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Low Rate of Progression Independent of Relapse Activity (PIRA) in Patients With Relapsing Multiple Sclerosis Treated With Cladribine Tablets

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RESEARCH IN CONTEXT

1. **More than 93% of PwMS treated with cladribine tablets were PIRA-free at month 24, in line with ARR and MRI data, [1, 2] supporting early use of short-course cladribine tablets for maximum disease control.**
2. **T25FW may be a convenient indicator of disease progression where full PIRA assessment is impractical.**

OBJECTIVES

To explore the treatment effect 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

In people with multiple sclerosis (PwMS), **early PIRA is associated** with **unfavourable long-term prognosis and disability accrual**. [3]

Previous assessments of PIRA [4, 5] were based on Expanded Disability Status Scale (EDSS) scores. However, inclusion of additional compositive measures provides a more comprehensive assessment of disease progression. [6] Therefore, we **evaluated both EDSS-based and composite-based PIRA and CDA**.

We **investigated PIRA**, RAW, **and CDA in PwMS treated with cladribine tablets in the 2-year MAGNIFY-MS** study (NCT03364036).

METHODS

- Six-month confirmed PIRA (no relapse occurring within 90 days of the event) was estimated using two definitions:
  - **PIRA** based on EDSS progression (6-month confirmed disability progression [6mCDP]), [7] or
  - **Composite (c)PIRA**, defined as the presence of 6mCDP, or 20% confirmed progression on either timed 25-foot walk (T25FW) or 9-hole peg test (9HPT). [6]
- Other outcomes were:
  - **RAW**, defined as any other 6mCDP event that did not qualify for a 6mPIRA event
  - **cRAW**, defined as any event (6mCDP, 20% progression on T25FW or 9HPT) within 90 days of relapse
  - **CDA**, which included any PIRA or RAW event, and
  - **cCDA**, which included any cPIRA or cRAW event.
- Time-to-first PIRA or cPIRA event over 24 months was estimated using the Kaplan–Meier method.
- All analyses were exploratory, performed for all participants or by subgroups:
  - **Tx-naïve** vs **Tx-experienced**
  - **Age** (**≤40** vs **>40 years**)
  - **Time since MS diagnosis** (**≤5 years** vs **>5 years**).

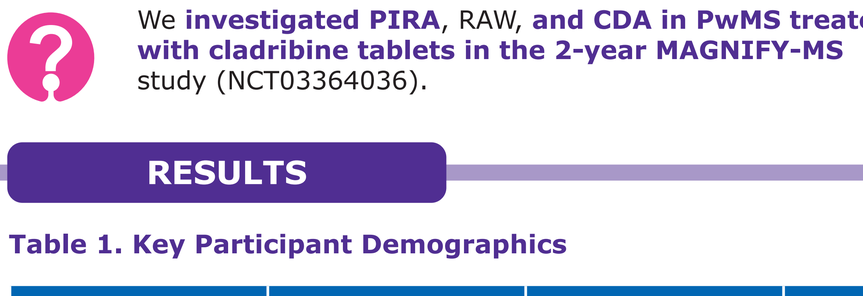
RESULTS

Table 1. Key Participant Demographics

Groups	Female, n (%)	Age, mean (SD)	Participants with HRA[a], n (%)	EDSS score >3 at BL[b], n (%)	≥1 T1 Gd+ lesion during BL period[c], n (%)	≥1 active T2 lesion (without T1 Gd+) during BL period[c], n (%)	Time since MS onset in years, mean (SD)	Number of relapses prior to BL[b] in months, mean (SD)
Tx-naïve (n=117)	76 (65.0)	37.6 (10.1)	100 (85.5)	28 (23.9)	58 (49.6)	27 (23.1)	3.7 (4.6)	2.1 (0.7)
Tx-experienced (n=153)	104 (68.0)	37.8 (9.5)	65 (42.5)	38 (24.8)	78 (51.0)	41 (26.8)	9.7 (7.6)	1.5 (0.7)
All participants (N=270)	180 (66.7)	37.7 (9.8)	165 (61.1)	66 (24.4)	136 (50.4)	68 (25.2)	7.1 (7.1)	1.7 (0.7)

[a]HRA was defined as ≥2 relapses in the previous year (i.e., the number of historical relapses within 12 months prior to BL ≥2) regardless of prior DMT use. [b]The BL measurement was the last non-missing measurement prior to the start of study medication. [c]The median BL period (screening – BL) had a duration of 35.0 days (range 16–92 days)
BL, baseline; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; HRA, high relapse activity; MS, multiple sclerosis; SD, standard deviation; Tx, treatment

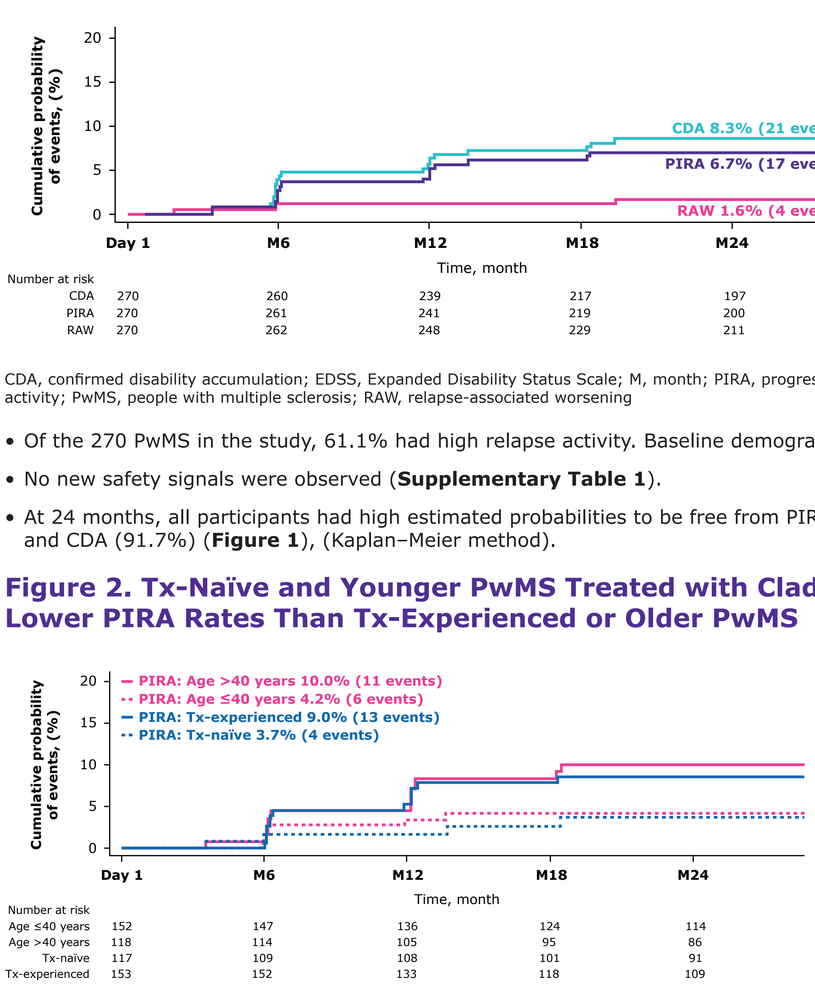
Figure 1. >93% of PwMS Treated with Cladribine Tablets were Free From EDSS-Based PIRA



CDA, confirmed disability accumulation; EDSS, Expanded Disability Status Scale; M, month; PIRA, progression independent of relapse activity; PwMS, people with multiple sclerosis; RAW, relapse-associated worsening

- Of the 270 PwMS in the study, 61.1% had high relapse activity. Baseline demographics are shown in **Table 1**.
- No new safety signals were observed (**Supplementary Table 1**).
- At 24 months, all participants had high estimated probabilities to be free from PIRA (93.3%), RAW (98.4%) and CDA (91.7%) (**Figure 1**), (Kaplan–Meier method).

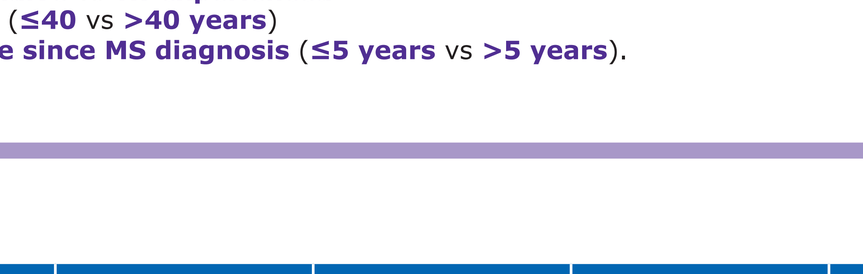
Figure 2. Tx-Naïve and Younger PwMS Treated with Cladribine Tablets had Lower PIRA Rates Than Tx-Experienced or Older PwMS



M, month; PIRA, progression independent of relapse activity; PwMS, people with multiple sclerosis; Tx, treatment

- Tx-naïve and PwMS aged <40 years had the lowest PIRA rates in the study (**Figure 2**).
- Time since diagnosis did not affect the probability of being free from PIRA at 24 months (95.1% for ≤5 years vs 92.1% for >5 years since diagnosis). Further investigation with longer duration and higher participant numbers are needed to confirm this effect.

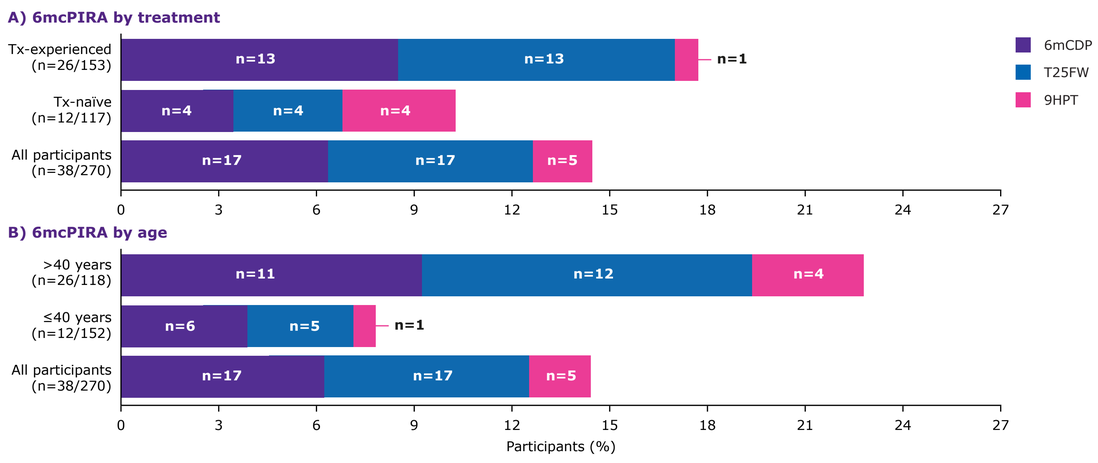
Figure 3. 85% of PwMS Treated with Cladribine Tablets were Free From cPIRA



c, composite; CDA, confirmed disability accumulation; M, month; PIRA, progression independent of relapse activity; PwMS, people with multiple sclerosis; RAW, relapse-associated worsening

- The Kaplan–Meier-estimated probability of being free from cPIRA, cRAW and cCDA was also high (**Figure 3**).
- The probability of being free from cPIRA, cRAW, and cCDA was higher in Tx-naïve than Tx-experienced PwMS (**Supplementary Figure 1**). In addition, age was a major contributing factor to overall cPIRA, with younger PwMS being more likely to be free from cPIRA than older PwMS (**Supplementary Figure 2**).

Figure 4. 6mCDP and T25FW Progression were the Largest Contributors to cPIRA



6m, 6-month; 9HPT, 9-hole peg test; c, composite; CDP, confirmed disability progression; PIRA, progression independent of relapse activity; T25FW, timed 25-foot walk; Tx, treatment

- Tx-naïve PwMS had equal component contribution to cPIRA rate, while in Tx-experienced PwMS, 6mCDP and T25FW were major contributors (**Figure 4A**). When cPIRA was analysed by age, the 9HPT had a smaller contribution in all groups (**Figure 4B**).

CONCLUSIONS

- **These results indicate low overall disability accrual (>93% free from PIRA and >91% free from CDA) in highly active PwMS treated with cladribine tablets.**
- **Tx-naïve and younger PwMS had lower PIRA, RAW, and CDA, supporting the benefit of early initiation of cladribine tablets treatment to reduce total disability accumulation.**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

References:
1. De Stefano N, et al. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4):e1187. 2. De Stefano N, et al. *Neurology*. 2023;100(17 Supplement 2):3042
3. Tur C, et al. *JAMA Neurol*. 2023;80(2):151–160. 4. Gärtner J, et al. *Mult Scler*. 2022;28(10):1562–1575
5. Ingwersen J, et al. *Sci Rep*. 2023;13(1):15003. 6. Müller J, et al. *JAMA Neurol*. 2023;80(11):1232–1245. 7. Lublin FD, et al. *Brain*. 2022;145(9):3147–3161

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Supplementary Materials

MAGNIFY-MS was a single-arm, open-label, 2-year, phase IV study, in which people with multiple sclerosis (PwMS) were treated with cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years), with 2 weeks of active treatment course per annual dose.

Participants were enrolled in the study between 28 May 2019 and 23 April 2019.

The main study design, including inclusion and exclusion criteria, and dosing regimen, has been reported by De Stefano N, et al. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4):e1187.

Supplementary Materials

Supplementary Table 1. Overview of Treatment-Emergent Adverse Events – Safety Analysis Set

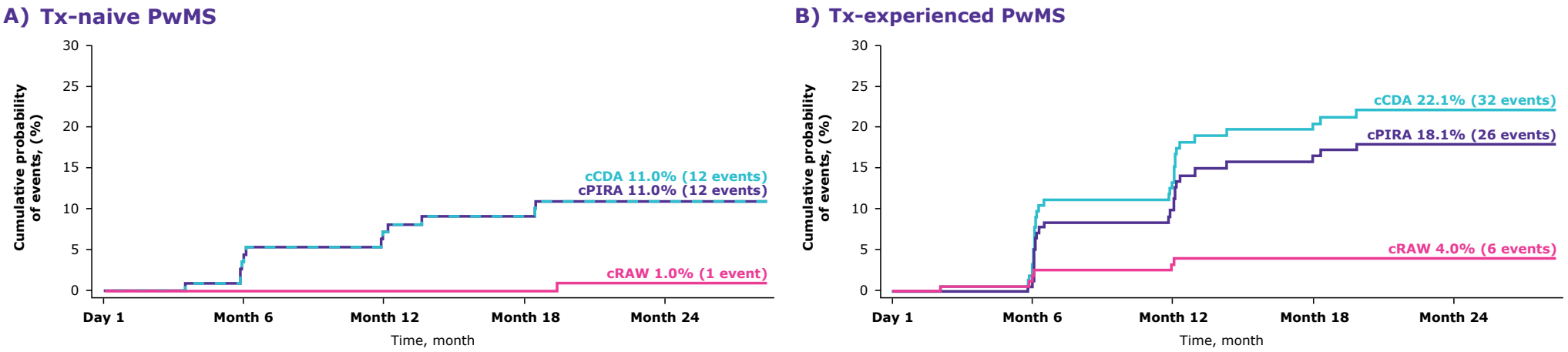
Number of Participants with:	Total N=270 (%)
Any TEAE*	227 (84.1)
Mild	114 (42.2)
Moderate	103 (38.1)
Severe	10 (3.7)
Any study treatment-related TEAE*	122 (45.2)
Mild	71 (26.3)
Moderate	47 (17.4)
Severe	4 (1.5)
Any serious TEAE	14 (5.2)
Any study treatment-related serious TEAE	0 (0.0)
Any TEAE leading to **temporary** discontinuation of study treatment	4 (1.5)
Any TEAE leading to **permanent** discontinuation of study treatment	1 (0.4)

Participants with ≥1 TEAE	Total N=270 (%)
Headache	87 (32.2)
Nasopharyngitis	57 (21.1)
Urinary tract infection	32 (11.9)
Fatigue	31 (11.5)
Nausea	31 (11.5)
Back pain	30 (11.1)
Lymphopenia	28 (10.4)
Upper respiratory tract infection	27 (10.0)
Diarrhoea	26 (9.6)
Pain in extremity	22 (8.1)
Alopecia	21 (7.8)
Dizziness	20 (7.4)

*Worst severity per participant is reported
TEAE, treatment-emergent adverse event

Supplementary Materials

Supplementary Figure 1. Tx-Naïve PwMS were More Likely to be Free From cCDA, cPIRA, and cRAW Events Than Tx-Experienced PwMS

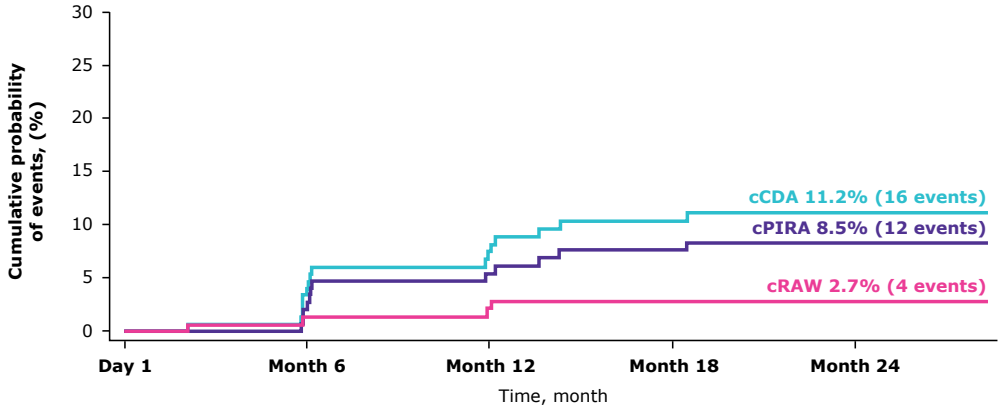


Supplementary Figure 1A) cRAW/cCDA = 8.3% (1/12); cPIRA/cCDA = 100.0% (12/12). Supplementary Figure 1B) cRAW/cCDA = 18.8% (6/32); cPIRA/cCDA = 81.3% (26/32).
c, composite; CDA, confirmed disability accumulation; PIRA, progression independent of relapse activity; PwMS, people with multiple sclerosis; RAW, relapse-associated worsening; Tx, treatment

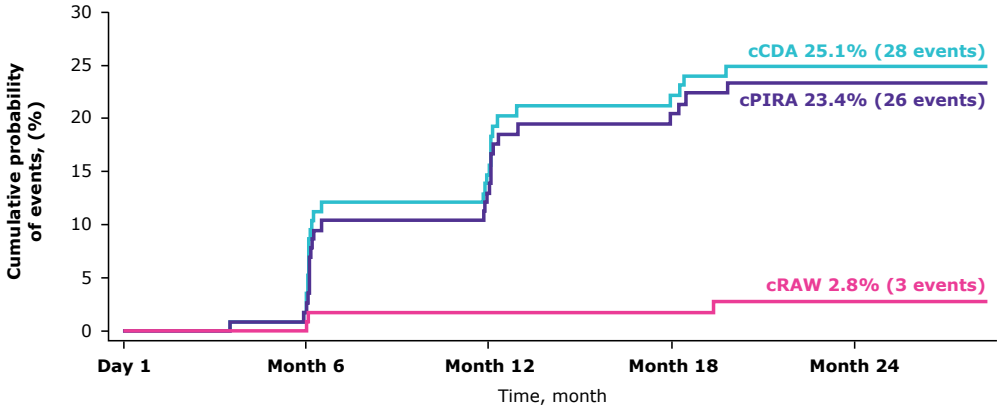
Supplementary Materials

Supplementary Figure 2. Younger PwMS were More Likely to be Free From cCDA, cPIRA, and cRAW Events Than Older PwMS

A) PwMS aged ≤40 years



B) PwMS aged >40 years



Supplementary Figure 2A) cRAW/cCDA = 25.0% (4/16); cPIRA/cCDA = 75.0% (12/16). Supplementary Figure 2B) cRAW/cCDA = 10.7% (3/28); cPIRA/cCDA = 92.9% (26/28).
c, composite; CDA, confirmed disability accumulation; PIRA, progression independent of relapse activity; PwMS, people with multiple sclerosis; RAW, relapse-associated worsening

At 24 months, the probability of being free from having a cPIRA event was higher in PwMS aged ≤40 years (91.5%; **Supplementary Figure 2A**) than in older PwMS (76.6%; **Supplementary Figure 2B**).

Similar results were observed for cCDA: Age ≤40 years (88.8%; **Supplementary Figure 2A**) *vs* age >40 years (74.9%; **Supplementary Figure 2B**).

Supplementary Materials

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