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Long-Term Effect of Cladribine Tablets on Disability Progression and Improvement: Insights from Pooled Analyses of CLARIFY-MS and MAGNIFY-MS Studies

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RESEARCH IN CONTEXT

1. **Low rates of overall disability accumulation were confirmed over four years after cladribine tablets initiation in a large population of people with highly active multiple sclerosis.**
2. **Lasting stability or CDI was achieved with short-course cladribine tablets therapy without chronic immunosuppression.[1]**

OBJECTIVES

To investigate the long-term effects of cladribine tablets on confirmed disability progression (CDP) and confirmed disability improvement (CDI) along with other clinical outcomes in people with multiple sclerosis (PwMS).

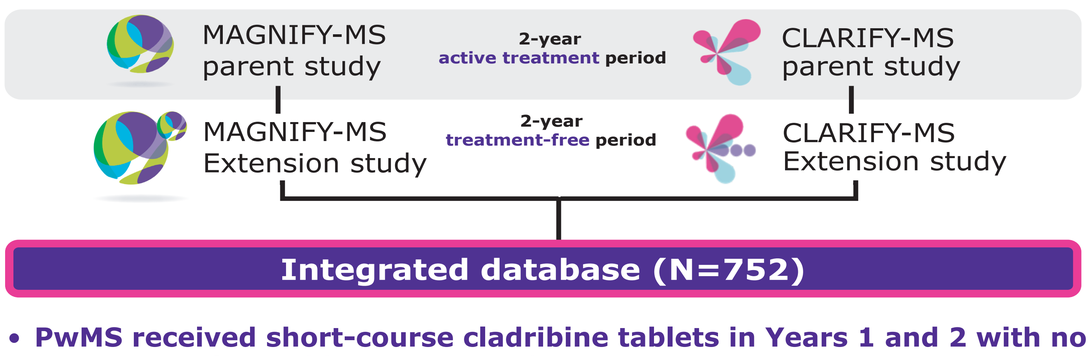
INTRODUCTION

- Cladribine tablets have been shown to reduce disease activity in PwMS, including progression independent of relapse activity and CDP.[1,2]
- CDI may serve as a valuable marker for identifying PwMS who experience the most pronounced benefit from cladribine tablets.
- Pooled data from an integrated database of clinical studies were used to investigate CDP and CDI in PwMS treated with cladribine tablets, as seen in **Figure 1**.

METHODS

- This was a 4-year analysis from an integrated database of the 2-year CLARIFY-MS and MAGNIFY-MS parent studies and their 2-year treatment-free Extension studies (**Figure 1**).

Figure 1. Study Design



- **PwMS received short-course cladribine tablets in Years 1 and 2 with no treatment planned in Years 3 and 4.**
- Time to first event was analysed by the non-parametric Kaplan-Meier (KM) method.
- Cognitive processing speed was assessed by Symbol Digit Modality Test (SDMT) score, and upper and lower limb mobility were assessed by the 9-hole peg test (9HPT) and the timed 25-foot walk (T25FW), respectively.
- P-values were used to characterise the subgroup differences but were not used for hypotheses testing.
- All analyses were exploratory. Outcomes were evaluated for all participants and by the following subgroups, based on parent study baseline (BL) demographics:
  - **Treatment (Tx)-naïve** vs **Tx-experienced**
  - **Age (≤50** vs **>50 years)**

Definitions:	
6-month CDP[a]	**6-month CDI[a]**
Increased EDSS score from BL of:	Decreased EDSS score from BL of:
≥1 point for BL EDSS score 0.5–5	≥1 point for BL EDSS score ≤5
≥0.5 points for BL EDSS score >5	≥0.5 points for BL EDSS score >5
≥1.5 points from BL EDSS score = 0	

[a]The 6-month CDP/CDI was reached when the increase/decrease was confirmed over a period of at least 6 months.
BL, baseline; **CDI**, confirmed disability improvement; **CDP**, confirmed disability progression; **EDSS**, Expanded Disability Status Scale.

- Stable was defined as without CDP or CDI.

RESULTS

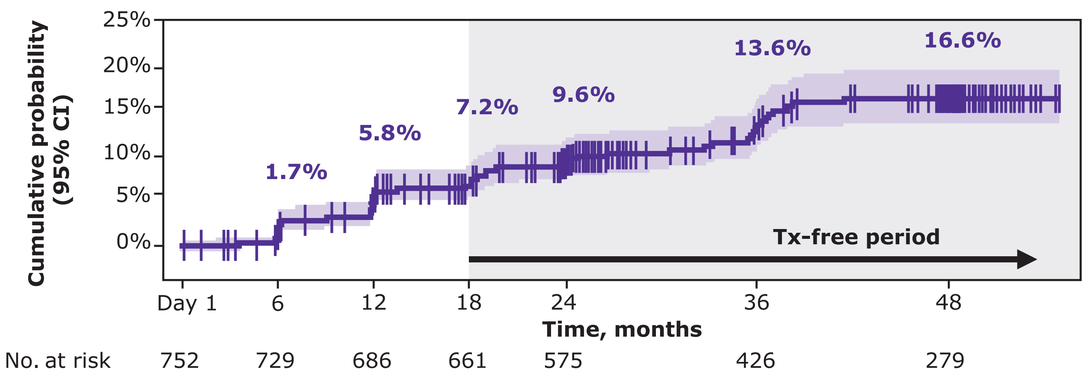
- A total of 752 PwMS (CLARIFY-MS, N=482; MAGNIFY-MS, N=270) were included (33.4% Tx-naïve; 88.4% aged ≤50 years). Participant BL demographics are shown in **Table 1**.
- By Month 48, most participants were stable (n=483, 64.2%, **Table 1**).

Table 1. Participant Baseline Demographics Grouped by CDP or CDI at Month 48

	CDP[a] (n=95)	CDI[a] (n=98)	Stable (n=483)
Age, years, mean (SD)	40.7 (9.8)	35.7 (9.2)	37.6 (10.2)
Time since MS diagnosis, months, mean (SD)	80.4 (77.3)	69.5 (80.1)	67.2 (73.9)
Number of relapses in the year before initiating cladribine tablets, mean (SD)	1.5 (0.7)	1.6 (0.7)	1.6 (0.7)
Participants with previous DMT use, n (%)	70 (73.7)	61 (62.2)	322 (66.7)

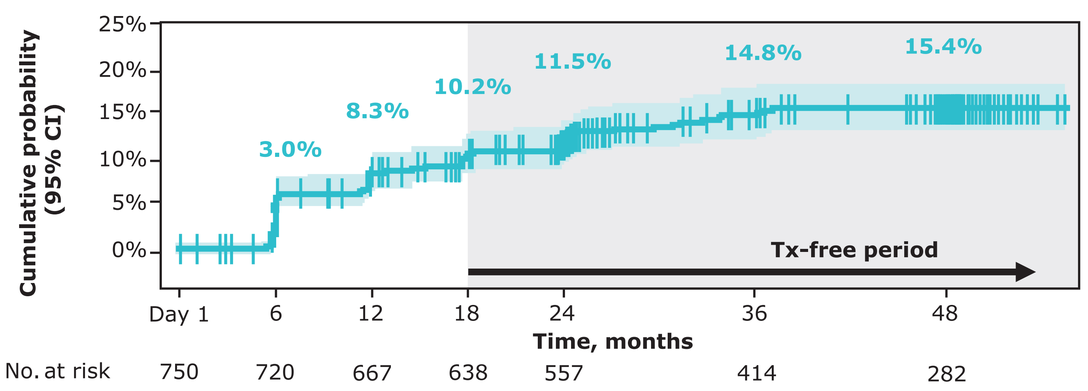
[a]The 6-month CDP/CDI was reached when the increase/decrease was confirmed over a period of at least 6 months.
CDI, confirmed disability improvement; **CDP**, confirmed disability progression; **DMT**, disease-modifying therapy; **MS**, multiple sclerosis; **SD**, standard deviation.

Figure 2. An Estimated 16.6% of PwMS Had CDP 4 Years After Initiating Cladribine Tablets



CDP, confirmed disability progression; **CI**, confidence interval; **PwMS**, people with multiple sclerosis; **Tx**, treatment.

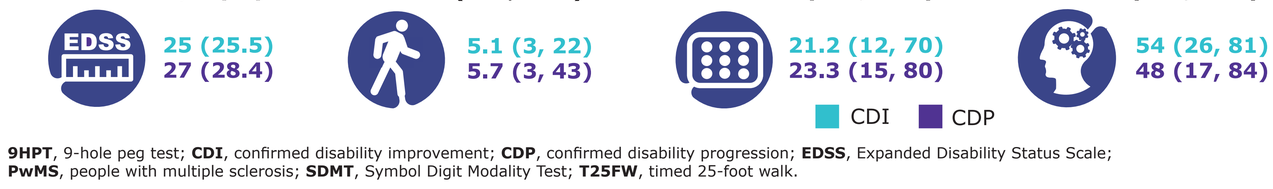
Figure 3. An Estimated 15.4% of PwMS Had CDI 4 Years After Initiating Cladribine Tablets



CDI, confirmed disability improvement; **CI**, confidence interval; **PwMS**, people with multiple sclerosis; **Tx**, treatment.

- By Month 48, the KM-estimated probability of CDP was low for the whole population (**Figure 2**).
  - The lowest CDP was recorded for the Tx-naïve group (14.3%) and PwMS aged ≤50 years (15.6%). However, this difference was not statistically significant (**Supplementary Table 1**).
- The KM-estimated probability of CDI by Month 48 for all participants was 15.4% (**Figure 3**). The rate of CDI was highest in the Tx-naïve (17.1%) and aged ≤50 years (16.3%, p=0.0462 vs >50 years) groups (**Supplementary Table 1**).
- Those with CDI at Month 48 were found to have had better BL scores on the T25FW, 9HPT and SDMT, while BL EDSS scores were similar across groups (**Figure 4**).

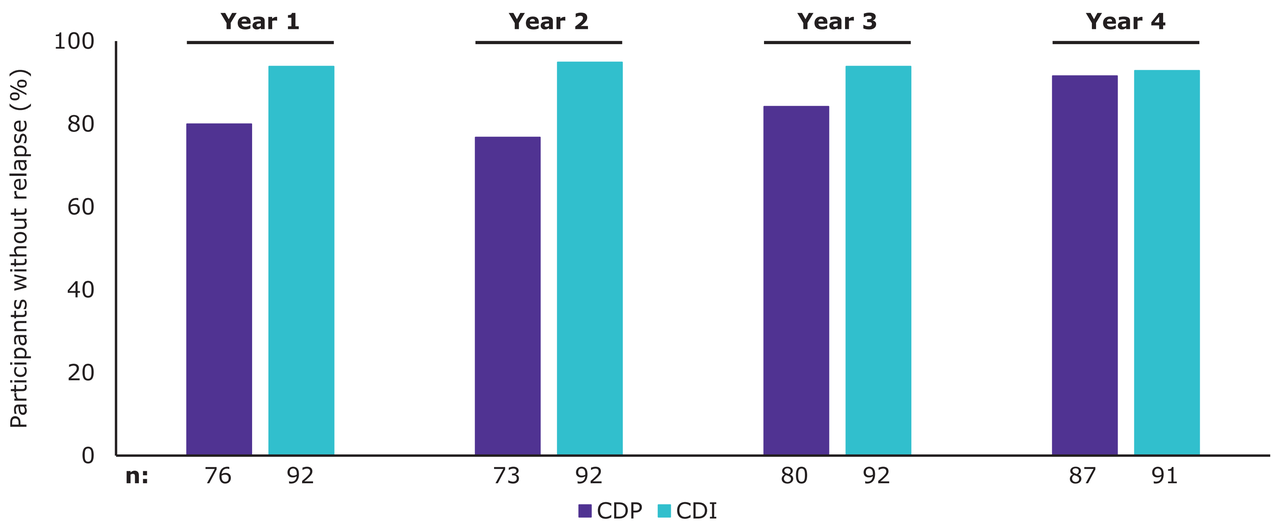
Figure 4. PwMS With CDI at Month 48 Had Better Baseline Mobility and Cognition Than Those with CDP



9HPT, 9-hole peg test; **CDI**, confirmed disability improvement; **CDP**, confirmed disability progression; **EDSS**, Expanded Disability Status Scale; **PwMS**, people with multiple sclerosis; **SDMT**, Symbol Digit Modality Test; **T25FW**, timed 25-foot walk.

- Freedom from relapse was higher in the CDI group compared to the CDP group during the entire 4-year observation (93.9%, 94.9%, 93.9%, and 92.9% versus 80.0%, 76.8%, 84.2%, and 91.6%, respectively [**Figure 5**]).

Figure 5. PwMS With CDI Had Higher Freedom From Relapse Versus Those With CDP



Stable participants are not shown.
CDI, confirmed disability improvement; **CDP**, confirmed disability progression; **PwMS**, people with multiple sclerosis.

- **Annualised relapse rate (ARR, mean [standard deviation]) was lower in participants with CDI than those with CDP;** in Year 1 (0.071 [0.295] vs 0.326 [0.763]; p=0.0034), Year 2 (0.052 [0.224] vs 0.264 [0.531]; p=0.0003), and Year 3 (0.092 [0.333] vs 0.243 [0.517]; p=0.0282). ARR was similar between groups in Year 4 (0.154 [0.529] vs 0.160 [0.466]; p=0.7150).
- **PwMS with CDP had a shorter time to first relapse than PwMS with CDI** (p<0.0001; **Supplementary Figure 1**). By Month 48, the probability of first relapse event was 51.6% in participants with CDP, 23.0% for those with CDI, and 24.7% in stable participants.
- Safety findings for cladribine tablets were reported in the individual studies.[3–6]

CONCLUSIONS

- **83.4% of participants were either stable or had confirmed disability improvement 4 years after initiating cladribine tablets.**
- **Younger, Tx-naive PwMS were more likely to experience improvement, supporting the early use of cladribine tablets.**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

References: 1. Wiendl H, et al. *Front Immunol*. 2025:16:1512189. 2. De Stefano N, et al. *Mult Scler Relat Disord*. 2024;92:106121. 3. De Stefano N, et al. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4):e1187. 4. Brochet B, et al. *Mult Scler*. 2023;29(14):1808–1818. 5. Selmaj K, et al. *Mult Scler Relat Disord*. 2024;92:106122. 6. De Stefano N, et al. *Mult Scler Relat Disord*. 2024;92:106123.

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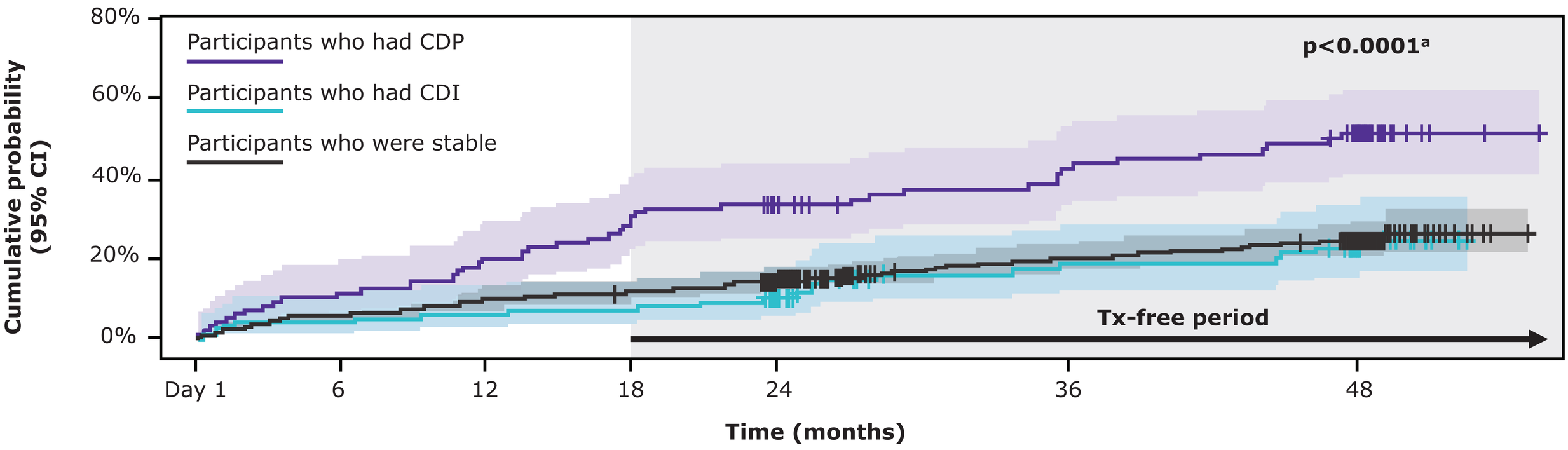
Supplementary Information

Supplementary Table 1. Estimated Cumulative Probability of CDI and CDP at Month 48

Participant group	CDP estimate (95% CI)	CDI estimate (95% CI)
All participants (n=752)	16.6 (13.9, 19.9)	15.4 (12.8, 18.4)
Treatment[a]		
Tx-naïve (n=251)	14.3 (10.1, 20.1)	17.1 (12.7, 22.7)
Tx-experienced (n=501)	17.8 (14.4, 21.9)	14.5 (11.5, 18.2)
Age		
≤50 years (n=665)	15.6 (12.8, 19.0)	16.3 (13.5, 19.5)
>50 years (n=87)	24.0 (15.7, 35.9)	8.7 (3.9, 18.7)
p-value[b]	0.1165	0.0462

[a]p-values not available for this group. [b]p-values were derived using z-score.
CDI, confirmed disability improvement; **CDP**, confirmed disability progression; **CI**, confidence interval; **Tx**, treatment.

Supplementary Figure 1. Lower Estimated Relapse Rates Were Observed in PwMS With CDI Than Those With CDP



[a]p-value at Month 48 from two-sided Log Rank test.
CDI, confirmed disability improvement; **CDP**, confirmed disability progression; **CI**, confidence interval; **PwMS**, people with multiple sclerosis; **Tx**, treatment.

Supplementary Materials:

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