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Long-term Effects of Cladribine Tablets Treatment on Cognition, Relapses, MRI and Safety Outcomes in Patients with Relapsing Multiple Sclerosis: 4-year Results from the CLARIFY-MS Extension Study

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RESEARCH IN CONTEXT

1. **These data demonstrate the continued efficacy of cladribine tablets (CladT) over 4 years including the treatment-free Year 3–4 period in terms of cognitive function, annualised relapse rate (ARR), and magnetic resonance imaging (MRI) activity.**
2. **Symbol Digit Modalities Test (SDMT) score changes at 48 months (vs baseline) echo those seen in the MAGNIFY-MS study at 24 months[1] and demonstrate continued preservation of cognitive ability in patients with relapsing multiple sclerosis (RMS) treated with CladT.**

OBJECTIVE

To report the 4-year data on cognitive function, efficacy and safety from the CLARIFY-MS Extension study.

INTRODUCTION

The 2-year, open-label, single-arm, phase 4 CLARIFY-MS (NCT03369665) study demonstrated improvements in health-related quality of life (HRQoL) and retained cognitive function in patients with RMS treated with CladT (3.5 mg/kg cumulative dose over 2 years).[2]

CLARIFY-MS Extension (NCT04776213), a follow-up study to CLARIFY-MS, assessed the effects of CladT on cognition and HRQoL in patients with RMS up to 4 years after the initial dose (**Supplementary Figure 1**).

METHODS

- No CladT treatment was planned as per protocol during the Extension study[a]
- Data were analysed for all patients combined, comprising both Tx (treatment)-naïve and Tx-experienced
- A 4-point change in SDMT scores is widely accepted as clinically relevant, whereas an 8-point change is considered as a more reliable change to determine cognitive decline in patients with MS at an individual level.[3] Therefore, a post-hoc analysis was conducted to assess individual 4- or 8-point[b,c] changes in SDMT scores at Month 48 vs CLARIFY-MS baseline

Study endpoints

Primary endpoint

Percentage of patients with no or minimal decline in cognitive function[d,e] at Year 4 (vs CLARIFY-MS baseline)

Other key selected endpoints

ARR[f]: Over the 4 years and 2-year Extension study

MRI[g]
- T1 gadolinium-enhancing (Gd+) lesions: over the 2-year Extension and 4-year total study periods
- New or enlarging T2 lesions: over the 2-year Extension study

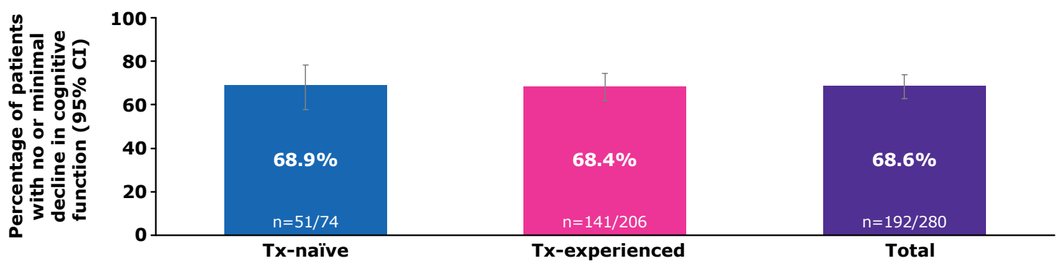
Safety: occurrences of AEs and serious AEs over the 2-year Extension study

[a]n=8 had CladT re-treatment and n=29 switched to another DMT during the 4-year observation period of the Extension study. [b]4-point change - Increase: change from CLARIFY-MS baseline in SDMT ≥4 at the Month 48 visit, stable: −4< change from CLARIFY-MS baseline in SDMT at the Month 48 visit <4, decrease: change from CLARIFY-MS baseline in SDMT ≤−4 at the Month 48 visit. [c]8-point change - Increase: change from CLARIFY-MS baseline in SDMT ≥8 at the Month 48 visit, stable: −8< change from CLARIFY-MS baseline in SDMT at the Month 48 visit <8, decrease: change from CLARIFY-MS baseline in SDMT ≤−8 at the Month 48 visit. [d]Defined as an improved or stable SDMT score or a decline of 4 points or less in the SDMT score, at 4 years after initial dose of CladT (Month 48) compared to SDMT score prior to initial dose of CladT (CLARIFY-MS baseline). [e]95% confidence intervals for SDMT scores were computed according to Wilson's score. [f]ARRs were estimated using Poisson regression model. [g]MRI and safety data were analysed descriptively.

RESULTS

- A total of 280 patients with RMS entered the CLARIFY-MS Extension study. There were 74 (26.4%) Tx-naïve patients and 206 (73.6%) Tx-experienced patients; females, 71.8% (n=201); mean age, 41.4 years. Full patient characteristics are presented in **Supplementary Table 1**

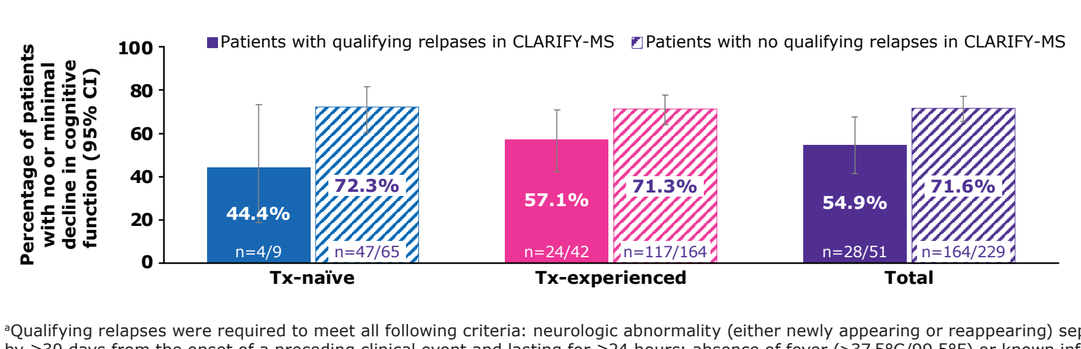
Figure 1: More than 68% of patients had no or minimal decline[a] in cognitive function (SDMT) from CLARIFY-MS baseline to Month 48



[a]Defined as an improved or stable SDMT score or a decline of 4 points or less in the SDMT score, at 4 years after initial dose of CladT (Month 48) compared to SDMT score prior to initial dose of CladT (CLARIFY-MS baseline).

CI, confidence interval; **CladT,** cladribine tablets; **SDMT,** Symbol Digit Modalities Test; **Tx,** treatment.

Figure 2: 72% of patients who did not have any qualifying relapses[a] during CLARIFY-MS had no or minimal decline in SDMT scores at Month 48 vs 55% of those who had relapses

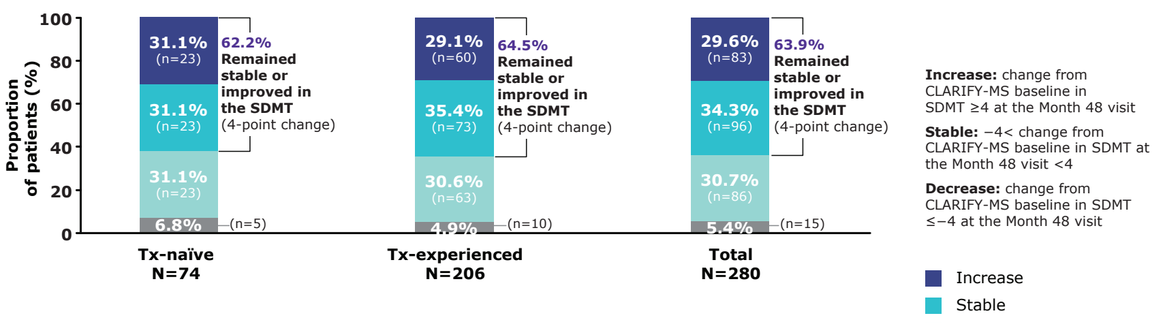


[a]Qualifying relapses were required to meet all following criteria: neurologic abnormality (either newly appearing or reappearing) separated by ≥30 days from the onset of a preceding clinical event and lasting for ≥24 hours; absence of fever (>37.5°C/99.5°F) or known infection; and objective neurologic impairment, correlating with the patient's reported symptoms, defined as either an increase in ≥1 of the functional system scores of the EDSS or an increase of the total EDSS score.

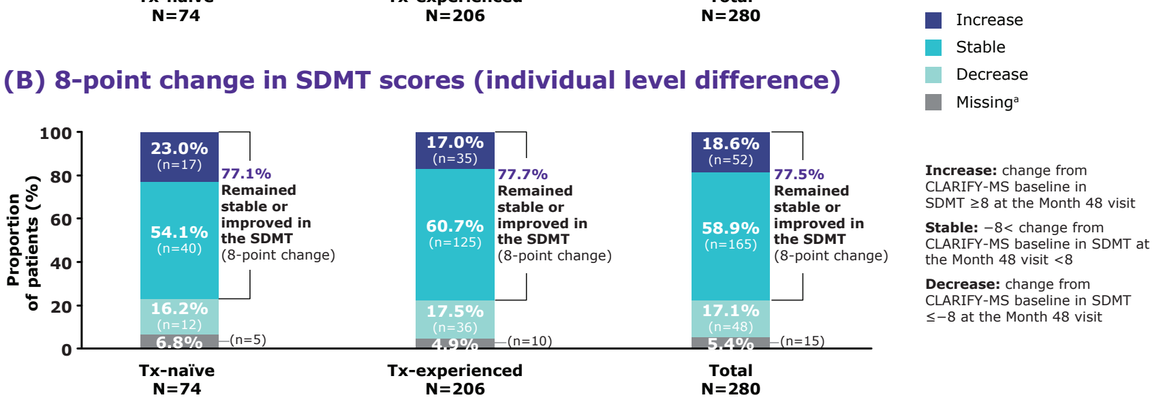
CI, confidence interval; **EDSS,** Expanded Disability Status Scale; **SDMT,** Symbol Digit Modalities Test; **Tx,** treatment.

Figure 3: As determined by an individual level 4- or 8-point change, a high proportion of patients had increased or stable SDMT scores at Month 48 vs the CLARIFY-MS baseline

(A) 4-point change in SDMT scores (individual level difference)



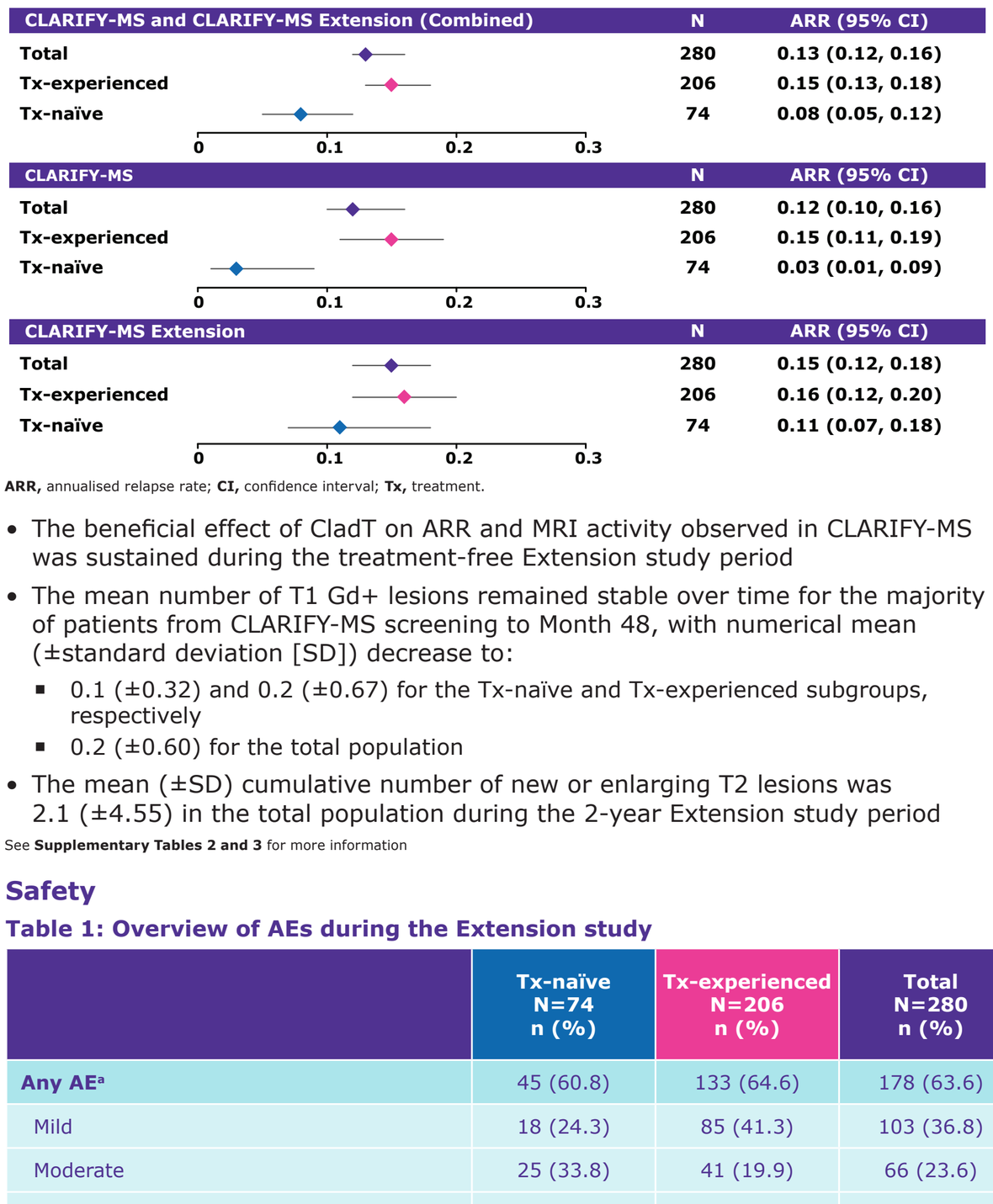
(B) 8-point change in SDMT scores (individual level difference)



[a]Missing: SDMT at CLARIFY-MS baseline or at Month 48 visit not available.

CI, confidence interval; **SDMT,** Symbol Digit Modalities Test; **Tx,** treatment.

Figure 4: Low ARRs were observed over 4 years, especially for Tx-naïve patients



ARR, annualised relapse rate; **CI,** confidence interval; **Tx,** treatment.

- The beneficial effect of CladT on ARR and MRI activity observed in CLARIFY-MS was sustained during the treatment-free Extension study period
- The mean number of T1 Gd+ lesions remained stable over time for the majority of patients from CLARIFY-MS screening to Month 48, with numerical mean (±standard deviation [SD]) decrease to:
  - 0.1 (±0.32) and 0.2 (±0.67) for the Tx-naïve and Tx-experienced subgroups, respectively
  - 0.2 (±0.60) for the total population
- The mean (±SD) cumulative number of new or enlarging T2 lesions was 2.1 (±4.55) in the total population during the 2-year Extension study period

See **Supplementary Tables 2 and 3** for more information

Safety

Table 1: Overview of AEs during the Extension study

	Tx-naïve N=74 n (%)	Tx-experienced N=206 n (%)	Total N=280 n (%)
Any AE[a]	45 (60.8)	133 (64.6)	178 (63.6)
Mild	18 (24.3)	85 (41.3)	103 (36.8)
Moderate	25 (33.8)	41 (19.9)	66 (23.6)
Severe	2 (2.7)	7 (3.4)	9 (3.2)
Any study treatment-related AE[a]	4 (5.4)	11 (5.3)	15 (5.4)
Mild	0	7 (3.4)	7 (2.5)
Moderate	2 (2.7)	4 (1.9)	6 (2.1)
Severe	2 (2.7)	0	2 (0.7)
Any serious AE	5 (6.8)	10 (4.9)	15 (5.4)
Any study treatment-related serious AE	2 (2.7)	0	2 (0.7)

[a]Worst severity per patient is reported. MedDRA version 26.0.

AE, adverse event; **MeDRA,** Medical Dictionary for Regulatory Activities; **Tx,** treatment.

- No AEs leading to study discontinuation, or any death was reported during the Extension study
- Urinary tract infection (1.1%) and herpes zoster (0.7%) were the most common study treatment-related AEs during the Extension study period (**Supplementary Table 4**)
- The observed malignancies showed no clustering. The malignancy rate was within the expected range for the entirety of patients treated with CladT

CONCLUSIONS

- **The CLARIFY-MS Extension study demonstrated sustained benefits of CladT treatment on cognition, relapse rates and MRI outcomes in patients with RMS up to 4 years after the initial dose of CladT. The safety profile of CladT was confirmed over 4 years and remains consistent with previous data.**

SCAN FOR AFFILIATIONS, DISCLOSURES AND SUPPLEMENTARY MATERIALS

References: 1. Vermersch P et al. *Mult Scler.* 2024;30:(1S)18–270 [P070]; 2. Brochet B et al. *Mult Scler.* 2023;29(14):1808–1818; 3. Weinstock Z et al. *Mult. Scler.* 2022;28:1101–1111.

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Supplementary Materials

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Author Disclosures

KS has received honoraria for speaking, consulting, and serving on advisory boards for Biogen, Celgene (BMS), Merck, Novartis, Roche, and TG Therapeutics.

DL has participated in speaker bureau for Almirall, Bayer, Biogen, 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.

BB has received consultancy fees, speaker fees, research grants (non-personal), or honoraria from Biogen, Celgene (BMS), Merck, Novartis, Roche, and Sanofi.

AS has served on advisory boards for Merck, Novartis, and Sanofi and has been invited to speak on behalf of Almirall, Biogen, Excemed, Merck, and Teva.

EKH has received honoraria/research support from Actelion (Janssen/J&J), Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva; has served on advisory boards for Actelion (Janssen/J&J), Biogen, Celgene(BMS), Merck, Novartis, Roche, and Sanofi, and has been supported by the Czech Ministry of Education – project Cooperatio 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 served on scientific advisory boards for Almirall, Bayer, Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva; and has received speaker honoraria from the same companies and non-personal research grants for his department from Biogen, Merck, Novartis, and Sanofi.

FPi has received research grants from Janssen, Merck, and Sanofi and fees as a member of the DMC in clinical trials with Lundbeck, Parexel, and Roche and preparation of witness statements for Novartis.

ASm, **AL** and **AN** are employees of Merck Healthcare KGaA, Darmstadt, Germany.

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, Bristol Myers Squibb/Celgene, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, MedDay, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF, and NMSS.

JL-S has accepted travel compensation from Biogen, Merck, and Novartis. Her institution receives the honoraria for talks and advisory board commitment as well as research grants from Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva.

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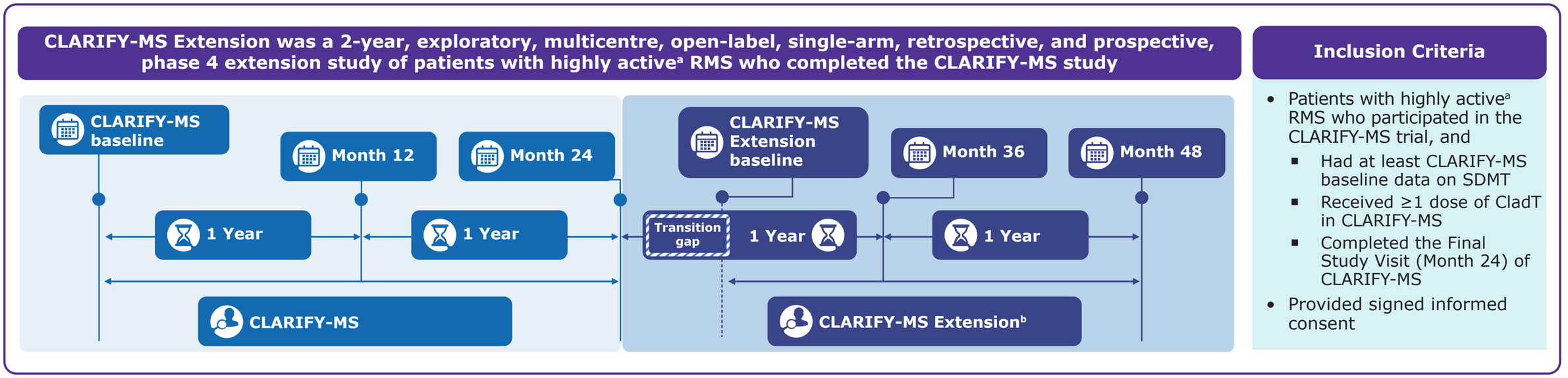
Supplementary Materials

Supplementary Figure 1: Study design



[a]Defined as one relapse in the previous year and ≥1 T1 gadolinium-enhancing lesions or ≥9 T2 lesions, while on therapy with other DMTs; or ≥2 relapses in the previous year, whether on DMT or not. [b]Months 36 and 48 were planned relative to the CLARIFY-MS baseline; a potential delay in Month 24 visit (i.e. the Final Study Visit of the CLARIFY-MS study) due to a delay in the initiation of the 2nd year CladT treatment did not affect the timing of Months 36 and 48. The CLARIFY-MS Extension baseline includes retrospective data collected from the potential transition gap (i.e., period between Month 24 and CLARIFY-MS Extension baseline) and prospective assessments.

CladT, cladribine tablets; **DMT,** disease-modifying therapy; **RMS,** relapsing multiple sclerosis; **SDMT,** Symbol Digit Modalities Test.

Supplementary Table 1: Baseline demographics and other disease characteristics

Characteristics	Tx-naïve N=74	Tx-experienced N=206	Total N=280
Female, n (%)[a]	49 (66.2)	152 (73.8)	201 (71.8)
Mean±SD age at informed consent, years[b]	39.4±12.1	42.1±9.7	41.4±10.4
Mean±SD time since onset of MS, months[a]	51.6±62.7	125.0±92.5	105.6±91.4
Number of relapses within 12 months prior to baseline, n (%)[a]			
0	0	2 (1.0)	2 (0.7)
1	22 (29.7)	140 (68.0)	162 (57.9)
2	49 (66.2)	58 (28.2)	107 (38.2)
>2	3 (4.1)	6 (2.9)	9 (3.2)
EDSS at baseline, n (%)[a]			
≤3	53 (71.6)	143 (69.4)	196 (70.0)
>3	21 (28.4)	63 (30.6)	84 (30.0)
Number of previous DMTs, n (%)[a]			
0	74 (100.0)	0	74 (26.4)
1	0	106 (51.5)	106 (37.9)
2	0	61 (29.6)	61 (21.8)
>2	0	39 (18.9)	39 (13.9)
Number of T1-Gd+ lesions, n (%)[a]			
No	44 (59.5)	131 (63.6)	175 (62.5)
Yes	24 (32.4)	59 (28.6)	83 (29.6)
Non-evaluable	6 (8.1)	16 (7.8)	22 (7.9)
Number of T2 lesions, n (%)[a]			
0	0	1 (0.5)	1 (0.4)
1–8	10 (13.5)	21 (10.2)	31 (11.1)
≥9	64 (86.5)	184 (89.3)	248 (88.6)

[a]CLARIFY-MS baseline; [b]Informed consent for CLARIFY-MS Extension study.

DMT, disease-modifying therapy; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **MS,** multiple sclerosis; **SD,** standard deviation; **Tx,** treatment.

Supplementary Materials

Supplementary Table 2: T1-Gd+ lesion count

Visit		Tx-naïve N=74		Tx-experienced N=206		Total N=280	
		Absolute	Absolute change from screening	Absolute	Absolute change from screening	Absolute	Absolute change from screening
CLARIFY-MS Screening	n (%)	68 (91.9)	-	190 (92.2)	-	258 (92.1)	-
	Mean±SD	**0.9±1.85**	**-**	**0.7±1.52**	**-**	**0.7±1.62**	**-**
CLARIFY-MS Month 24	n (%)	65 (87.8)	61 (82.4)	187 (90.8)	178 (86.4)	252 (90.0)	239 (85.4)
	Mean±SD	**0.1±0.48**	**-0.6±1.60**	**0.1±0.38**	**-0.6±1.47**	**0.1±0.41**	**-0.6±1.50**
CLARIFY-MS Extension Month 36	n (%)	65 (87.8)	60 (81.1)	187 (90.8)	172 (83.5)	252 (90.0)	232 (82.9)
	Mean±SD	**0.1±0.50**	**-0.7±1.88**	**0.1±0.70**	**-0.5±1.54**	**0.1±0.65**	**-0.6±1.63**
CLARIFY-MS Extension Month 48	n (%)	67 (90.5)	61 (82.4)	183 (88.8)	168 (81.6)	250 (89.3)	229 (81.8)
	Mean±SD	**0.1±0.32**	**-0.7±1.85**	**0.2±0.67**	**-0.5±1.68**	**0.2±0.60**	**-0.6±1.73**

Gd+, gadolinium-enhancing; **SD,** standard deviation; **Tx,** treatment.

Supplementary Table 3: New or enlarging T2 lesion count

Period		Tx-naïve N=74	Tx-experienced N=206	Total N=280
Year 3 Visit	n (%)	62 (83.8)	186 (90.3)	248 (88.6)
	Mean±SD	1.4±3.29	1.0±2.98	1.1±3.06
Year 4 Visit	n (%)	63 (85.1)	174 (84.5)	237 (84.6)
	Mean±SD	0.9±1.73	1.1±2.75	1.1±2.52
Extension Study Period - Cumulative number of new or enlarging T2 lesions[a]	n (%)	62 (83.8)	183 (88.8)	245 (87.5)
	Mean±SD	2.3±4.35	2.0±4.63	2.1±4.55

[a]Cumulative number of new or enlarging T2 lesions: Sum of number of new or enlarging T2 lesions during Year 3 and Year 4 Visit Period.

SD, standard deviation; **Tx,** treatment.

Supplementary Table 4: Tx-related AEs (Extension study)

Preferred term	Tx-naïve N=74 n (%)	Tx-experienced N=206 n (%)	Total N=280 n (%)
Patients with at least one AE	4 (5.4)	11 (5.3)	15 (5.4)
Urinary tract infection	0	3 (1.5)	3 (1.1)
Herpes zoster	1 (1.4)	1 (0.5)	2 (0.7)
Lymphopenia	1 (1.4)	0	1 (0.4)
Epiploic appendicitis	0	1 (0.5)	1 (0.4)
Large intestine polyp	0	1 (0.5)	1 (0.4)
Nausea	0	1 (0.5)	1 (0.4)
Asthenia	0	1 (0.5)	1 (0.4)
COVID-19	0	1 (0.5)	1 (0.4)
Oral herpes	0	1 (0.5)	1 (0.4)
Rhinitis	0	1 (0.5)	1 (0.4)
Muscular weakness	0	1 (0.5)	1 (0.4)
Chronic myeloid leukaemia	1 (1.4)	0	1 (0.4)
Papillary thyroid cancer	1 (1.4)	0	1 (0.4)

AEs reported during the Extension study Period (>0.04% in the total group). MedDRA version 26.0.

AE, adverse event; **COVID-19,** Coronavirus disease 2019; **MeDRA,** Medical Dictionary for Regulatory Activities; **Tx,** treatment.