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Improvements in Health-related Quality of Life and Preserved Cognitive Function in Patients With Relapsing Multiple Sclerosis: 4-year Results From the CLARIFY-MS Extension Study

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RESEARCH IN CONTEXT

Improvements in physical and mental health, and the cognitive stability observed during the treatment-free period Years 3–4 highlights the durability of the short course cladribine tablets (CladT) on the overall quality of life of patients with highly active relapsing multiple sclerosis (RMS).

OBJECTIVES

To report 4-year health-related quality of life (HRQoL) and cognitive function (mental processing speed and memory) data from the CLARIFY-MS Extension study.

INTRODUCTION

The CLARIFY-MS parent study (NCT03369665) showed that treatment with cladribine tablets (CladT) improved HRQoL and preserved cognitive function in patients with highly active relapsing multiple sclerosis (RMS) over 2 years[1,2]

The 2-year, exploratory, multicenter, open-label, single-arm, Phase 4 CLARIFY-MS Extension study (NCT04776213), a follow-up to the parent study, assessed the effect of CladT treatment on HRQoL and cognitive function up to 4 years after the initial dose of CladT in patients with highly active RMS who completed the parent study

METHODS

- The parent study included a 2-year active dosing period, followed by a treatment-free period for the majority of patients in Years 3–4 of the Extension study, during which further treatment was not planned
- Data were analyzed for all patients combined (N=280), comprising treatment (Tx)-naïve (n=74) and Tx-experienced (n=206) patients

Key endpoints reported here:

Changes in HRQoL (MS Quality of Life [MSQoL]-54 physical and mental health composite scores [PHCS, MHCS]) at 4 years (Month [M] 48) after the initial dose of CladT vs parent study baseline (BL)

Changes in mental processing speed and memory as measured by Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) at 4 years (M48) after the initial dose of CladT vs parent study BL

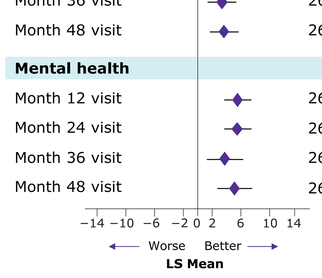
- Based on expert recommendations and earlier research,[1,3] an improvement of at least 5 points in the MSQoL-54 PHCS and MHCS was considered clinically relevant. Therefore, additional analysis was conducted to assess 5-point changes in the MSQoL-54 PHCS and MHCS from BL to M48
- The MSQoL-54 scores were assessed using mixed-effects linear regression and BICAMS scores were analyzed descriptively
- Correlation between MSQoL-54 scores and respective BICAMS parameter scores were assessed using Pearson correlation

RESULTS

- At the parent study BL, participants had a mean (standard deviation) age of 38.4 (10.4) years, and the majority were female (71.8% [n=201/280])
- Out of the 201 patients with MSQoL-54 scores available at both parent study BL and M48, 45.8% (n=92/201) and 45.3% (n=91/201) of the patients showed a ≥5 point change in the MSQoL-54 PHCS and MHCS from the parent study BL to M48, respectively

Figure 1. Significant improvements in HRQoL were observed over 4 years (vs parent study baseline)

Total (N=280)	n	LS mean [95% CI]	p-value
Physical health			
Month 12 visit	265	5.75 [4.18, 7.33]	<0.0001
Month 24 visit	265	5.45 [3.85, 7.05]	<0.0001
Month 36 visit	265	3.38 [1.37, 5.39]	0.0011
Month 48 visit	265	3.69 [1.71, 5.67]	0.0003
Mental health			
Month 12 visit	265	5.53 [3.64, 7.42]	<0.0001
Month 24 visit	265	5.50 [3.50, 7.49]	<0.0001
Month 36 visit	265	3.76 [1.27, 6.26]	0.0033
Month 48 visit	265	5.13 [2.73, 7.53]	<0.0001

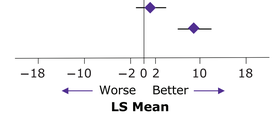


The LS Means were calculated using the repeated measures linear model. MSQoL-54 scores were available at both BL and at least one post BL for 265 participants.
BL, baseline; CI, confidence interval; HRQoL, health-related quality of life; LS, least-squares; MSQoL-54, Multiple Sclerosis Quality of Life 54-item instrument.

- The MSQoL-54 PHCS (p=0.0003) and MHCS (p<0.0001) improved significantly at M48 vs parent study BL (**Figure 1**). At M24 and M48, change in PHCS and MHCS were higher in the Tx-naïve subgroup than in the Tx-experienced subgroup (**Supplementary Figure 1**)
- In the physical health component, 'health perception, energy and health distress' showed significant improvements in MSQoL-54 scores. Similarly, in the mental health component, substantial improvement were observed in the 'health distress and emotional wellbeing' subscales from the parent study BL to M48 (**Figure 2**)
- All BICAMS parameter scores remained stable over 4 years in the total population (**Figure 3**) and both subgroups (**Supplementary Figure 2**)
- Positive (low-to-moderate) correlations were observed between SDMT (PHCS, r=0.41; MHCS, r=0.35), CVLT-II (r=0.27; r=0.24), and BVMT-R (r=0.36; r=0.29) scores and MSQoL-54 scores at M48 (**Supplementary Figure 3**)

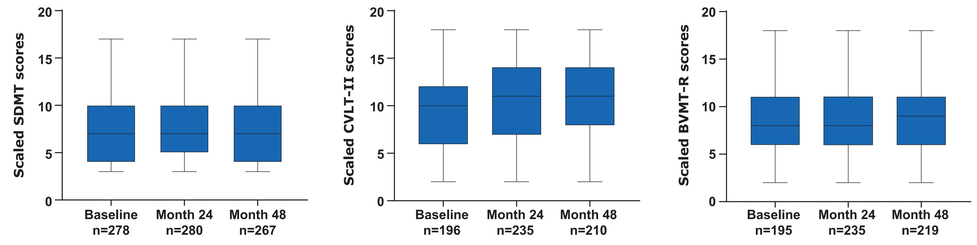
Figure 2. Significant improvement in most MSQoL-54 subscales were observed from the parent study baseline to Month 48

Composite score and scale	n	LS mean [95% CI]	p-value
Physical health composite	265	3.69 [1.71, 5.67]	0.0003
Physical health	265	−0.11 [−2.66, 2.45]	0.9349
Health perceptions	265	5.25 [3.02, 7.48]	<0.0001
Energy	265	4.91 [2.56, 7.26]	<0.0001
Role limitations due to physical problems	265	6.65 [1.98, 11.31]	0.0055
Social function	265	2.04 [−0.40, 4.48]	0.1011
Pain	265	2.98 [0.46, 5.50]	0.0209
Health distress[a]	265	9.00 [6.10, 11.89]	<0.0001
Sexual function	265	−1.15 [−4.58, 2.29]	0.5112
Mental health composite	265	5.13 [2.73, 7.53]	<0.0001
Emotional wellbeing	265	4.66 [2.32, 7.00]	0.0001
Role limitations due to emotional problems	265	6.97 [1.92, 12.01]	0.0070
Overall quality of life	265	3.10 [1.01, 5.20]	0.0039
Cognitive function	265	1.44 [−1.16, 4.03]	0.2757
Health distress[a]	265	9.00 [6.10, 11.89]	<0.0001



[a]The 'health distress' is a common component of both physical and mental health domains.
CI, confidence interval; LS, least-squares; MSQoL-54, Multiple Sclerosis Quality of Life 54-item instrument.

Figure 3. Mental processing speed, and verbal and visual memory, were preserved over 4 years[a]



[a]The central horizontal line represents the median value; Box: Q1–Q3 values; whisker: minimum and maximum values.
BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT-II, California Verbal Learning Test-second edition; Q, quartile; SDMT, Symbol Digit Modalities Test.

CONCLUSIONS

The CLARIFY-MS Extension study demonstrated improvements in HRQoL and preserved cognitive function (mental processing speed, verbal and visuospatial memory) in CladT-treated patients with highly active RMS up to 4 years after the initial dose, including the treatment-free period Years 3–4

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

References: 1. Brochet B, et al. *Mult Scler.* 2023;29(14):1808-1818.
2. Selmaj K, et al. Poster presented at ECTRIMS 2024. P846.
3. Petracca M, et al. *Front Neurol.* 2024;15:1394867.

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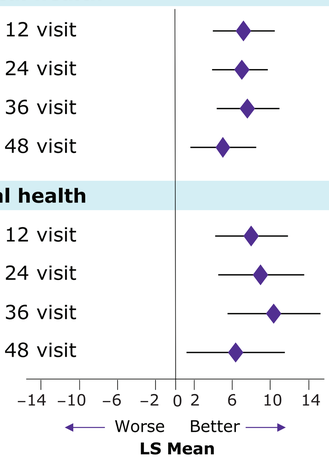
SUPPLEMENTARY MATERIAL

Supplementary Figure 1. Changes in MSQoL-54 scores from CLARIFY-MS parent study baseline to Month 48

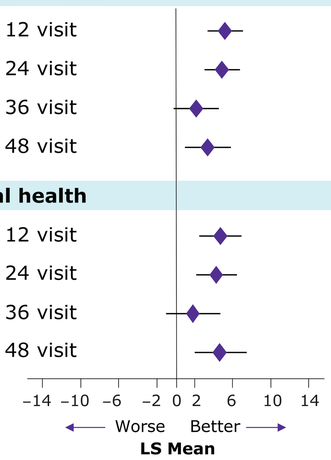
(A) Tx-naïve subgroup

Total (N=74)	n	LS mean [95% CI]	p-value
Physical health			
Month 12 visit	70	7.05 [3.94, 10.17]	<0.0001
Month 24 visit	70	6.87 [3.89, 9.84]	<0.0001
Month 36 visit	70	7.43 [4.22, 10.65]	<0.0001
Month 48 visit	70	4.95 [1.62, 8.28]	0.0044
Mental health			
Month 12 visit	70	7.78 [4.10, 11.46]	<0.0001
Month 24 visit	70	8.78 [4.45, 13.11]	0.0001
Month 36 visit	70	10.12 [5.41, 14.82]	<0.0001
Month 48 visit	70	6.23 [1.24, 11.22]	0.0155



(B) Tx-experienced subgroup

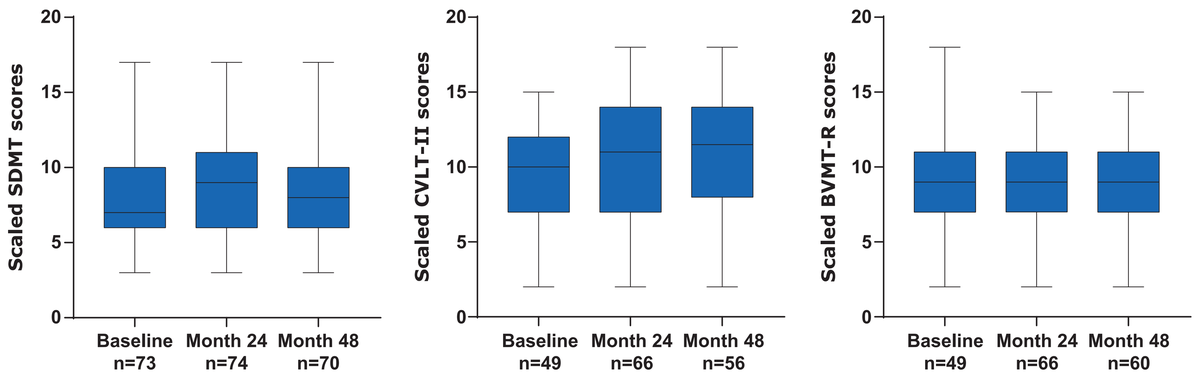
Total (N=206)	n	LS mean [95% CI]	p-value
Physical health			
Month 12 visit	195	5.32 [3.45, 7.19]	<0.0001
Month 24 visit	195	4.96 [3.09, 6.83]	<0.0001
Month 36 visit	195	2.23 [−0.17, 4.63]	0.0684
Month 48 visit	195	3.47 [1.04, 5.90]	0.0054
Mental health			
Month 12 visit	195	4.81 [2.57, 7.05]	<0.0001
Month 24 visit	195	4.37 [2.19, 6.56]	0.0001
Month 36 visit	195	1.89 [−1.00, 4.77]	0.1979
Month 48 visit	195	4.78 [2.00, 7.56]	0.0009



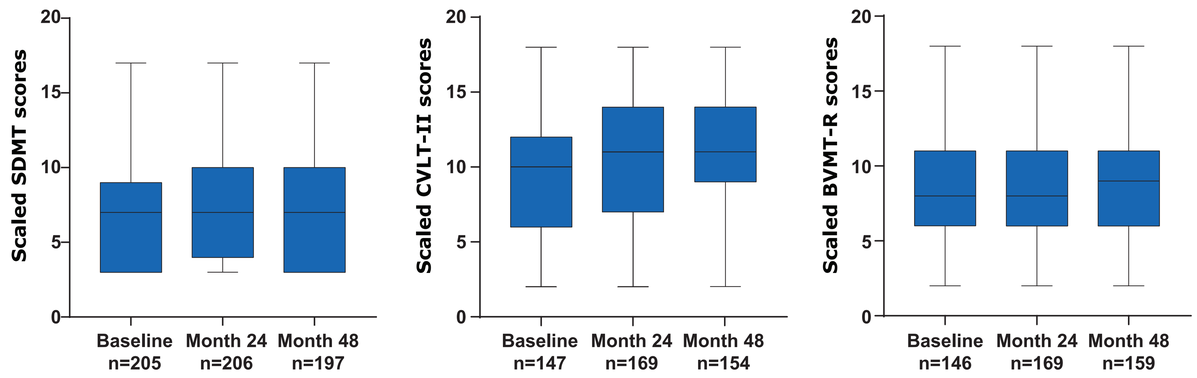
CI, confidence interval; LS, least-squares; MSQoL-54, Multiple Sclerosis Quality of Life 54-item instrument; Tx, treatment.

Supplementary Figure 2. BICAMS scores over 4 years in subgroups

(A) Tx-naïve subgroup

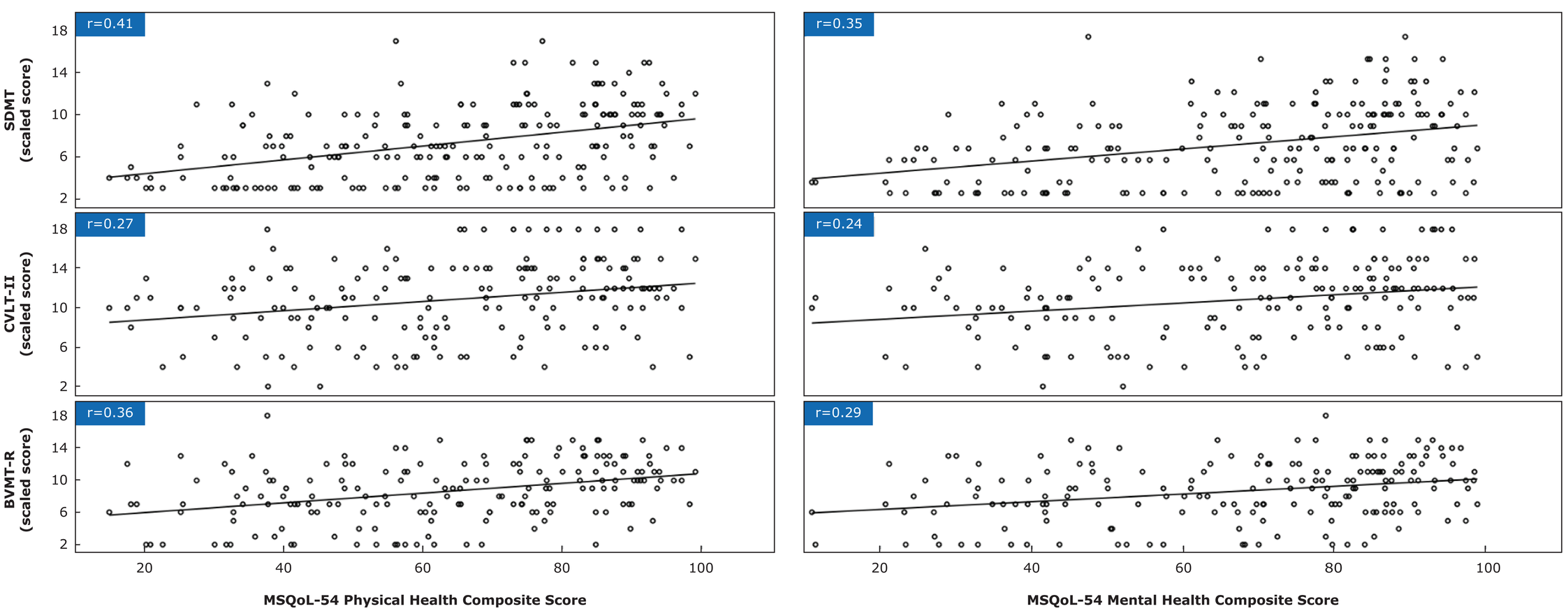


(B) Tx-experienced subgroup



The central horizontal line represents the median value; Box: Q1–Q3 values; whisker: minimum and maximum values.
BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test–Revised; CVLT–II, California Verbal Learning Test–II; Q, quartile; SDMT, Symbol Digit Modalities Test; Tx, treatment.

Supplementary Figure 3. Correlations between BICAMS parameters and MSQoL-54 scores at Month 48[a]



[a]Reference values for correlation coefficient (r) - Low: r=0.10–0.29; moderate: r=0.30–0.59; high: r=0.60–1.00
BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test–Revised; CVLT–II, California Verbal Learning Test–II; MSQoL-54, Multiple Sclerosis Quality of Life 54-item instrument; SDMT, Symbol Digit Modalities Test.

SUPPLEMENTARY MATERIAL

Author Affiliations

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Author Disclosures

DL has participated in speaker bureau for Almirall, Bayer, Biogen, Bristol-Myers Squibb, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, and Teva; has received consultancy fees from Bayer, Biogen, BMS, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, and Teva; and has received research grants from Bayer, Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, and Novartis.

BB has received consultancy fees and speaker fees from Celgene (Bristol-Myers Squibb), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi.

EKH has received honoraria/research support from Actelion (Janssen/Johnson and Johnson), Biogen, Celgene (Bristol-Myers Squibb), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, and Teva; has served on advisory boards for Actelion (Janssen/Johnson and Johnson), Biogen, Celgene (Bristol-Myers Squibb), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi, and has been supported by the Czech Ministry of Education–project Cooperation LF1, research area Neuroscience, and the project National Institute for Neurological Research (Programme EXCELES, ID project No LX22NPO5107)–funded by the European Union-Next Generation EU.

FP has received personal compensation for speaking activities or serving on advisory board for Alexion, Almirall, Biogen, Bristol-Myers Squibb, Johnson and Johnson, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi. He further received research grants by Alexion, Almirall, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, Health Italian Minister, and MIUR. He is an Associate Editor of *Frontiers in Neurology*.

XM has received compensation for lecture honoraria and travel expenses, participation in scientific meetings, clinical trial steering committee membership, or clinical advisory board participation for his institution in recent years from AbbVie, Actelion, Alexion, Bial PD, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Hoffmann-La Roche, Immunic Therapeutics, Janssen, MedDay, Medscape, Mylan, Nervgen, Neuraxpharm, Novartis, Peervoice, Samsung-Bioepis, Sandoz, Sanofi-Genzyme, Teva, TG Therapeutics, Excemed, ECTRIMS, MSIF, and NMSS or any of their affiliates.

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AS is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany.

MD is employee of Merck Santé S.A.S., Lyon, France, an affiliate of the healthcare business of Merck KGaA, Darmstadt, Germany.

KS has received honoraria for speaking, consulting, and serving on advisory boards for Biogen, Celgene (Bristol-Myers Squibb), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and TG Therapeutics.

ASo has served on advisory boards for Almirall and the healthcare business of Merck KGaA, Darmstadt, Germany and has been invited to speak on behalf of the same companies. She has received research grants from the Italian MS Society.

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