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Cladribine Tablets Show Low 4-Year PIRA Rates in MS: Insights from Pooled Analyses of CLARIFY-MS and MAGNIFY-MS Studies

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RESEARCH IN CONTEXT

1. **Short-course cladribine tablets provide long-term control of disability progression with low rates of PIRA, RAW, and CDA in people with highly active multiple sclerosis. This is especially notable in younger patients, supporting early treatment initiation.**
2. **Older PwMS also benefit from cladribine tablets, showing low PIRA rates and sustained control of disability accumulation over time.**

OBJECTIVES

To investigate the long-term effects of cladribine tablets on progression independent of relapse activity (PIRA), relapse-associated worsening (RAW), and confirmed disability accumulation (CDA) in people with multiple sclerosis (PwMS).

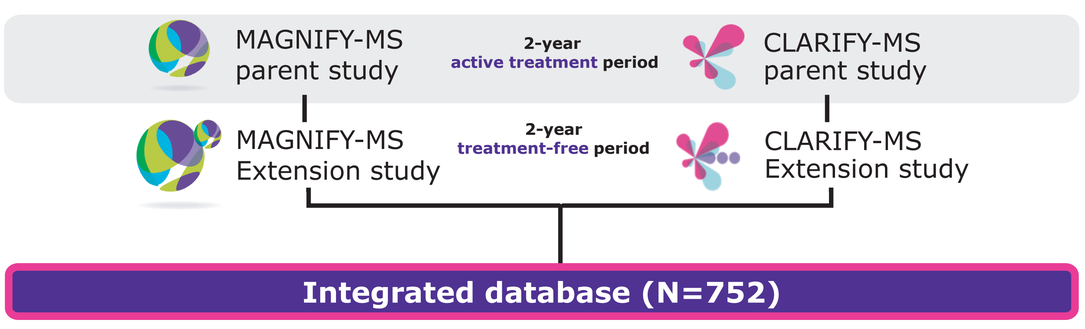
INTRODUCTION

- PwMS acquire disability over time (CDA) via inflammatory (RAW) and neurodegenerative (PIRA) processes,[1] with rates of PIRA in relation to RAW increasing with age.[2]
- Disability progression is traditionally measured as worsening of symptoms through increased Expanded Disability Status Scale (EDSS) score.[3,4]
- PIRA has become a standard measure of long-term disability accumulation that is not attributable to relapse activity and is a significant concern for treating physicians and PwMS.[5]

METHODS

- This was a 4-year pooled 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.**
- PIRA was assessed in accordance with the recommended harmonised method.[5]
- Time to first event was analysed by the non-parametric Kaplan-Meier (KM) method.
- All analyses were exploratory. Outcomes were evaluated for all participants and by the following subgroups, based on parent study baseline (BL) demographics:
  - Age subgroups were investigated to explore PIRA in **younger** (**≤40** vs **>40 years**) and **older** (**≤50** vs **>50 years**) PwMS.
  - PIRA was also analysed by treatment (Tx) history (**Tx-naïve** vs **Tx-experienced**).

Outcome type	Definition (all events confirmed over ≥6 months)
Confirmed disability progression (CDP)	Increased EDSS: ≥1.5 points from BL EDSS 0; ≥1 point from BL EDSS 0.5–4.5; ≥0.5 points from BL EDSS ≥5.
PIRA	CDP with no relapse within 90 days
RAW	CDP not qualifying as PIRA
CDA	Any PIRA or RAW event
Composite (c)PIRA	CDP **or** 20% progression on either the timed 25-foot walk (T25FW) or 9-hole peg test (9HPT), with no relapse within 90 days
cRAW	CDP **or** 20% progression on either the T25FW or 9HPT not qualifying as a cPIRA event
cCDA	Any cPIRA or cRAW event

RESULTS

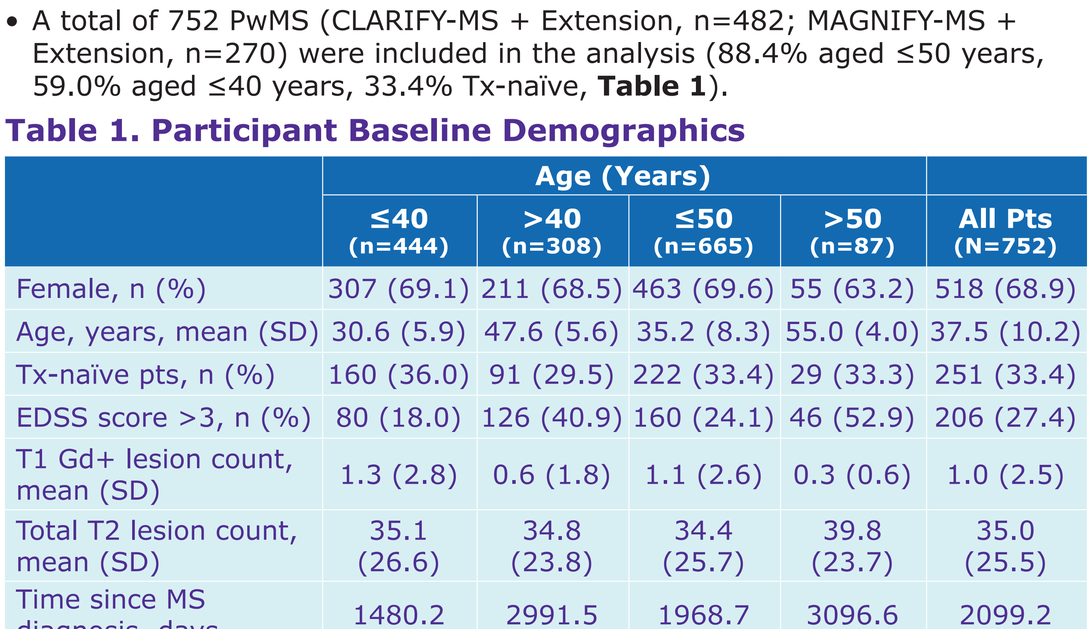
- A total of 752 PwMS (CLARIFY-MS + Extension, n=482; MAGNIFY-MS + Extension, n=270) were included in the analysis (88.4% aged ≤50 years, 59.0% aged ≤40 years, 33.4% Tx-naïve, **Table 1**).

Table 1. Participant Baseline Demographics

	Age (Years)				
	≤40 (n=444)	**>40 (n=308)**	**≤50 (n=665)**	**>50 (n=87)**	**All Pts (N=752)**
Female, n (%)	307 (69.1)	211 (68.5)	463 (69.6)	55 (63.2)	518 (68.9)
Age, years, mean (SD)	30.6 (5.9)	47.6 (5.6)	35.2 (8.3)	55.0 (4.0)	37.5 (10.2)
Tx-naïve pts, n (%)	160 (36.0)	91 (29.5)	222 (33.4)	29 (33.3)	251 (33.4)
EDSS score >3, n (%)	80 (18.0)	126 (40.9)	160 (24.1)	46 (52.9)	206 (27.4)
T1 Gd+ lesion count, mean (SD)	1.3 (2.8)	0.6 (1.8)	1.1 (2.6)	0.3 (0.6)	1.0 (2.5)
Total T2 lesion count, mean (SD)	35.1 (26.6)	34.8 (23.8)	34.4 (25.7)	39.8 (23.7)	35.0 (25.5)
Time since MS diagnosis, days, mean (SD)	1480.2 (1666.0)	2991.5 (2754.6)	1968.7 (2186.7)	3096.6 (2855.8)	2099.2 (2300.4)
Number of relapses in the year before initiating cladribine tablets, mean (SD)	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)

EDSS, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **MS**, multiple sclerosis; **Pts**, participants; **SD**, standard deviation; **Tx**, treatment.

Figure 2. Low Probabilities of PIRA, RAW, and CDA Were Observed in PwMS 4 Years After Initiating Cladribine Tablets

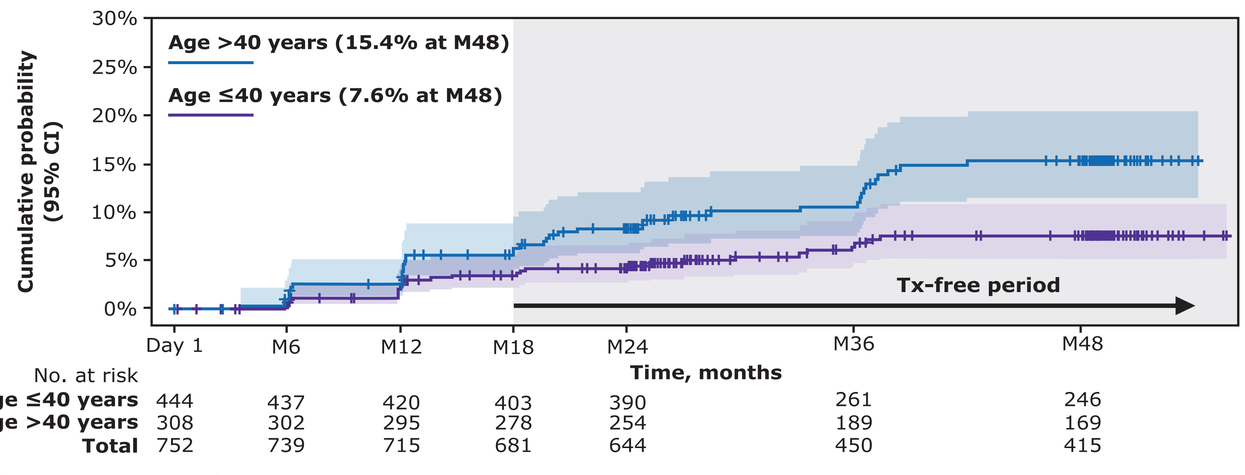


First PIRA, RAW, and CDA events are presented. CDA includes only the first event of PIRA or RAW.
CDA, confirmed disability accumulation; **M**, month; **PIRA**, progression independent of relapse activity; **PwMS**, people with multiple sclerosis; **RAW**, relapse-associated worsening; **Tx**, treatment.

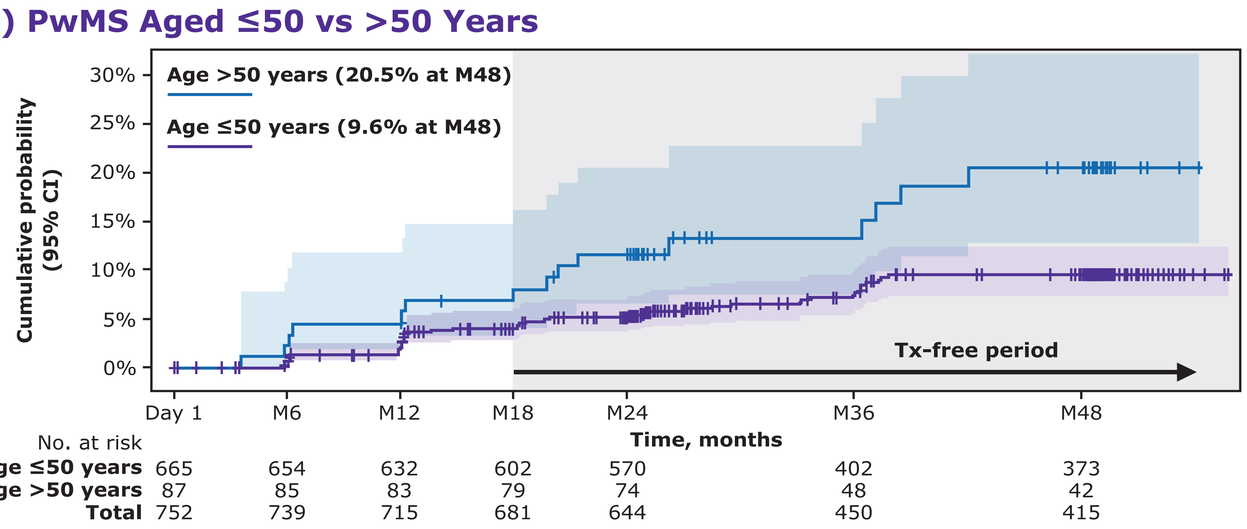
- By 48 months, all participants had a low estimated probability of PIRA (10.8%), RAW (6.3%), and CDA (16.4%, **Figure 2**).

Figure 3. Lower Probability of PIRA Was Observed in Younger PwMS in the Tx-Free Period

a) PwMS Aged ≤40 vs >40 Years



b) PwMS Aged ≤50 vs >50 Years



CI, confidence interval; **M**, month; **PIRA**, progression independent of relapse activity; **PwMS**, people with multiple sclerosis; **Tx**, treatment.

- 48-month PIRA probability was:
  - **Overall low in both younger and older PwMS**, indicating the effectiveness of cladribine tablets across age groups (**Figure 3**).
  - Age-dependent: Younger PwMS had the lowest probability of PIRA (**Figure 3**).
  - Similar between Tx-naïve vs Tx-experienced (10.5% vs 11.0%, **Supplementary Figure 1**) subgroups.

Composite PIRA

- KM-estimated probabilities by Month 48 were: cPIRA 24.8%, cRAW 8.7%, cCDA 30.6%. T25FW was the main contributor to cPIRA events (55.9%), followed by 6-month CDP (42.2%). cPIRA probabilities were higher in older PwMS (>40 years: 33.4% vs ≤40 years: 18.6%) but similar between treatment groups (Tx-naïve: 22.9% vs Tx-experienced: 25.7%).

CONCLUSIONS

- **These findings demonstrate long-term control of both inflammatory and non-inflammatory components of disability accumulation and disease progression in a large cohort of cladribine tablets-treated PwMS.**
- **Nine out of ten PwMS treated with cladribine tablets were estimated to be free from PIRA and >83% free from CDA by Year 4.**
- **Lowest rates of PIRA, RAW, and CDA were in younger PwMS, supporting early initiation of cladribine tablets treatment to achieve maximum benefit.**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

References: 1. Tur C, et al. *JAMA Neurol*. 2023;80(2):151–160. 2. Müller J, et al. *JAMA Neurol*. 2023;80(11):1232–1245. 3. Gärtner J, et al. *Mult Scler*. 2022;28(10):1562–1575. 4. Ingwersen J, et al. *Sci Rep*. 2023;13(1):15003. 5. Lublin FD, et al. *Brain*. 2022;145(9):3147–3161.

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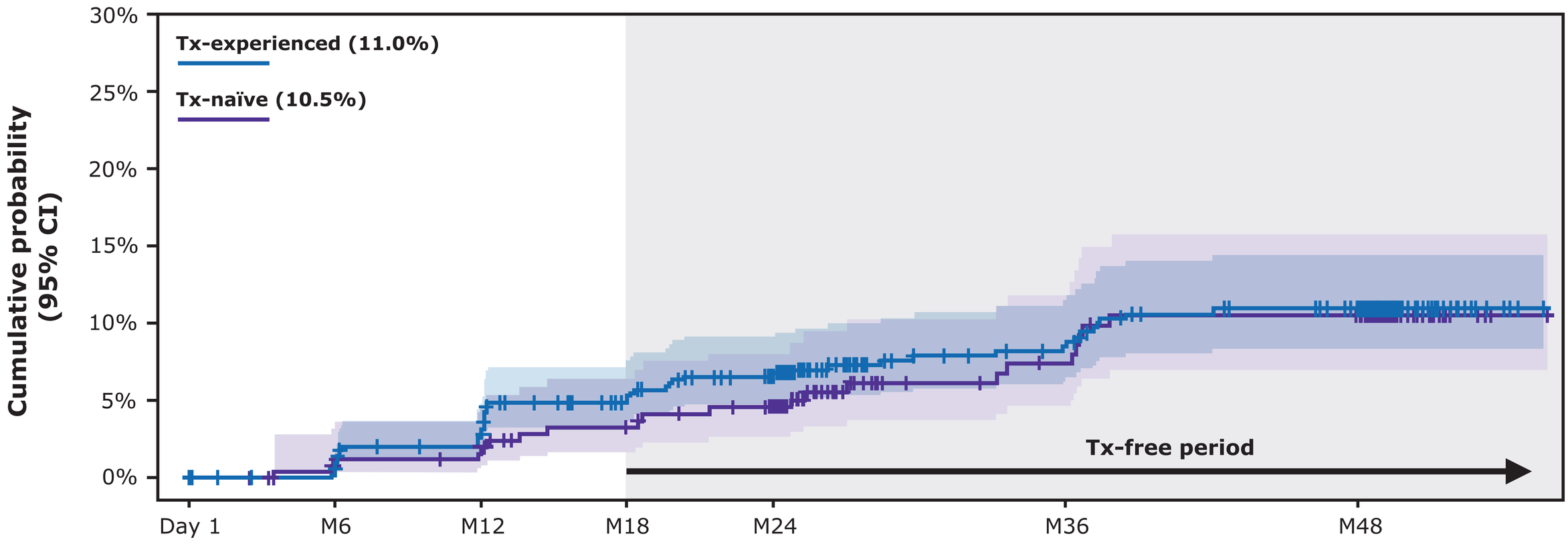
Supplementary Information

Supplementary Figure 1. Probability of PIRA Was Similar Regardless of Prior Treatment Experience 4 Years After Initiating Cladribine Tablets



No. at risk							
Tx-naïve	251	244	238	228	215	150	142
Tx-experienced	501	495	477	453	429	300	273
Total	752	739	715	681	644	450	415

CI, confidence interval; **M**, month; **PIRA**, progression independent of relapse activity; **Tx**, treatment.

Supplementary Materials:

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