Stabilization of Cognitive Function in Patients With Highly Active Relapsing Multiple Sclerosis Treated With Cladribine Tablets During the 2-Year CLARIFY-MS Study

D. Langdon[1], B. Brochet[2], E. K. Havrdova[3], J. Lechner-Scott[4,5], X. Montalban[6], F. Patti[7], F. Piehl[8], K. Selmaj[9], A. Solari[10], N. Alexandri[11], A. Nolting[11], A. Lehn[11], A. Smyk[11], on behalf of the CLARIFY-MS Investigators

[1]Department of Psychology, Royal Holloway, University of London, Egham, UK; [2]INSERM U 1215, University of Bordeaux, Bordeaux, France; [3]Charles University, First Medical Faculty, Department of Neurology and Center for Clinical Neuroscience, Prague, Czech Republic; [4]University of Newcastle, Newcastle, NSW, Australia; [5]Division of Neurology, John Hunter Hospital, Newcastle, NSW, Australia; [6]Department of Neurology-Neuroimmunology Centre of Multiple Sclerosis of Catalonia (Cemcat), University Hospital Vall d'Hebron, Barcelona, Spain; [7]Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, University of Catania, and Azienda Ospedaliero Universitaria Policlinico "G Rodolico"- San Marco, University of Catania, Italy; [8]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [9]Center for Neurology, Lodz, Poland; [10]Unit of Neuroepidemiology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [11]The healthcare business of Merck KGaA, Darmstadt, Germany.

CONCLUSION

Cognitive function, including processing speed, verbal and visuospatial memory remained stable over two years of treatment with CladT in both pre-treatment naïve and previously DMT-exposed patients with highly active RMS

INTRODUCTION

- Cognitive impairment, a common manifestation of multiple sclerosis (MS), can develop subtly over time or, more rarely, in association with acute inflammatory relapses. Approximately 40%–70% of patients with MS experience cognitive impairment, which negatively impacts their quality of life (QoL)[1]
- Existing data sets from controlled trials of cladribine tablets (CladT) reported numerous clinical and safety outcomes; however, these do not include a comprehensive evaluation of CladT's effects on cognitive function
- The CLARIFY-MS study (NCT03369665) evaluated the health-related QoL of patients with highly active relapsing MS (RMS) treated with CladT. The study also assessed CladT's effects on cognitive function using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery

OBJECTIVE

To analyze the effect of CladT on cognitive function over a two-year period in patients with highly active RMS from the CLARIFY-MS study

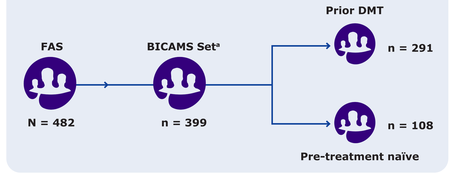
METHODS

- CLARIFY-MS was a 2-year, prospective, open-label, single-arm, multicenter, phase IV study **(Supplementary Figure 1)**
- Patients with highly active RMS were recruited per the Summary of Product Characteristics of CladT, and eligible patients received CladT at a cumulative dose of 3.5 mg/kg over 2 years
  - Highly active RMS was defined as one relapse in the previous year and ≥1 T1 gadolinium-enhancing lesion or ≥9 T2 lesions, while receiving treatment with other disease-modifying therapies (DMTs); or ≥2 relapses in the previous year, whether on DMT treatment or not

METHODS

- The BICAMS battery was designed to assess the cognitive function of patients with MS and has been validated for quick and easy-to-administer assessments[2]
- The BICAMS battery comprised:
  - Symbol Digit Modalities Test (SDMT)
  - California Verbal Learning Test-II (CVLT-II; first 5 recalls)
  - Brief Visuospatial Memory Test-Revised (BVMT-R; first 3 recalls)
- Changes in cognitive function compared with Baseline were measured using the paper-based version of BICAMS at Months 12 and 24; higher scores indicate better performance
- **BICAMS Set:** All patients from the full analysis set enrolled in a country where BICAMS was applied **(Figure 1)**
- The BICAMS battery was implemented in countries where a validated local language translation of both CVLT-II and BVMT-R were available
- Subgroup analyses were performed for patients who did not receive any DMTs before CladT (the pre-treatment naïve subgroup) and those who received DMTs at any time prior to the start of treatment with CladT (the prior DMT subgroup)
- Correlations between BICAMS parameters and the annualized percentage brain volume change (PBVC) from Baseline to Month 24 were assessed

Figure 1: Patient population analyzed



[a]Local translations were available in Australia, Belgium, Czech Republic, France, Greece, Hungary, Italy, Lithuania, Norway, Poland, Portugal, Spain, and the United Kingdom. In Belgium, only French versions were available. As each patient's native language was not reported in the clinical database, all patients from Belgium were included in the BICAMS set.

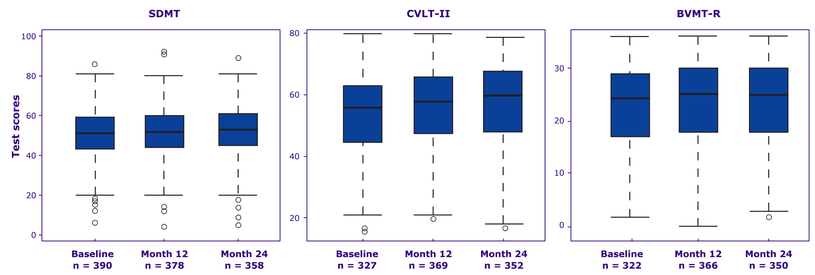
BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; **DMT**, disease-modifying therapy; **FAS**, full analysis set

RESULTS

BICAMS Scores

- SDMT scores remained stable over time, with no absolute changes recorded at Months 12 and 24 versus Baseline **(Figure 2; Supplementary Table 1A)**
- CVLT-II and BVMT-R scores increased numerically from Baseline to Month 12; these increments were sustained through Month 24 **(Figure 2; Supplementary Tables 1B,C)**
- BICAMS scores did not differ substantially between the pre-treatment naïve and prior DMT subgroups **(Supplementary Tables 1A-C)**

Figure 2: BICAMS scores over time (BICAMS Set)[a]



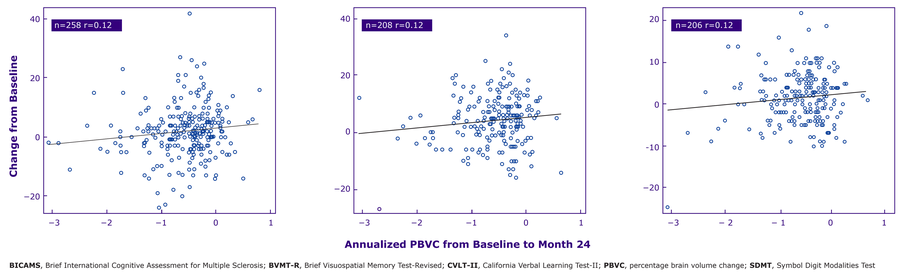
[a]Practice effects were not evaluated

BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; **BVMT-R**, Brief Visuospatial Memory Test-Revised; **CVLT-II**, California Verbal Learning Test-II; **SDMT**, Symbol Digit Modalities Test

BICAMS Scores and PBVC

- No correlation was observed between annualized PBVC from Baseline to Month 24 and changes in BICAMS parameters **(Figure 3)**

Figure 3: Correlation of BICAMS scores with brain volume



BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; **BVMT-R**, Brief Visuospatial Memory Test-Revised; **CVLT-II**, California Verbal Learning Test-II; **PBVC**, percentage brain volume change; **SDMT**, Symbol Digit Modalities Test

GET ADDITIONAL CONTENT

REFERENCES: 1. DeLuca GC, et al. *Brain Pathol*. 2015;25(1):79–98; 2. Langdon DW, et al. *Mult Scler*. 2012;18(6):891–898.

DISCLOSURES: DL has participated in speaker bureau for Almirall, Bayer, Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, and Teva; and has received consultancy fees from Bayer, Biogen, 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, speaker fees, research grants (non-personal), or honoraria from Biogen, Celgene (BMS), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi. **EKH** has received honoraria/research support from Actelion (Janssen/J&J), Biogen, Celgene (BMS), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, and Teva; and has served on advisory boards for Actelion (Janssen/J&J), Biogen, Celgene (BMS), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi. **JL-S** has accepted travel compensation from Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, and Novartis. Her institution received the honoraria for talks and advisory board commitments as well as research grants from Biogen, Celgene (BMS), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, and Teva. **XM** has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with AbbVie, Actelion, Alexion, Biogen, Celgene (BMS), EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, MedDay, the healthcare business of Merck KGaA, Darmstadt, Germany, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS. **FPa** has served on scientific Advisory Boards for Almirall, Bayer, Biogen, Celgene (BMS), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, and Teva; he also received speaker honoraria from the same companies and non-personal research grants for his department from Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, and Sanofi. **FPi** has received research grants from the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, and Sanofi, and fees for serving as a member of the DMC in clinical trials with Parexel, Lundbeck and Roche. **KS** has received honoraria for speaking, consulting and serving for advisory boards for Biogen, Celgene (BMS), the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and TG Therapeutics. **AS** has served on advisory boards for the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, and Sanofi, and has been invited to speak on behalf of Almirall, Biogen, Excemed, the healthcare business of Merck KGaA, Darmstadt, Germany, and Teva. **NA, AN, AL** and **ASm**, are employees of the healthcare business of Merck KGaA, Darmstadt, Germany.

Medical writing assistance was provided by Pritorthi Bhattacharjee of Merck Specialties Pvt. Ltd., Bengaluru, India, an affiliate of Merck KGaA, Darmstadt, Germany.

Presented at ACTRIMS Forum | 23–25 February 2023 | San Diego, California, USA

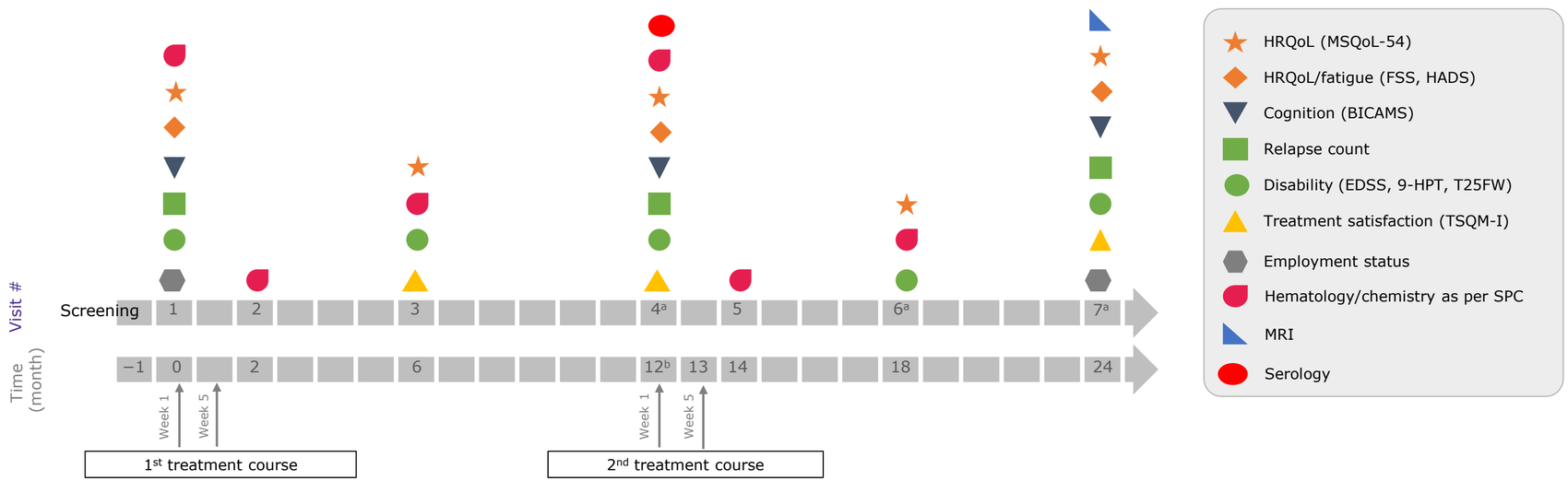
This study was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

February 2023

Supplementary Figure 1: CLARIFY-MS key inclusion criteria and study Design

Key Inclusion Criteria

- **Aged ≥18 years**
- **EDSS score ≤5.0**
- **Diagnosed with highly active relapsing MS**
  Defined as one relapse in the previous year and ≥1 T1 gadolinium-enhancing lesions or ≥9 T2 lesions while on therapy along with other DMTs or ≥2 relapses in the previous year regardless of DMT



[a]0–3-month window for these trial visits. [b]Second treatment course may be delayed for some patients.

#, number; **9-HPT,** Nine-Hole Peg Test; **BICAMS,** Brief International Cognitive Assessment for Multiple Sclerosis; **DMT,** disease-modifying therapy; **EDSS,** Expanded Disability Status Scale; **FSS,** Fatigue Severity Scale; **HADS,** Hospital Anxiety and Depression Scale; **HRQoL,** health-related quality of life; **MRI,** magnetic resonance imaging; **MSQoL-54,** Multiple Sclerosis Quality of Life-54 instrument; **RMS,** relapsing multiple sclerosis; **SPC,** summary of product characteristics; **T25FW,** Timed 25-Foot Walk; **TSQM,** Treatment Satisfaction Questionnaire for Medication.

Supplementary Table 1A: SDMT scores over time

		Pre-treatment naïve (n = 108)		Prior DMT (n = 291)		Total (N = 399)	
Visit	**Statistic**	**Absolute**	**Absolute change from Baseline**	**Absolute**	**Absolute change from Baseline**	**Absolute**	**Absolute change from Baseline**
Baseline	**n (%)**	106 (98.1)	–	284 (97.6)	–	390 (97.7)	–
	Median	**52.5**	–	**50.0**	–	**51.0**	–
	Q1; Q3	45.0; 60.0	–	41.5; 58.0	–	43.0; 59.0	–
	Min; Max	15; 86	–	6; 81	–	6; 86	–
Month 12	**n (%)**	100 (94.3)	98 (92.5)	278 (97.2)	273 (95.5)	378 (96.4)	371 (94.6)
	Median	**54.0**	2.0	**51.0**	1.0	**52.0**	2.0
	Q1; Q3	49.0; 61.0	−2.0; 6.0	43.0; 60.0	−3.0; 5.0	44.0; 60.0	−2.0; 6.0
	Min; Max	12; 92	−19; 24	4; 91	−46; 31	4; 92	−46; 31
Month 24	**n (%)**	97 (95.1)	95 (93.1)	261 (93.2)	256 (91.4)	358 (93.7)	351 (91.9)
	Median	**55.0**	1.0	**52.0**	2.0	**53.0**	2.0
	Q1; Q3	48.0; 62.0	−2.0; 6.0	44.0; 61.0	−3.0; 6.0	45.0; 61.0	−3.0; 6.0
	Min; Max	15; 81	−24; 27	6; 89	−24; 42	6; 89	−24; 42

DMT, disease-modifying therapy; **SDMT,** Symbol Digit Modalities Test

Supplementary Table 1B: CVLT-II scores over time

		Pre-treatment naïve (n = 108)		Prior DMT (n = 291)		Total (N = 399)	
Visit	**Statistic**	**Absolute**	**Absolute change from Baseline**	**Absolute**	**Absolute change from Baseline**	**Absolute**	**Absolute change from Baseline**
Baseline	**n (%)**	87 (80.6)	–	240 (82.5)	–	327 (82.0)	–
	Median	**56.0**	–	**55.5**	–	**56.0**	–
	Q1; Q3	46.0; 62.0	–	45.0; 64.0	–	45.0; 63.0	–
	Min; Max	15; 77	–	21; 80	–	15; 80	–
Month 12	**n (%)**	99 (93.4)	79 (74.5)	270 (94.4)	227 (79.4)	369 (94.1)	306 (78.1)
	Median	**56.0**	3.0	**59.0**	4.0	**58.0**	3.0
	Q1; Q3	45.0; 64.0	−5.0; 7.0	48.0; 66.0	−2.0; 10.0	48.0; 66.0	−2.0; 9.0
	Min; Max	20; 79	−16; 48	20; 80	−23; 22	20; 80	−23; 48
Month 24	**n (%)**	97 (95.1)	77 (75.5)	255 (91.1)	213 (76.1)	352 (92.1)	290 (75.9)
	Median	**60.0**	5.0	**60.0**	5.0	**60.0**	5.0
	Q1; Q3	47.0; 67.0	0.0; 11.0	48.0; 68.0	−1.0; 10.0	48.0; 68.0	−1.0; 11.0
	Min; Max	18; 79	−27; 55	17; 79	−32; 34	17; 79	−32; 55

CVLT-II, California Verbal Learning Test-II; **DMT,** disease-modifying therapy

Supplementary Table 1C: BVMT-R scores over time

		Pre-treatment naïve (n = 108)		Prior DMT (n = 291)		Total (N = 399)	
Visit	**Statistic**	**Absolute**	**Absolute change from Baseline**	**Absolute**	**Absolute change from Baseline**	**Absolute**	**Absolute change from Baseline**
Baseline	**n (%)**	86 (79.6)	–	236 (81.1)	–	322 (80.7)	–
	Median	**24.0**	–	**23.5**	–	**24.0**	–
	Q1; Q3	18.0; 28.0	–	17.0; 29.0	–	17.0; 29.0	–
	Min; Max	3; 36	–	2; 36	–	2; 36	–
Month 12	**n (%)**	100 (94.3)	79 (74.5)	266 (93.0)	223 (78.0)	366 (93.4)	302 (77.0)
	Median	**25.0**	2.0	**25.0**	2.0	**25.0**	2.0
	Q1; Q3	17.5; 29.0	−2.0; 5.0	19.0; 30.0	−2.0; 5.0	18.0; 30.0	−2.0; 5.0
	Min; Max	2; 35	−21; 23	0; 36	−16; 16	0; 36	−21; 23
Month 24	**n (%)**	97 (95.1)	76 (74.5)	253 (90.4)	210 (75.0)	350 (91.6)	286 (74.9)
	Median	**24.0**	2.0	**25.0**	2.0	**25.0**	2.0
	Q1; Q3	20.0; 30.0	−2.0; 6.0	19.0; 30.0	−2.0; 5.0	19.0; 30.0	−2.0; 5.0
	Min; Max	2; 35	−25; 22	3; 36	−10; 16	2; 36	−25; 22

BVMT-R, Brief Visuospatial Memory Test-Revised; **DMT,** disease-modifying therapy