-related activities. In CLARIFY-MS, participants received CladT at a cumulative dose of 3.5 mg/kg over 2 years, with 2 weeks of active treatment per course (weeks 1 and 5 of each year). Each treatment week comprised 4 or 5 days on which a participant received 10 mg or 20 mg of CladT (1 or 2 tablets) as a single daily dose, depending on body weight. Treatment was completed by the M24 visit [16, 17].

### Objectives

This post hoc analysis aimed to assess the cognitive function and employment status of participants treated with CladT during the 2-year CLARIFY-MS study. Correlations between the changes in cognitive function and annualised percentage brain volume change (PBVC) from baseline to M24 were also assessed.

### Cognitive Assessments and PBVC

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), a recommended cognitive assessment tool for PwMS, is endorsed by an expert consensus committee of experienced neurologists and neuropsychologists [1] and has been validated in 26 countries [18].

It comprises the SDMT, California Verbal Learning Test, Second Edition (CVLT-II; first five recall trials), and Brief Visuospatial Memory Test–Revised (BVMT-R; first three recall trials). The entire BICAMS battery takes approximately 15 min to complete and does not require specialised equipment or significant cognitive assessment expertise [1].

In this study, a paper-based version of BICAMS was administered to the participants to assess their cognitive function at baseline and at M12 and M24. The CVLT-II, BVMT-R, and SDMT were completed in all countries where local language translations of both CVLT-II and BVMT-R were available and then included in the study analysis wherein the questionnaire language translation was validated. After completion by participants, the BVMT-R was scored on-site, and scores were reviewed independently by a central reader. Higher BICAMS test scores indicate better cognitive performance. Magnetic resonance imaging was used to measure PBVC over time.

### Employment Assessments

The employment status of the participants was determined on a non-ordered categorical scale using an employment survey at baseline and M24/end of study (EOS). Participants were asked to select the option that best described their current employment status from the following choices: unemployed, on sick leave, employed part-time, employed full-time, in education, or homemaker.

### Statistical Analysis

Participants who received ≥ 1 dose of CladT were included in the treated set (TS). The BICAMS set comprised all participants in the TS from countries where BICAMS was administered. Raw BICAMS test scores at M12 and M24 were compared with those at baseline. The SDMT is considered the gold standard for cognitive testing in PwMS [19]. A 4-point change in SDMT scores is widely accepted as a clinically

meaningful change at a group level, whereas an 8-point change is considered more reliable to determine cognitive decline in PwMS at an individual level [20]. In this study, both 4- and 8-point changes in SDMT scores from baseline to M24 were analysed using Wilson's score method in the TS. Changes in SDMT scores were categorised as increase (change of ≥ +4 or +8 points in the SDMT score from baseline), stable (4- or 8-point change in the SDMT score from baseline) or decrease (change of ≤ −4 or −8 points in the SDMT score from baseline). Shifts in SDMT score categories from M12 to M24 versus the change from baseline to M12 were also analysed. Pearson's correlation coefficient was used to measure the correlations between individual BICAMS parameters and annualised PBVC from baseline to M24. The current employment status was measured in the TS at baseline and M24. Subgroup analyses were conducted for participants who did not receive DMTs before CladT treatment (treatment [Tx]-naïve subgroup) and those who received DMTs at any time before CladT treatment (Tx-experienced subgroup). All analyses were exploratory. BICAMS and employment status data were analysed descriptively.

# RESULTS

## Participant Demographics and Clinical Characteristics

The demographics and baseline disease characteristics of the CLARIFY-MS participants have been reported previously [16, 17]. In brief, 482 participants received ≥ 1 dose of CladT and were included in the TS. The mean (standard deviation [SD]) age of the participants was 37.4 (10.4) years, and most were female (70.1%). The mean (SD) time since MS onset was 99.1 (89.8) months, and most participants (99.2%) experienced ≥ 1 relapse during the 12-month period before CladT treatment (Table S1) [16]. Of the 482 participants in the TS, 399 were included in the BICAMS set (Tx-naïve subgroup, $n = 108$; Tx-experienced subgroup, $n = 291$). All 482 participants in the TS completed the employment survey at baseline.

The median (Q [quartile]1; Q3) SDMT and BVMT-R scores remained stable during the study: SDMT—baseline, 51.0 (43.0; 59.0); M12, 52.0 (44.0; 60.0); and M24, 53.0 (45.0; 61.0); BVMT-R—baseline, 24.0 (17.0; 29.0); M12, 25.0 (18.0; 30.0); and M24, 25.0 (19.0; 30.0) (Fig. 1). The median (Q1; Q3) CVLT-II scores increased from 56.0 (45.0; 63.0) at baseline to 60.0 (48.0; 68.0) at M24 (Fig. 1). The respective BICAMS parameter scores were similar across subgroups and were comparable to the overall BICAMS set

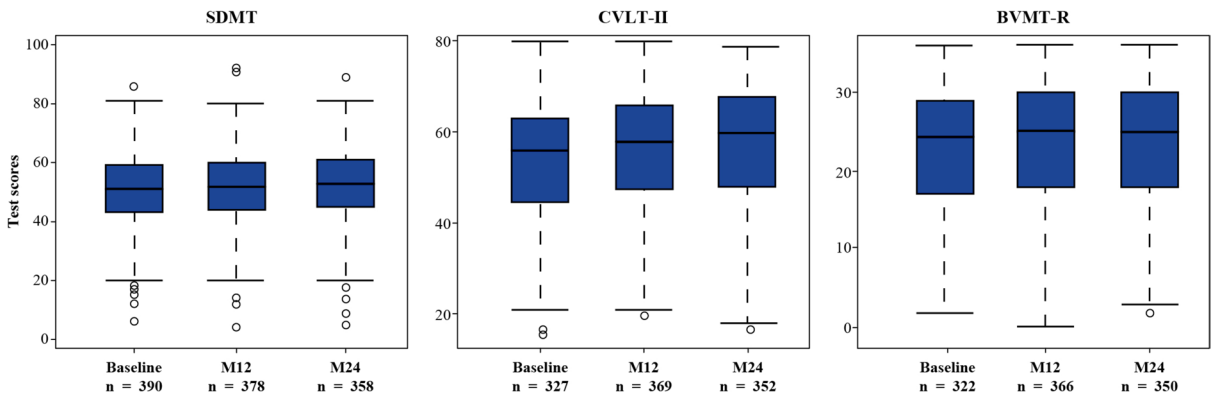



**Fig. 1** BICAMS scores over time (BICAMS set). BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test–Revised; CVLT-II, California Verbal Learning Test, Second Edition; M, month; SDMT, Symbol Digit Modalities Test

at baseline. These scores did not differ substantially between the subgroups from baseline to M12 and M24.

### Change in SDMT categories: individual-level ≥ 4- and ≥ 8-point change

As determined by an individual-level ≥ 4-point change in SDMT scores, a high proportion of participants in the TS (68.9%; *n* = 332/482) had increased (35.5%; 171/482) or stable (33.4%; 161/482) scores, whereas 18.3% (88/482) recorded a decrease at M24 versus baseline (Fig. 2). A higher proportion of participants in the Tx-experienced subgroup had a ≥ 4-point increase in SDMT scores (37.9%; 132/348) than those in the Tx-naïve subgroup (29.1%; 39/134) at M12 versus baseline. The proportion of participants who recorded a decrease in SDMT scores was similar across both subgroups. Overall, 87.6% (*n* = 374/482) of participants had stable (60.6%; 292/482) or increased (17.0%; 82/482) 8-point change in SDMT scores at an individual level, whereas 9.5% (46/482) recorded a decrease at M24 versus baseline (Fig. 2). Changes in

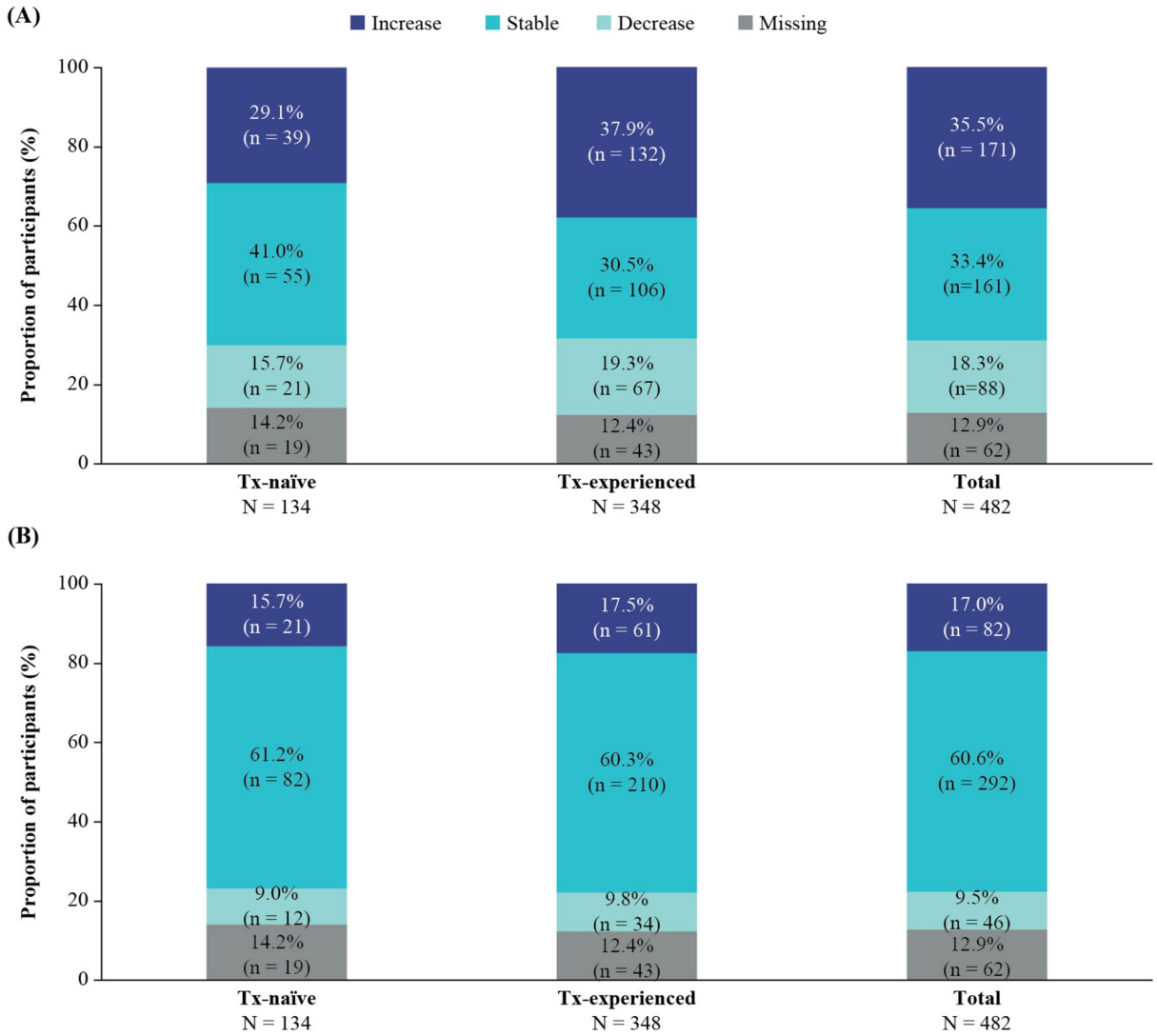



**Fig. 2** Individual-level changes in SDMT score categories from baseline to M24 (TS): **A** 4-point change and **B** 8-point change. M, month; SDMT, Symbol Digit Modalities Test; TS, treated set; Tx, treatment

SDMT scores were similar across both subgroups. SDMT scores for the TS are reported in Table S2.

### Shifts in SDMT categories: individual-level ≥ 4- and ≥ 8-point change

In the TS, 14.1% ($n = 68/482$) of the participants had a ≥ 4-point increase in SDMT scores from baseline to M12 and were stable from M12 to M24 (Fig. 3; Table S3). Among participants whose SDMT scores decreased between baseline and M12, 52.7% (49/93) had increased SDMT scores between M12 and M24.

When considering a ≥ 8-point change, 11.5% ($n = 55/482$) of the participants recorded an increase in SDMT scores from baseline to M12 and were stable between M12 and M24 (Fig. 3; Table S4). Among participants who had a decrease in SDMT scores between baseline and M12, 35.0% (14/40) recorded an increase between M12 and M24. Similar trends were observed across subgroups.

### BICAMS Scores and PBVC

Annualised PBVC data (from baseline to M24) were available for 327 participants. The mean (SD) annualised PBVC was low during the study (–0.59 [0.57]), with 57.8% (189/327) and 42.2% (138/327) of the participants having an annualised PBVC of ≤ –0.4% and > –0.4%, respectively. No correlation was observed between annualised PBVC and BICAMS parameters (Fig. 4).

### Overall Employment Status

The employment status of the participants was mostly stable, with no major differences

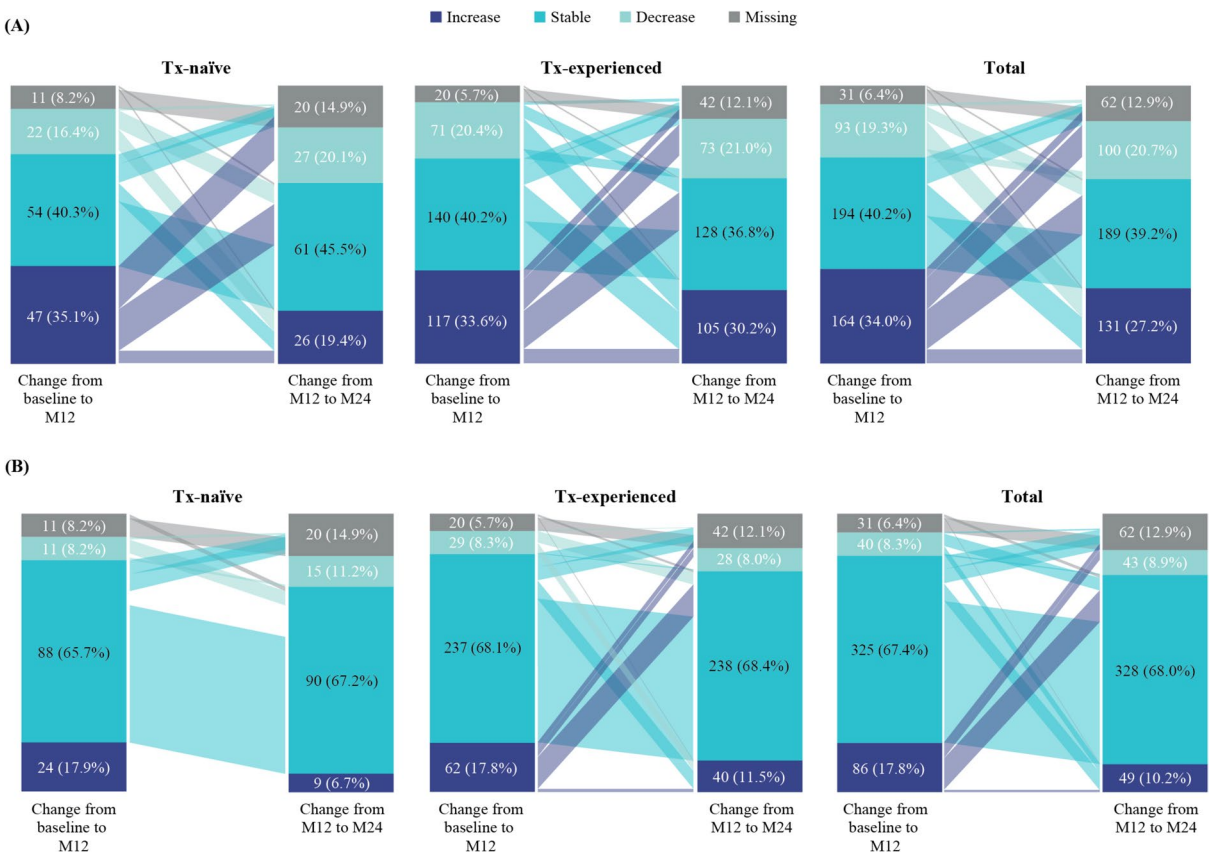



**Fig. 3** Shifts in SDMT categories (TS): **A** 4-point change and **B** 8-point change. M, month; SDMT, Symbol Digit Modalities Test; TS, treated set; Tx, treatment

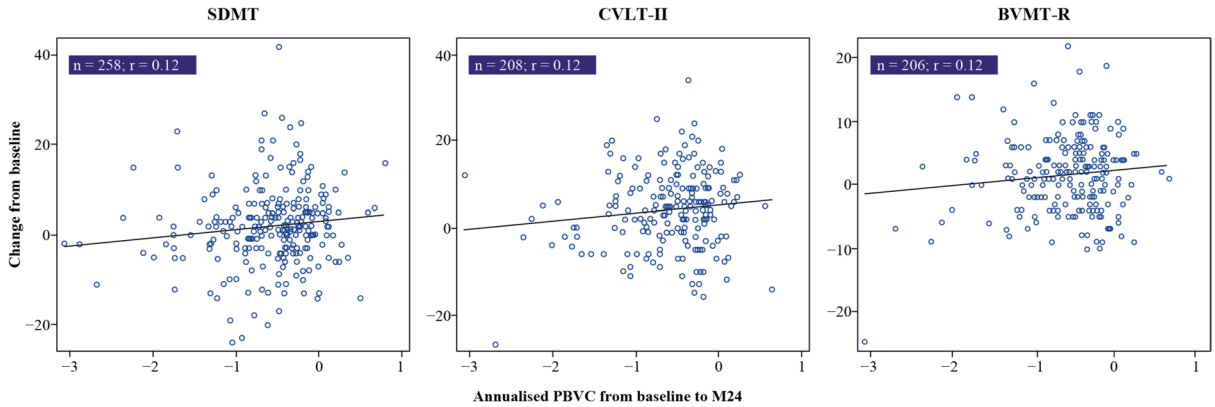



**Fig. 4** Correlation of change in BICAMS scores with annualised PBVC from baseline to M24. BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test–Revised; CVLT-II, California Verbal Learning Test, Second Edition; M, month; PBVC, percentage brain volume change; SDMT, Symbol Digit Modalities Test

observed between baseline and M24/EOS in the TS: full-time employment (47.5% [229/482] vs 43.4% [209/482]), part-time employment (11.6% [56/482] vs 12.2% [59/482]), unemployment (16.2% [78/482] vs 19.1% [92/482]), sick leave (7.7% [37/482] vs 5.8% [28/482]), education (7.7% [37/482] vs 3.3% [16/482]), and homemaker (9.3% [45/482] vs 6.6% [32/482]) (Fig. 5). Results for the Tx-naïve and Tx-experienced subgroups were generally consistent with those of the TS (Fig. 5). Employment data were missing for 46 participants at M24/EOS.

## DISCUSSION

This post hoc analysis of phase IV CLARIFY-MS data showed that the overall cognitive function of CladT-treated participants with highly active RMS remained stable over the 2-year study period. As determined by a clinically meaningful 4- and 8-point change, a high proportion of participants had increased or stable SDMT scores at M24 versus baseline. The mean annualised PBVC in participants was low, and no correlation was observed between the change in BICAMS parameter scores and annualised PBVC. Employment status was stable over 2 years. A high proportion of participants in full-time employment at baseline experienced no change in employment status by M24/EOS post-CladT treatment. These data augment the existing published clinical trial findings on the efficacy of CladT [14, 15] and further contribute to our understanding of the effect of CladT on the HRQoL of people with highly active RMS.

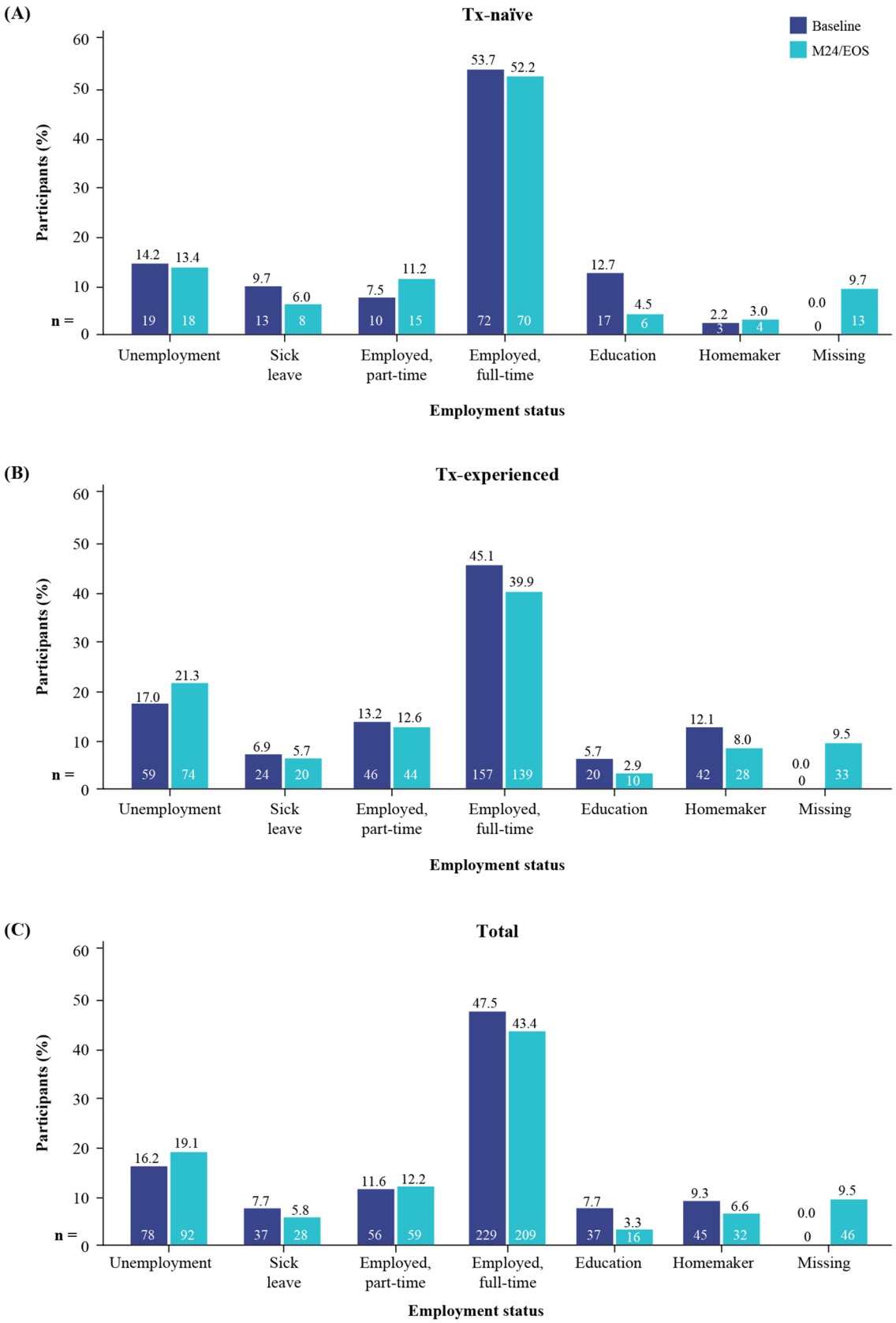
Cognitive impairment, characterised by deficits in episodic memory, attention, executive functioning, visuospatial perception, and IPS, is experienced by 40%–70% of PwMS [21]. Several studies have linked cognitive impairment to reduced HRQoL in PwMS [3, 4, 22]. Improvements in HRQoL in participants with highly active RMS treated with CladT 3.5 mg/kg cumulative dose over 2 years during CLARIFY-MS have been previously reported [16]. Over the 2-year study period, treatment with CladT significantly improved the MSQoL-54 PHCS and MHCS, with a sizeable proportion of participants experiencing clinically relevant improvements in HRQoL [16].

Neurological damage begins early in the course of MS [23], and cognitive decline can precede physical disability and may even occur before the first appearance of MS clinical symptoms [24]. However, data on cognitive function in untreated patients with MS are scarce, and the relevant studies in the published literature utilise different assessment tools, making direct comparisons difficult. In a study evaluating the effect of interferon beta-1b (IFNβ-1b)

on cognitive function in patients with MS, the untreated control group ($N=23$) showed a decrease in scores across the components of the Brief Repeatable Battery of Neuropsychological Tests at year 1 compared with baseline [25]. Similarly, in the phase III, randomised, placebo-controlled TEMSO core study, a reduction in cognitive function, as measured by the Paced Auditory Serial Addition Test 3, was observed in placebo-treated patients with MS at year 2 ($N=329$) compared with baseline [26]. These data suggest that patients with MS who are left untreated may experience a gradual progression of cognitive decline even over a short period of time. Early treatment with high-efficacy therapies (HETs) can improve long-term clinical outcomes by reducing neurological damage [27]. IPS is among the most affected cognitive domains in PwMS [1, 19]. The SDMT, a measure of IPS, is considered the most sensitive cognitive test for PwMS [28]. Owing to its predictive ability, sensitivity, specificity, straightforward administration, and patient-friendliness, the SDMT is commonly utilised in clinical settings to identify PwMS who are at the risk of cognitive decline [29, 30]. Previously, a single-centre study involving people with clinically definite MS ($N=234$) and healthy controls ($N=67$) demonstrated that participants across different MS phenotypes performed worse on the SDMT than healthy controls. The raw mean (standard error) SDMT scores were as follows: healthy controls (mean [SD] age: 44.1 [13.8] years), 60.2 (1.6); relapsing–remitting MS (RRMS; $n=108$; 35.5 [8.8] years), 54.3 (1.3); secondary progressive MS ($n=71$; 45.1 [8.2] years), 45.1 (1.6); primary progressive MS ($n=55$; 53.9 [11.6] years), 47.8 (1.9) [31]. A 4-point change in SDMT scores is deemed clinically significant at a group level, while an 8-point change is regarded as more reliable at an individual level [20].

While some studies have documented the effect of HETs on IPS using a 4-point threshold, studies reporting an 8-point change in SDMT scores are scarce [32–35]. In the phase IIIb CASTING study ($N=680$; baseline: mean [SD] age, 34.2 [8.6] years; mean [SD] SDMT score, 53.8 [13.0]), the majority of people with RMS treated with ocrelizumab had improved or stable 4-point (improved, 29.0%; stable, 32.8%) and 8-point (improved, 15.0%; stable, 59.1%) changes in SDMT scores at week 96 versus baseline [36, 37]. In the CLARIFY-MS study ($N=482$; baseline: mean [SD] age, 37.4 [10.4] years[16]; mean [SD] SDMT score, 50.7 [12.9]), a high proportion of CladT-treated participants had increased or stable SDMT scores at M24 compared with baseline, as evaluated using a 4-point (improved, 35.5%; stable, 33.4%) or 8-point (improved, 17.0%; stable, 60.6%) change. These findings may suggest similar benefits with CladT and ocrelizumab treatment for IPS in people with RMS [33, 34, 38]. In line with the findings of CLARIFY-MS, the results from the 2-year prospective, open-label, single-arm, phase IV MAGNIFY-MS study ($N=270$) also showed a high proportion of participants with highly active RMS treated with CladT experiencing clinically relevant improvements or stability in SDMT scores at M24 versus baseline (Kaplan–Meier estimates: 4-point—confirmed improvement, 43%; stable, 45%; worsened, 12%; 8-point—confirmed improvement, 22%; stable, 74%; worsened 4%), suggesting the possible benefits of CladT in managing cognitive symptoms in such populations [39].

Most studies assessing the effects of HETs on cognition have either focused on specific aspects of cognition or been conducted in small cohorts of PwMS [32–35, 38, 40–43]. A comprehensive neuropsychological assessment of cognitive function is lengthy and requires specialised tools, which may not be available in most MS clinics. BICAMS, a quick and easy-to-administer battery of cognitive tests, does not require specialised tools and helps to look beyond IPS into broader aspects of cognition such as immediate verbal learning (CVLT-II) and visuospatial memory (BVMT-R), which may also be impaired in PwMS [1]. Limited BICAMS data are available for HETs used in RMS. CASTING and ENSEMBLE are two open-label phase IIIb clinical studies of ocrelizumab, conducted in Tx-naïve and Tx-experienced people with RMS, respectively. At baseline, the mean (SD) age was 32.4 (9.1) years in ENSEMBLE and 34.2 (8.6) years in CASTING. The mean (SD) BICAMS parameter scores at baseline were as follows: SDMT, 55.3 (12.9) and 53.8 (13.0); BVMT-R, 23.3 (7.0) and 25.0 (6.4) for ENSEMBLE and CASTING, respectively. The mean (SD) baseline CVLT-II score in ENSEMBLE


(A)
Tx-naïve
Baseline
M24/EOS
Participants (%)
60
50
40
30
20
10
0
n =
14.2
13.4
19
18
9.7
6.0
13
8
7.5
11.2
10
15
53.7
52.2
72
70
12.7
4.5
17
6
2.2
3.0
3
4
0.0
9.7
0
13
Unemployment
Sick leave
Employed, part-time
Employed, full-time
Education
Homemaker
Missing
Employment status
(B)
Tx-experienced
Participants (%)
17.0
21.3
59
74
6.9
5.7
24
20
13.2
12.6
46
44
45.1
39.9
157
139
5.7
2.9
20
10
12.1
8.0
42
28
0.0
9.5
0
33
Unemployment
Sick leave
Employed, part-time
Employed, full-time
Education
Homemaker
Missing
Employment status
(C)
Total
Participants (%)
16.2
19.1
78
92
7.7
5.8
37
28
11.6
12.2
56
59
47.5
43.4
229
209
7.7
3.3
37
16
9.3
6.6
45
32
0.0
9.5
0
46
Unemployment
Sick leave
Employed, part-time
Employed, full-time
Education
Homemaker
Missing
Employment status

◂**Fig. 5** Employment status of the participants at baseline and M24/EOS. **A** Tx-naïve subgroup, **B** Tx-experienced subgroup, and **C** total population. EOS, end of study; M, month; TS, treated set; Tx, treatment

(*n* = 181) was 54.6 (10.8) [36]. In CLARIFY-MS, the baseline BICAMS parameter scores of participants were generally comparable to those of the ENSEMBLE and CASTING studies (BICAMS set: mean [SD] SDMT, 50.3 [12.6]; CVLT-II, 53.8 [12.4]; BVMT-R, 22.4 [7.8]); however, the CLARIFY-MS participants were slightly older at baseline (mean [SD] age, 37.4 [10.4] years) [16] and had highly active RMS.

CLARIFY-MS is the first prospective study to report the effects of CladT on cognitive function in a substantial population of people with highly active RMS and is among the few studies with a large number of PwMS completing the BICAMS battery (*N* = 399) at different time points over 2 years. The findings of this study also show that overall cognitive function comprising IPS (SDMT), verbal learning (CVLT-II), and visuospatial memory (BVMT-R) remained stable over 2 years in CladT-treated participants (BICAMS set). Cognitive decline often starts early in the disease course [24] and may continue despite the use of DMTs [2]. In CLARIFY-MS, CladT-treated participants who were early in their disease course and those previously on other DMTs had stable BICAMS scores over the 24 months of the study. The majority of participants in both subgroups had increased or stable SDMT scores (TS) at M24 versus baseline, as determined using clinically meaningful 4- and 8-point thresholds. These findings suggest that overall cognitive function was largely preserved in both Tx-naïve and Tx-experienced people with highly active RMS treated with CladT during the 2-year CLARIFY-MS study.

In PwMS, brain atrophy starts early, often before diagnosis, and gradually progresses if left untreated [8]. Untreated PwMS experience a 0.50–1.35% loss of brain volume annually, compared with 0.10–0.50% loss in healthy adults [44, 45]. The yearly brain volume loss (BVL) rate in CLARIFY-MS participants was close to that reported in healthy adults in the same mean age range of 37 years [44], indicating that CladT treatment may slow pathological BVL in people with highly active RMS. To distinguish between pathological and physiological changes in MS, a PBVC cut-off of –0.4% annually was previously proposed [44]. In this study, most participants treated with CladT were within this cut-off. Previous studies have shown that brain atrophy is more pronounced in PwMS with mild disability and poor cognitive performance [8, 46, 47]. In the CLARIFY-MS study, no correlation was observed between annualised PBVC and the change in cognitive function.

Owing to disability accumulation and cognitive decline, PwMS are less likely to be employed as their disease progresses [48]. Unemployment has been linked to reduced HRQoL and poorer mental health in PwMS [6, 49]. HETs have been associated with greater improvements in the amount of work, attendance, and productivity than conservative injectable platform therapies [13]. The coronavirus disease (COVID-19) pandemic had detrimental effects on employment, resulting in unemployment, absenteeism, and reduced working hours globally [50]. PwMS, owing to their general work-related limitations [51] and difficulties in accessing care during COVID-19, were more prone to changes in their employment status [52]. A systematic review and meta-analysis of 49 observational studies involving 17,364 PwMS during the COVID-19 pandemic found that 43% experienced a change in employment status. The unemployment rate was 39%, with 47% either unemployed or retired. Unemployment and retirement were positively associated with glatiramer acetate use ($p = 0.004$) but negatively associated with other immunosuppressants ($p = 0.032$), siponimod ($p < 0.001$), and CladT ($p = 0.021$). The prevalence of retirement was negatively associated with the use of HETs ($p = 0.004$), fingolimod ($p = 0.014$), and CladT ($p < 0.001$). About 10% of PwMS worked part-time and 34% full-time, with part-time work positively influenced by fingolimod ($p = 0.032$), alemtuzumab ($p = 0.04$), and CladT ($p = 0.02$) [53]. Overall, cohorts with higher CladT use were less likely to be out of the workforce and more likely to be in part-time employment during the COVID-19 pandemic. In the CLARIFY-MS study, > 40% of the participants treated with CladT remained in

full-time employment and > 10% in part-time employment over 24 months. Given that the 24-month data for CLARIFY-MS were collected during the COVID-19 pandemic, which substantially affected employment, the stability in the employment status of the participants reported here is encouraging.

### Study limitations

The CLARIFY-MS study had a single-arm design with no control group for comparison; therefore, results at each time point were compared with baseline wherever applicable. Here, the observed stability over 2 years in cognitive function and employment status of the participants is relative to study baseline, and causal inferences may not be drawn. In CLARIFY-MS, the SDMT was administered three times over the 2-year period, with 12-month intervals between each administration. We believe the practice effect is likely to be minimal given that significant practice effects tend to occur in more frequent testing schedules, as seen in the DECIDE study [54], where SDMT was administered seven times over 144 weeks, with shorter 24-week intervals in patients with RMS treated with natalizumab. Previous research in PwMS has shown that the CVLT-II is susceptible to learning effects, especially during the first year of repeated testing, with scores stabilizing between 12- and 24-month assessments [55]. In CLARIFY-MS, CVLT-II scores showed slight improvements from baseline to M12 and M24 in participants treated with CladT. Given that the CVLT-II was administered at 12-month intervals during this study, the influence of prior practice effects beyond the first 12 months may be limited. A correlation between individual BICAMS parameter score changes and PBVC after 2 years could not be established; moreover, the current literature on such an association is equivocal [56–59]. As cognitive impairment in MS progresses over time, studies conducted over a longer duration may provide a better picture of the cognitive changes in this population. Considering that CLARIFY-MS was conducted over 2 years, an additional 2-year extension study (NCT04776213) [60] was conducted with most of these participants over a longer period. Although CLARIFY-MS investigated changes in the employment status of the participants over time, it did not assess reasons underlying these changes or their impact on participants' overall quality of life.

## CONCLUSIONS

A high proportion of CLARIFY-MS participants had increased or stable IPS at M24 as determined using clinically meaningful 4- and 8-point changes in SDMT scores versus baseline. Overall, cognitive function, including verbal learning and visuospatial memory, remained stable over 2 years as compared with baseline in participants treated with CladT. Most CladT-treated participants who were in full-time employment at baseline retained their employment status even after 2 years in the study. The employment status of the participants remained stable even in the M24 data which was collected during the COVID-19 pandemic. The stability in overall cognitive function and employment status of the participants during CLARIFY-MS adds to the previously reported positive HRQoL findings for CladT in people with highly active RMS, supporting its overall benefits in MS treatment.

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***Data Availability.*** The datasets generated during and/or analysed during the current study are not publicly available, as any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's Data Sharing Policy. All requests should be submitted in writing to Merck's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavour to gain agreement to share data in response to requests.

## *Declarations*

***Conflict of Interest.*** The authors declare the following potential conflicts of interest: Bruno Brochet has received consultancy fees and speaker fees from Merck and Sanofi. Dawn Langdon has participated in speaker bureaus for Almirall, Bayer, Biogen, Bristol Myers Squibb (BMS), Merck, Novartis, Roche, Sanofi, and Teva; has received consultancy fees from Bayer, Biogen, BMS, Merck, Novartis, and Teva; and has received research grants from Bayer, Biogen, Merck, and Novartis. Dawn Langdon is an Editorial Board member of *Neurology and Therapy*, and was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Eva Kubala Havrdova received financial support for conference travel, and/or speaker honoraria, and/or research support, and/or consultant fees from Actelion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, and Teva. She has been supported by the Czech Ministry of Education—project Cooperatio LF1, research area Neuroscience—and by the General University Hospital in Prague project MH CZ-DRO-VFN64165. Jeanette Lechner-Scott has received travel compensation from Biogen, Merck, and Novartis. Her institution receives honoraria for talks and advisory board commitments as well as research grants from Biogen, Merck, Novartis, and Roche. Xavier Montalban's institution has received compensation for lecture honoraria and travel expenses, participation in scientific meetings, clinical trial steering committee membership, or clinical advisory board participation in recent years from AbbVie, Actelion, Alexion, AstraZeneca, Autolus, Bial PD, Biogen, BMS/Celgene, Genzyme, Hoffmann-La Roche, Immunic Therapeutics, Indivi, Janssen Pharmaceuticals, Juvisé Pharmaceutical, Lilly, MedDay, Medscape, Merck, Mylan-Viatris, Nervgen, Neuraxpharm, Novartis, PeerVoice, Rewind Therapeutics, Samsung-Biosys, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Zenas Biopharma, Excemed, ECTRIMS, MSIF, and NMSS, or any of their affiliates. Francesco Patti has received personal compensation for speaking activities or serving on advisory boards from Alexion, Almirall, Biogen, BMS, Johnson & Johnson, Merck, Novartis, Roche, and Sanofi. He has also received research grants from Alexion, Almirall, the Italian Ministry of Health, Merck, MIUR, Novartis, Roche, and Sanofi. He is Associate Editor of *Frontiers in Neurology*. Francesco Patti is an Editorial Board member of *Neurology and Therapy*. He was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Fredrik Piehl has received research grants from Janssen, Merck, and Sanofi; fees for serving as a member of the DMC in clinical trials with Lundbeck, Parexel, and Roche; and fees for the preparation of witness statements for Novartis. Alessandra Solari has served on advisory boards for Almirall and Merck and has been invited to speak on behalf of the same companies. She has also received research grants from the Italian MS Society. Raymond Hupperts has received institutional research grants and fees for lectures and advisory boards from Biogen, Merck, and Sanofi. Nektaria Alexandri, Annette

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***Ethical Approval.*** The CLARIFY-MS study was conducted in accordance with the principles outlined in the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice. This study was approved by independent ethics committees or institutional review boards at each study site. Participants provided written informed consent prior to the initiation of any study-related activities. Details of all institutional review boards and ethics committees are available in Supplementary Table S5.



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